CLINICAL STUDY PROTOCOL

Full Study Title:

PROState **P**athway **E**mbedded **C**omparative **T**rial

Short Study title / Acronym:

Imperial Prostate Study 3
IP3-PROSPECT

PROSPECT

Product: N/A

Development Phase: Phase II/III

Sponsor: Imperial College London

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CONTACT LIST

Chief Investigator

Name: Professor Hashim U Ahmed
Address: Room 5L28, 5th Floor, Laboratory Block, Charing Cross Hospital Campus, Imperial College London, Fulham Palace Road, London W6 8RF
Tel: 0203 311 1673
Fax: N/A
Email: hashim.ahmed@imperial.ac.uk

Sponsor

Sponsor's Name: Imperial College London
Address: Research Governance and Integrity Team (RGIT), Room 215, Level 2, Medical School Building, St Mary's Campus, Norfolk Place, London W2 1PG

Name of contact person: Ruth Nicholson
Title: Head of Research Governance and Integrity
Tel: Tel: 0207 594 1872
Email: r.nicholson@imperial.ac.uk

Funder

Funder's name: Wellcome Trust
Address: Gibbs Building, 215 Euston Road, London, NW1 2BE, UK

Clinical queries should be directed to the Clinical Trial Manger who will direct the query to the appropriate person:

Clinical Trial Manager

Name: Ms Puja Jadav
Address: Imperial Prostate
Division of Surgery, Charing Cross Hospital, 5L15, Laboratory Block, Fulham Palace Road, London, W6 8RP
Tel: 0207 594 7271 | 0751 348 0679
Email: p.jadav@imperial.ac.uk

ICTU Operations

Name: Mrs Natalia Klimowska-Nassar
Address: Imperial College Trials Unit & Division of Surgery
1st Floor, Stadium House, 68 Wood Lane, London W12 7RH
Tel: 0207 594 3424
Email: n.klimowska@imperial.ac.uk

Name: Dr Thiagarajah Sasikaran
Address: Imperial College Trials Unit & Division of Surgery
1st Floor, Stadium House, 68 Wood Lane, London W12 7RH
Tel: 0207 594 6017
Email: t.sasikaran@imperial.ac.uk

Senior Statistician

Name: Dr Francesca Fiorentino
Address: Imperial College Trial Unit & Department of Surgery and Cancer
Queen Elisabeth the Queen Mother Building (10th Floor/1091) St Mary's Hospital
Imperial College London, Praed Street, London, W2 1NY
Tel: 0203 312 3761

Co-Investigators

Mr Edward Bass
Clinical Coordinator
Clinical Research Fellow and Specialist Trainee in Urology, Division of Surgery, Charing Cross Hospital, 5L15, Laboratory Block, Fulham Palace Road, London, W6 8RP

Mr Mathias Winkler
Consultant Urological Surgeon
Charing Cross Hospital
Imperial College Healthcare NHS Trust
Fulham Palace Road, London, W6 8RF
Email : mathias.winkler@nhs.net

ADMINISTRATIVE INFORMATION

This document is a trial protocol describing IP3-PROSPECT, a study sponsored by Imperial College London, coordinated by ICTU-Surgery. It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments

may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial management team.

The study will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) UK Policy Framework for Health and Social Care . International sites will comply with the principles of GCP as laid down by ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC, the European Directive 2001/20/EC (where applicable), the EU Tissue and Cells Directives 2004/23/EC, 2006/17/EC and 2006/86/EC and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and Imperial College London.

COMPLIANCE

Participating sites will inform the trial management team as soon as they are aware of a possible serious breach of compliance, so that ICTU-Surgery can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

ABBREVIATIONS

cmRCT	Cohort Multiple Randomised Control Trial
CRF	Case Report Form
CTA	Clinical Trials Agreement
ECOG	Eastern Co-operative Oncology Group
EQ5D-5L	European Quality of Life Instrument (5 dimensions, 5 levels)
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICTU	Imperial Clinical Trials Unit
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
mpMRI	Multiparametric Magnetic Resonance Imaging
NCRN	National Cancer Research Network
NHS	National Health Service
NHSCR	National Health Service Care Register
NIHR	National Institute for Health Research
PIS	Participant Information Sheet

PROMS	Patient Reported Outcome Measures
PSA	Prostate Specific Antigen
QoL	Quality of Life
RCT	Randomised Control Trial
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Group
TRUS	Transrectal Ultrasound
TWiCS	Trials Within Cohorts
USS	Ultrasound

KEYWORDS:

prostate cancer; clinical trials; cohort multiple randomised control trial

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TRIAL SUMMARY

TITLE	**PROS**tate **P**athway **E**mbedded **C**omparative **T**rial
AIM	• To assess the feasibility and acceptability of a cohort multiple randomised controlled trial (cmRCT) in patients with prostate conditions • To assess acceptance rates to entry into the cohort • To assess acceptance to future randomised interventions or changes in management to compare against standard care • To assess acceptance to future embedded randomised interventions (changes in diagnostic and therapeutic pathways) • To assess the feasibility of collecting regular health status and clinical data as well as patient reported outcomes (PROMS) within the cohort
DURATION	**PILOT** • Months 0 – 6: Set-up • Month 7 – 16: Recruitment • Months 17 – 22: Close out and analysis **MAIN STUDY** • Months 1-8 cohort recruitment • Months 9-18: Embedded randomised interventions • Months 19-24: Longitudinal follow-up
DESIGN	Cohort Multiple Randomised Controlled Trial (cmRCT) design (aka Trials Within Cohorts [TWICS])
SAMPLE SIZE	Acceptability and Feasibility sample size: 80 patients The actual cohort sample will not be restricted as the overall number needed will be dependent on future randomised interventions and therefore there is no maximum number. If the feasibility number is met then we will continue recruiting for the entire recruitment period with no upper limit on numbers and continue beyond the existing recruitment period if further funding allows and pending approval by REC.
ACCEPTABILITY OBJECTIVES	• To determine what proportion of patients with a clinical suspicion for prostate cancer will participate in an cmRCT. • To evaluate the proportion of patients approached agreeing to participate in the longitudinal cohort from men approached for take part. • To explore barriers and facilitators to the implementation of a cmRCT in order to improve and inform patient and/or physician trial information, study processes, interventions, and recruitment and retention of patients. This will be carried out by qualitative assessments in the following areas. - To investigate by interview the patient experiences and perspectives on: ▪ Trial participation, ▪ The point at which men are approached by the research team to enter the cohort, ▪ Barriers and facilitators to consent to participate in the cohort, ▪ Barriers and facilitators to consent to future random selection to undergo a healthcare intervention or change in management, ▪ Acceptability of monitoring of health status and the tools used to do this in the cohort.

	- To investigate by interview the experiences and perspectives of healthcare professionals (doctors and clinical nurses, research staff, NHS admin and management) on; ▪ Trial design and information given to patients and healthcare professionals, ▪ Feasibility of random selection of participants to future interventions, ▪ Tools used for measuring health status.
FEASIBILITY OBJECTIVES	• To determine the feasibility of recruitment and logistical implementation of different data collection in centres based in different institutions. This will be broken down into the following sub-questions; o Evaluating how the patients are successfully identified and the option of how inclusion in the trial is presented to them. o Evaluating the practicalities of the consent process and of presenting the invitation. o Evaluate PROMS response rates at baseline and pre-determined intervals following from the point of recruitment into the study and explore factors that can promote optimal patient response rate and thereby improve data collection. o To evaluate completeness and fidelity of clinical data on the men who participate in the cohort.
ELIGIBILITY CRITERIA	**Inclusion Criteria** **Patients** 1. Men aged 18 years old and over who are referred for investigations for urinary symptoms or elevated serum prostate specific antigen (PSA) levels or other risk factors for possible prostate malignancy OR Men aged 18 years or older with a diagnosis of prostate cancer on active surveillance or referred from another centre for consideration of surgery, radiotherapy or ablative therapy to the prostate. 2. An understanding of the English language sufficient to understand written and verbal information about the trial and consent process. 3. Estimated life expectancy of 5 years or more. 4. Signed informed consent. **Healthcare professionals** 1. Consultant Urologists, Uroradiologists, Oncologists, Nurses and Urology specialty trainees, research and management staff. **Exclusion Criteria** **Patients** 1. Men who are unable to give informed consent. **Healthcare professionals** 1. Not involved in the care of prostate cancer patients in either research, clinically and managerial bases.
ACCEPTABILITY ENDPOINTS	• Proportion of those approached consenting to inclusion in the PROSPECT cohort at the original point of contact by the research team. This will be calculated on an ongoing basis and will be reviewed at the first 6-month timepoint.

	• To investigate by interview the experiences and perspectives of patients who; - Consented to inclusion in the cohort study, - Declined to enter into the cohort, - Consented to inclusion in the cohort initially but who subsequently requested to leave the cohort, • The opinions of healthcare professionals (clinical and management) involved in the care of patients recruited into the cohort. We will interview at least 5 doctors and clinical nurses, up to 5 research staff and up to 5 management staff. We will conduct interviews at 6 and 12 months from the opening of PROSPECT (as appropriate) following thematic analysis of the initial interviews. We will perform semi-structured interviews that focus on implementation, practicality and efficiency of PROSPECT.
FEASIBILITY ENDPOINTS	• Evaluation of the number of men approached to enter PROSPECT against the number of men referred to the participating centres for investigation of prostate cancer. • We will conduct a review of the pathway by which we approach men to invite them to the cohort. Part of this will be included in the qualitative interviews with men and healthcare professionals. Particular points of interest will be the timing of consent process, the trial personnel who gain consent, and the number of men who give consent who are subsequently not diagnosed with prostate cancer. • Participants will be given a standard Quality of Life Questionnaire (EQ5D-5L) at the point at which they consent to inclusion into PROSPECT. We will calculate the completeness of this data one year after opening and on an ongoing basis. • All participants will be asked to complete PROMS on disease specific quality of life at the following points; o Recruitment to cohort. o 0-6, 6, 12, 18 & 24 months from recruitment to cohort o Yearly questionnaires thereafter during inclusion in the cohort and provided the study is open. o Once the primary outcome measures are reached (approx. 80 patients), the follow up period will be reduced to 3 months. • Feasibility of collecting data from the participating centres evidenced by the completeness of data for cohort participants including: o *Subject Data*: age, co-morbidities, ECOG/WHO Performance Status, ethnic risk, family history o *Disease Characteristics*: PSA, MRI (prostate volume, MRI score), biopsy type and findings, TNM stage if cancer o *Treatment Data*: modality, follow-up, adjuvant/salvage treatments, mortality o We will conduct this analysis at one year after opening PROSPECT and yearly thereafter, as long as the study is open, in order to monitor any trends in data return on participants. o Once the primary outcome measures are reached (approx. 80 patients), the follow up period will be reduced to 3 months.

1. BACKGROUND

1.1 SUMMARY

Traditionally, level one evidence is obtained from two-arm, or 3-arm, randomised controlled trials (RCT) of a new treatment(s) and compare it to an established treatment in which neither the patient nor the doctor knows who is taking what, until the end of the study ('double-blind'). The treatment allocation is based on chance and the blinding minimises bias. When one of the treatments is surgery this design may not always be ethical or practical. Unfortunately, in trials involving surgery or complex interventions, a variety of factors can lead to the failure to accrue sufficient participants in many traditional RCT designs. This has been particularly highlighted in localized prostate cancer RCTs, where 12 RCTs evaluating different interventions in localised prostate have failed to recruit, many in the last 5 years. The same issue has occurred recently in trials of localized bladder cancer (surgery versus radiotherapy) and renal cancer (surgery versus surveillance; surgery versus ablation) as well as other non-urological disease spaces.

Our proposal will explore a trial design called the cohort-multiple RCT (cmRCT) or as it has been recently coined, the Trials WithIn Cohorts (TWICS) design. This design has been used in a number of disease areas, both benign and cancer. We have chosen prostate conditions since they are extremely common and if malignancy occurs the majority of men with the disease are regarded as living with a chronic condition due to its long natural history and in which innovative approaches, interventions, treatments or changes in management might have a significant patient benefit and impact on the NHS. It therefore fits the cmRCT design very well. Nonetheless, the lessons we learn in this study will be of relevance to other disease spaces.

The TWICS or cmRCT design is currently being used in elderly patients, risk of falls, depression, hip fracture, Yorkshire Health Study, scleroderma, breast cancer, colorectal cancer, bladder cancer and kidney cancer, to name a few. In total, a recent systematic review showed that there were 18 ongoing cmRCT studies with 6 in the UK.

We want to test the acceptability and feasibility of the cmRCT in the prostate pathway. As this is the first time that we are trying out this method we need to first pilot it. In the first part of the study, we want to evaluate the following. What is the accrual rate? What do patients and their healthcare professionals think of the cmRCT design? Is the data we collect robust? What are the resource requirements of such a study? We will then test a number of novel interventions or changes in the pathway and compared them to standard care in the cohort that we recruit.

1.2 RATIONALE FOR PROSPECT

Recently published RCTs have reinforced the limitations and uncertainty of current diagnostic and therapeutic pathways for men with prostate cancer(1). Two RCTs (PLCO (2) and EPSRC (3)) compared screening (10yr lead-time bias) to no screening and demonstrated no overall survival benefit and a small prostate-cancer specific survival benefit in EPSRC. However, there was significant over-diagnosis and over-treatment (4). Another two RCTs compared surgery versus watchful waiting. SPCG4 showed improved all-cause and prostate-specific mortality in

unscreened men with absolute reductions of 6% at 15 years(5). PIVOT showed no improvement in overall or prostate cancer-specific mortality in men detected in the early PSA-screening era (absolute mortality differences <3%) (6,7). Equally, preliminary results from a trial of external beam radiotherapy showed no benefit in overall or disease-specific mortality compared to watchful waiting among men with non-PSA detected clinically localized prostate cancer (8). The recent PROTECT RCT showed no cancer specific survival differences between the three arms of radical prostatectomy, radical radiotherapy and active monitoring in men diagnosed as a result of PSA screening; PROTECT did show improvements in metastases-free survival using radical therapy overactive monitoring [9]. All these studies demonstrate that there is significant uncertainty around treatment options for men with prostate cancer and therefore a need for further comparative effectiveness research to guide treatment options.

The problem is that doing trials in which the interventions are significantly different and in which one arm contains surgery has always been difficult. We recently conducted a review of all RCTs in prostate cancer treatment evaluations that have failed to accrue over the last 10 years (10). We found five UK and six international RCTs evaluating novel interventions in non-metastatic prostate cancer that closed prematurely due to slow recruitment usually resulting from lack of patient and physician equipoise. This was despite pre-RCT feasibility questionnaires and surveys demonstrating that there was apparent equipoise on the research question to warrant these RCTs.

There have been certain exemplar cases that have succeeded such as the ProtecT study (11) and PIVOT (12). However, the cost to achieve this has been high (PROTECT £25M; PIVOT $8M). Moreover, they have been slow to initiate (2-4yrs) and report (10-15yrs) leading to physicians questioning their external validity when they do eventually report [13-15]. A recent RCT funded by the NIHR-HTA in the UK, called PART, struggled to accrue (16) with another, SPCG-15, run by the very successful Scandinavian Prostate Cancer Group has also failed to accrue (17). The SPCG successfully conducted SPCG4 – the RCT of watchful waiting versus surgery from about 20 years ago - so this points to the current climate for running comparative effectiveness research having changed since SPCG4, PIVOT and ProTecT. Recently, other urological RCTs comparing different treatments in bladder cancer and renal cancer have also failed to accrue [18-20]. The problems with RCTs in surgery, particularly, have been comprehensively reviewed recently in an UK National Cancer Research Institute review (21).

Persisting with our current model of acquiring evidence in this space therefore has a high chance of failing. The alternative, because we struggle to recruit to standard RCTs, is to give up and stop further innovations being evaluated within robust RCTs. Neither option is appropriate or acceptable. The third option is to determine whether a novel trial design might work (22). The European Medicines Agency states in one of its guidelines that "*One approach for a given study might be to consider the study population as a cohort in which to implement the most appropriate design for each objective, thus ensuring alignment of each objective to the best possible design and analysis*" (23). Further, the MRC Guidelines for Evaluating Complex Interventions states that novel designs could be justified in areas of difficulty in conducting standard RCTs (24). *Namely, "Preference trials and randomised consent designs*: *Practical or ethical obstacles to randomisation can sometimes be overcome by the use of non-standard designs*. *Where patients have very strong preferences among treatments, basing treatment allocation on patients' preferences, or randomising patients before seeking*

consent, may be appropriate." Certainly, in the area of prostate diseases, high quality clinical research and investigation of novel strategies in patients with prostate diseases has been sufficiently difficult in the recent past, so that the evaluation of a new way of running clinical trials is warranted.

The Cohort Multiple RCT

We propose using the cohort-multiple RCT (cmRCT) or the Relton/Nicholls design (25) also known as the Trials WithIn Cohorts (TWiCS). Others have recently supported the evaluation of such designs and many RCTs are now successfully underway using it (26).

A more detailed account of the study design will be covered in the next section (Section 3). This approach is currently being evaluated in ethics committee approved studies in a variety of diseases, such as depression (NIHR-HTA CASPER, 08/19/04) (27, 28); NIHR DiRECT (Exeter) (29)), obesity (30, 31), falls in the elderly (NIHR-HTA REFORM, 09/77/01) (32), cognitive behavioural therapy in schizophrenia (Canadian Institute of Health Research (33)), prevention of cardiovascular disease through a polypill (34, 35), ulcerative colitis (NIHR-HTA CONSTRUCT, 06/78/03) (36), elderly care (NIHR HS&DR 12/130, CLASSIC (Salford) and scleroderma (37).

The £1.5M funded bladder cancer 'Roberts Study' and the MRC (UK) funded NEST Study in kidney cancer are both cmRCTs in Kings College London (REC: London - Fulham Research Ethics Committee 17/LO/1975 [38] and The Royal Free Hospital (East Midlands - Derby Research Ethics Committee 19/EM/0004, respectively [39].

In the Netherlands the cmRCT design has also been approved for the investigation of new cancer interventions. The University of Utrecht is successfully running cmRCTs in colorectal cancer (alongside the Dutch Colorectal Cancer Group), breast cancer and cancers with spinal metastases (PICNIC) (40-46). The Utrecht group have successfully recruited to all three cohorts with 80-90% of those patients approached so far accepting both consent to the cohort and consent to future random selection for new (but un-named) treatments. So far, between October 2013 and July 2016, they have recruited 1,308 participants. In this period, 1308/1486 (88%) patients who were invited for participation in UMBRELLA consented to cohort participation. Of these patients, 1138 (87%) gave broad consent for randomisation to future interventions. Return rate for PROMs at baseline was 80% and varied from 67 to 74% during follow-up [40,47].

Figure 1b: UMBRELLA study of breast cancer cohort showing staged consent (from Young-Afat et al, 2016)

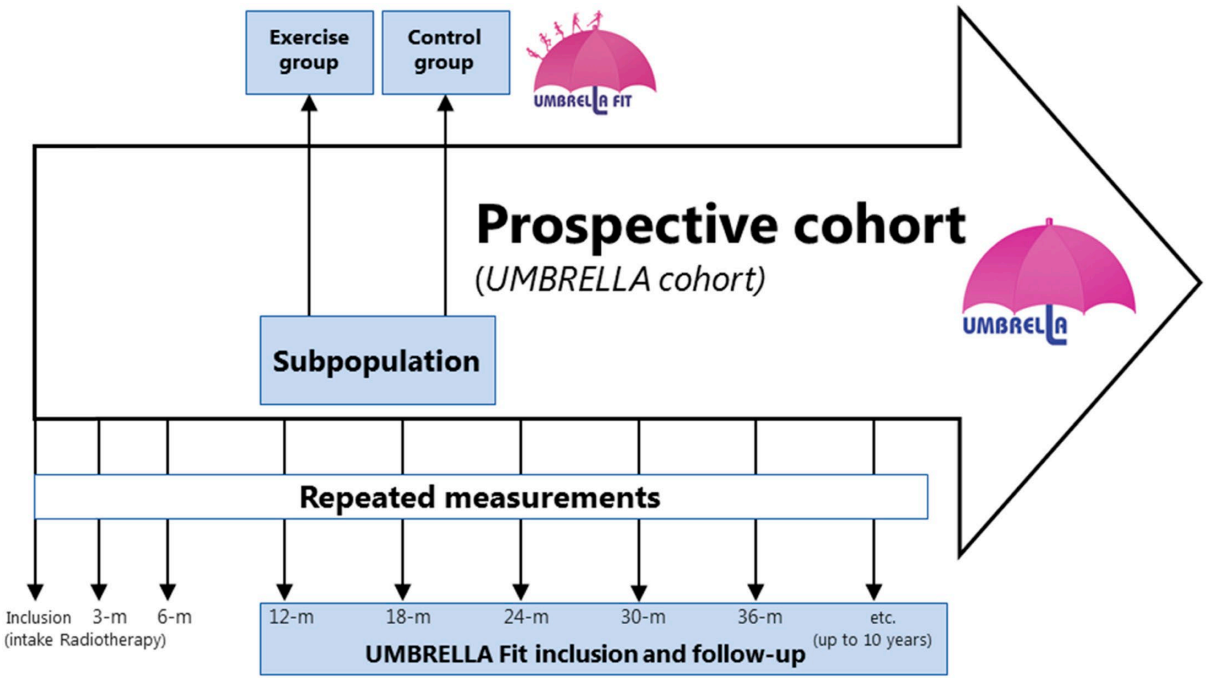
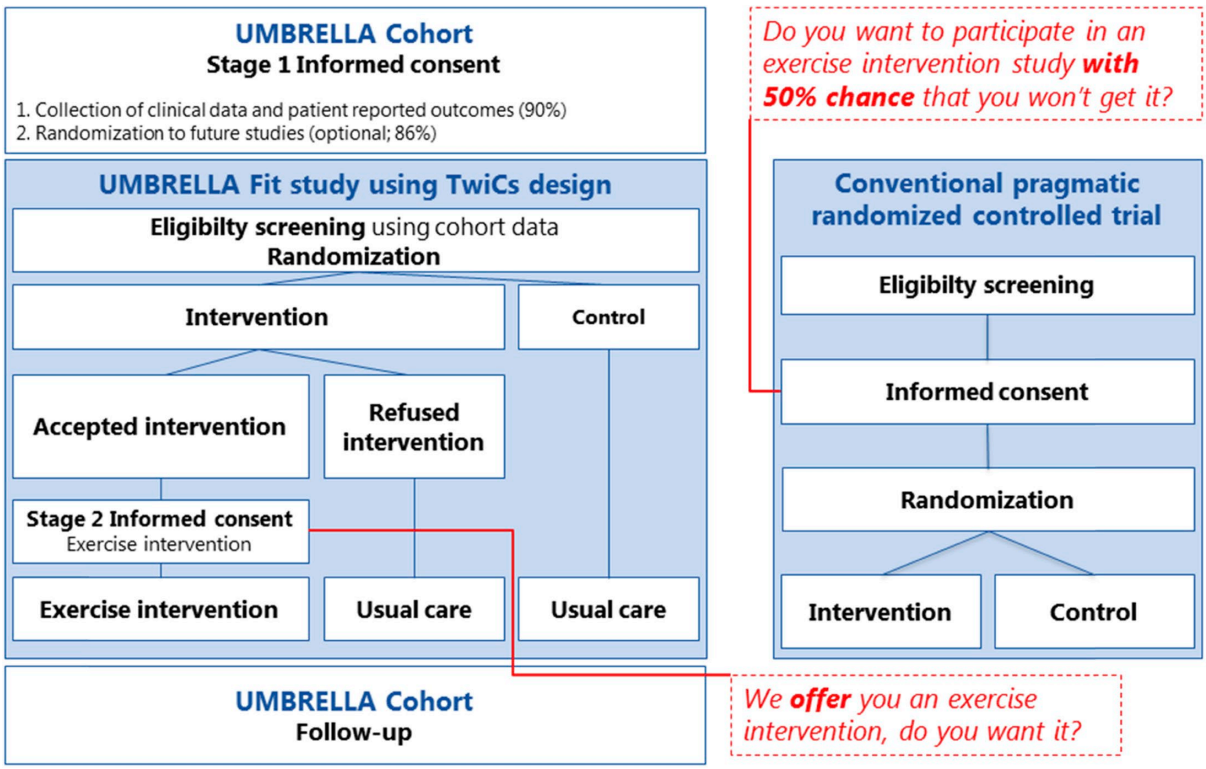


Figure 1b: UMBRELLA study of breast cancer cohort showing staged consent (from Gal et al, 2019)



The cmRCT design and longitudinal framework seems to be successful in conditions where patients affected may transition from different health states over time. The cmRCT design also works well in spaces where Patient Reported Outcome Measures (PROMs), healthcare utilisation and vital status are important outcome measures. Research of patient outcomes in non-metastatic prostate cancer and benign prostate disease is similar to the outcomes of interest in chronic diseases in many respects and as such we believe the cmRCT will lend itself well to the investigation of novel interventions in prostate conditions. If successful, the design could be evaluated in other disease processes in which RCTs are traditionally difficult to deliver to.

Our proposal for a cmRCT approach has several other potential advantages in that it might allow greater access to RCTs than the current trial system since all eligible men have an equal chance of being recruited. It might also avoid disrupting existing service provision as well as being able to run trials in a very efficient and cost-saving manner (48). The cmRCT design that we propose represents a potential paradigm shift in the way we might conduct comparative effectiveness research and will allow us to investigate new interventions using a robust method in difficult-to-recruit disease spaces.

Our proposal seeks to reverse the order in which the question and the framework are realised. Typically, “infrastructure” follows a “question” and the infrastructure is disbanded after the trial. We propose to first establish the infrastructure (cohort) in a defined geographic population with case ascertainment, PROMs for functional and vital status, linkage to local institution records for prostate disease status, linkage to national databases for healthcare utilisation and linkage to death registries. Key questions could in future be addressed by embedding multiple RCTs into this infrastructure such as refining surgical techniques; methods to manage side-effects of different treatments; monitoring strategies after different therapies; surgical methods; and pre-operative targeted molecular therapies.

A Lancet editorial discussed the virtues of trial designs that consider multiple interventions, at the same time showing that trial costs could be halved by doing so (49). So for instance, if we were just to run 3 separate RCTs then each trial would cost an estimated £7.8 million. Our proposed trial design, if successful, would allow additional research questions to be answered at less cost to funders and in a more timely fashion to benefit patients and the NHS. A further attraction of the cmRCT that warrants explicit consideration here is the beneficial consequences on power calculations and rate of recruitment to prospective trials from already having the control group in place. This will allow quicker completion of trial accrual, faster publication of results, increased trial efficiency and reduced trial waste and redundancy. These are important, as there has been a lot of debate recently about the delays that are incurred through trial set-up (50, 51).

Patient and public involvement is at the core of all our research from conception to delivery. The Chief Investigator has presented the issues around this to 40 members of the Mount Vernon Prostate Support Group and with the Maggie’s Cancer Centre Prostate Support Group in Charing Cross Hospital. All the men present stated a reluctance to participate in head-to-head RCTs, but discussions around the novel cmRCT design were positive. A number of men in this focus group commented that the cmRCT would lead to greater patient access to trials and innovative therapies. The results of these deliberations were published (52).

Our group also conducted a consensus meeting of 63 members, facilitated by the Chief Investigator, to consider trial designs for localized prostate cancer. There were five patient representatives alongside triallists and methodologists as well as physicians [10]. The patient and public representatives provided key input into all discussions at whole group level and within break-out sessions. They again stated a reluctance to participate in head-to-head RCTs, whilst accepting the need for robust data to change practice. The group reinforced the need to consider alternative trial designs that might be more acceptable to patients and support recruitment [10]. This proposal has thus originated from patient concerns and has a design largely driven by involved patients and public as well as key trial methodologists and experts in the field.

1.3 TRIAL AIMS

In the pilot phase of PROSPECT we are interested in investigating the a) acceptability and feasibility of establishing the cohort of men, i.e. putting the questions of Point of Consent One to men being referred for investigation of prostate cancer, and b) observing the cohort over the study period and collecting data on the participants pertaining to their disease, their treatment and their health status.

A) Acceptability

AIM 1.1: To determine what proportion of men with a clinical suspicion for prostate cancer will participate in a cmRCT.

OBJECTIVE 1.1a: To evaluate proportion of patients approached who agree to participate in the longitudinal cohort. This will be done by calculating the participation rates from men approached for invitation to PROSPECT.

AIM 1.2: To explore barriers and facilitators to implementation of a cmRCT in order to improve and inform patient and/or physician trial information, study processes, interventions, and recruitment and retention of patients. This will be carried out by qualitative assessments in the following areas.

OBJECTIVE 1.2a: To investigate by interview the patient experiences and perspectives on;

- Trial participation,
- The point at which men are approached by the research team to enter the cohort,
- Barriers and facilitators to consent to participate in the cohort,
- Barriers and facilitators to consent to future random selection to undergo a new healthcare intervention,
- Acceptability of monitoring of health status and the tools used to do this in the cohort.

OBJECTIVE 1.2b: To investigate by interview the experiences and perspectives of healthcare professionals (doctors, nurses and admin staff) on;

- Trial design and information to patients and healthcare professionals,

- Feasibility of future random invitation of participants to interventions,

- Tools used for measuring health status.

B) FEASIBILITY

AIM 2.1: To determine the feasibility of recruitment and logistical implementation of PROSPECT in different data collecting centres based in different institutions. This will be broken down into the following sub-questions;

OBJECTIVE 2.1a: Evaluating how the patients are successfully identified and the option of how inclusion in the trial is presented to them.

OBJECTIVE 2.1b: Evaluate patient questionnaire response rates for pre-treatment quality of life.

OBJECTIVE 2.1c: Evaluate patient questionnaire response rates at pre-determined intervals following on from the point of recruitment into the trial to determine how we might promote optimal patient response rate and improve data collection.

OBJECTIVE 2.1d: To evaluate completeness and fidelity of clinical data on the men who participate in the cohort.

2. OUTCOMES AND ENDPOINTS

2.1. ACCEPTABILITY OUTCOMES

OUTCOME 1.1a. Rate of consent to inclusion to PROSPECT cohort at the original point of contact by the research team. This will be calculated on an ongoing basis and will be reviewed at 6 months and one year from opening and at the end of the study period

OUTCOME 1.1b. To investigate by interview the experiences and perspectives of patients who:

- Consented to inclusion in the cohort study,

- Declined to enter into the cohort,

- Consented to inclusion in the cohort initially but who subsequently requested to leave the cohort,

We will perform structured thematic interviews. Initially, we will aim to interview at least five men who consent to participate in PROSPECT and at least 5 men who decline to participate in PROSPECT. We will also ask to interview any men who initially agree to participate in

PROSPECT who subsequently ask to be withdrawn. We will use purposive sampling to ensure our sample relates to the UK population in terms of wealth / income, ethnicity and age. Men will continue to be approached for interview until the qualitative sample is representative of these factors. Recruitment for qualitative interviews will continue until no further themes emerge.

Interviews will be conducted by the researchers who will follow the Interview Questionnaire Template whilst allowing for some flexibility in the direction and emphasis of the discussion. The templates are formed of a group of pre-determined topics and open questions to explore them. More direct closed questions may be used subsequently with flexibility as above. The interviews will be recorded and transcribed in house before analysis and theme-based extraction of the reasons behind men's decision regarding inclusion in the cohort. Direct quotes may be used in subsequent publications, but these will always be non-identifiable to the individual interviewed. If during the course of the five interviews feedback demonstrates new emerging themes, then consideration will be given to interviewing more men in order to give a broad and fully representative picture of the reasons behind men's decisions. Results from the thematic interrogation of these interviews will be formally fed back to the TMG as well as put into writing for peer-reviewed publication.

OUTCOME 1.1e. The opinions of healthcare professionals who regularly look after men with prostate problems will be sought. We will interview at least 5 doctors and nurses and if necessary up to 10, up to 5 research and management staff. We will conduct interviews at 6 and 12 months from the opening of PROSPECT, as appropriate depending on the first round of responses. We will perform semi-structured interviews that focus on implementation, practicality and efficiency of PROSPECT. There will be a different Interview Questionnaire Template for interviews with healthcare professionals.

2.2. FEASIBILITY OUTCOMES

OUTCOME 2.1a: Evaluation of the number of men approached to enter PROSPECT against the number of men referred to the participating centres for investigation of prostate cancer.

OUTCOME 2.1b: We will conduct a review of the pathway by which we approach men to invite them to the cohort. Part of this will be included in the qualitative interviews with men and healthcare professionals. Particular points of interest will be the timing of consent process, the trial personnel who gain consent, and the number of men who give consent who are subsequently not diagnosed with prostate cancer.

OUTCOME 2.1c: Participants will be given a standard Quality of Life Questionnaire (EQ5D-5L) at the point at which they consent to inclusion into PROSPECT. We will calculate the completeness of this data at 6 and 12 months after opening and on an ongoing basis as long as the study is open.

NB - Once the primary outcome measures are reached (approx. 80 patients), the follow up period will be reduced to 3 months.

OUTCOME 2.1d: All participants will be asked to complete questionnaires on disease specific quality of life at the following points;

- Recruitment to cohort.
- 0-6, 6, 12, 18, 24 months from recruitment to cohort
- Yearly questionnaires thereafter during inclusion in the cohort if trial remains open (i.e., post pilot phase).

NB - Once the primary outcome measures are reached (approx. 80 patients), the follow up period will be reduced to 3 months.

We will use three self-reporting quality of life validated questionnaires. The responses from the questionnaires will be of value as they will provide an informative vignette of the experience of men after the diagnosis of prostate cancer and we can compare these against the experience of men who are investigated for but not diagnosed with prostate cancer. In terms of evaluating the feasibility of the cmRCT design, PROSPECT will calculate the rates of response from participants with these questionnaires. Questionnaire response rates will also inform our understanding of the acceptability of the cmRCT design study to patients.

OUTCOME 2.1e: Feasibility of collecting data from the participating centres evidenced by the completeness of data for cohort participants including;

i. *Subject Data*: age, co-morbidities, ECOG/WHO Performance Status, ethnic risk, family risk

ii. *Disease Characteristics*: PSA, MRI (volume, score), biopsy findings (cancer or not, grade if cancer, length of maximum cancer, other pathology), TNM stage if cancer

iii. *Treatment Data*: modality, follow-up, adjuvant and salvage treatments, mortality

We will conduct this analysis at one year after opening the PROSPECT and yearly thereafter in order to monitor any trends in improving or faltering data accrual on participants, as long as the study is open.

3. STUDY DESIGN

3.1 Design

The key features of a cmRCT are;

1. Explicitly consented recruitment of a large cohort of patients with the condition of interest.
2. Regular measurement of relevant outcome measures for the whole cohort prospectively in the long-term.

3. Facility to re-approach cohort participants, who are randomly selected from eligible patients within the cohort, inviting them to undergo intervention of interest to researchers with eligible patients not randomly selected entering the control standard care group (see study flowchart 3.3 / 3.4).

4. "Patient-centred" informed consent. The consent process aims to replicate that used in the routine health care setting. Once the patient has been randomly selected for a randomised novel intervention from the eligible patients within the cohort, the second consent process should include detailed and specific information pertaining to the particular intervention or change in management they are being invited to undergo for comparison. Such information will be written and advised using patient representatives and undergo review following submission to REC.

5. Comparison of the outcomes in the randomly selected patients with the outcomes in eligible patients not randomly selected.

6. Capacity for multiple randomised controlled trials over time within the cohort simultaneously.

This structure can be seen in the cmRCT flow diagrams (Section 3.3, 3.4).

3.2 CONSENT

For men who are participating in the cmRCT there are two points of consent:

3.2.1 POINT OF CONSENT ONE

At Point of Consent One men who are referred for investigation of prostate cancer will be asked two questions. The first question relates to whether they are willing to join the cohort and have data collected directly from them over time on a regular basis. This data will include health-related quality-of-life data (at recruitment, 0-6, 6, 12, 18 & 24 months post recruitment), linkage to their medical records so that researchers can know what happens to them over time, and access to other data about them held on national health registry databases. Also, at point of consent one, prospective participants will be asked (second question) whether they agree to being randomly selected in the future to interventions or changes in management in order to compare to standard care. We will explain that this second invitation will be on a random basis. In other words, everyone eligible within the cohort will have the same chance of being randomly selected. The patient would still have the option of saying 'no' after the random selection when they are approached.

3.2.2 POINT OF CONSENT TWO

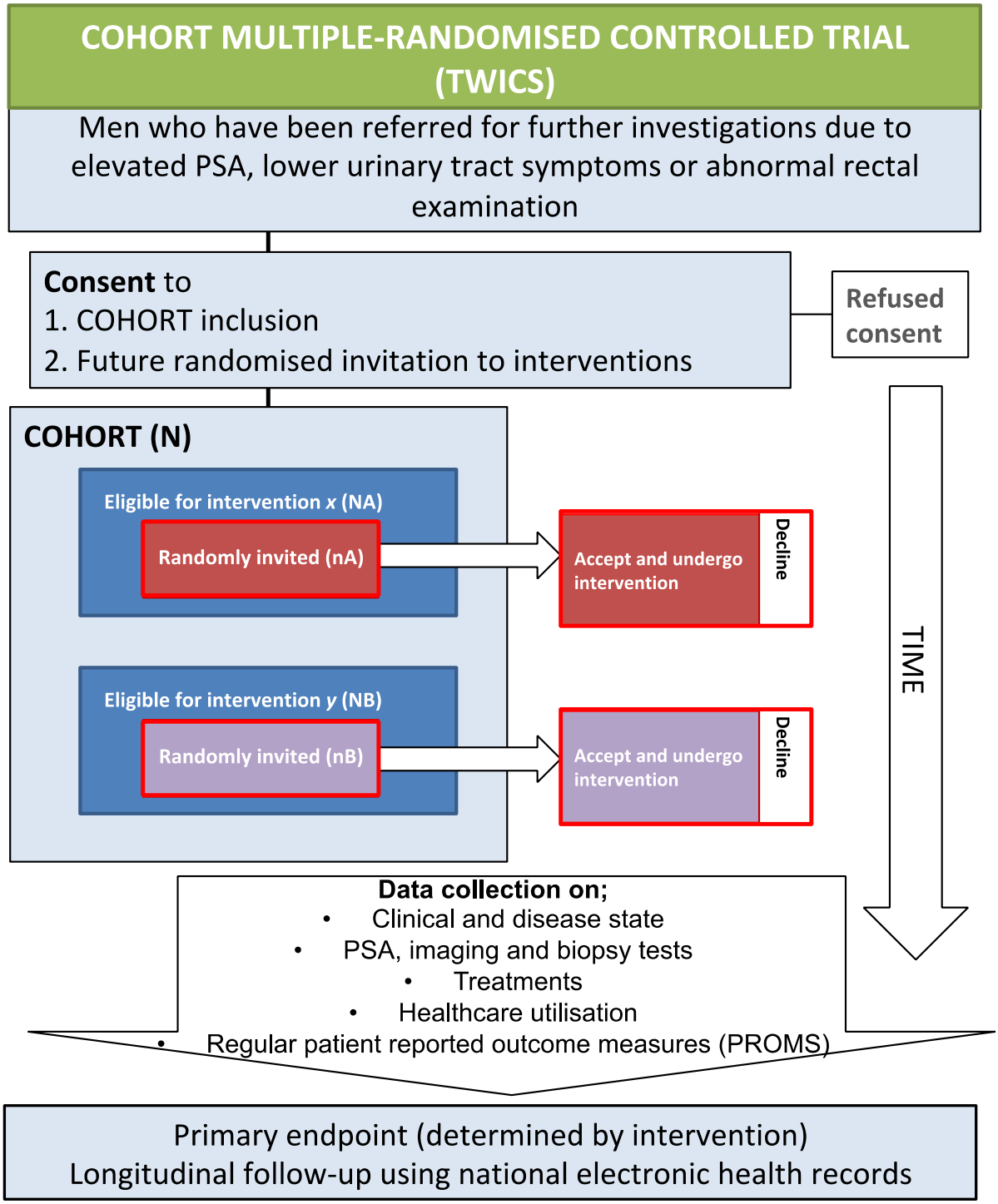
The second point of consent is the invitation to undergo an intervention or change in management that the research team wishes to compare to standard care. Participants will

have already agreed to the possibility of being invited to undergo intervention at Point of Consent One (i.e. enrolment into the cmRCT). The participant will have been randomly selected from amongst all the eligible men for the given intervention from within the large cmRCT cohort prior to being approached by the trial team. Then, the trial team will approach the participant and invite him to undergo the intervention. This will entail a comprehensive consent process that pertains directly to the intervention being proposed in a patient-centred manner. The participant can agree or refuse to undergo the intervention. If he does not wish to undergo the treatment he will continue under follow-up in PROSPECT.

Participants undergoing intervention will continue to have follow-up in the same manner as men who have not been randomised from within the cohort and thus provide outcome data to form the control arm. Comparison of the outcomes of those men who underwent trial intervention against those who did not will allow us to analyse the effectiveness of the intervention in as robust a manner as possible given that the key feature of randomisation when creating the control vs. the intervention arms has been preserved. As such, the control arm of the cmRCT will be similar to the intervention arm in all features, known and unknown, except the intervention of interest. This will allow us to maintain the epistemological superiority of the data we produce for evaluating new tests or treatments whilst getting to this point in a way that might be more acceptable to patients and therefore more likely to be successful and efficient for researchers.

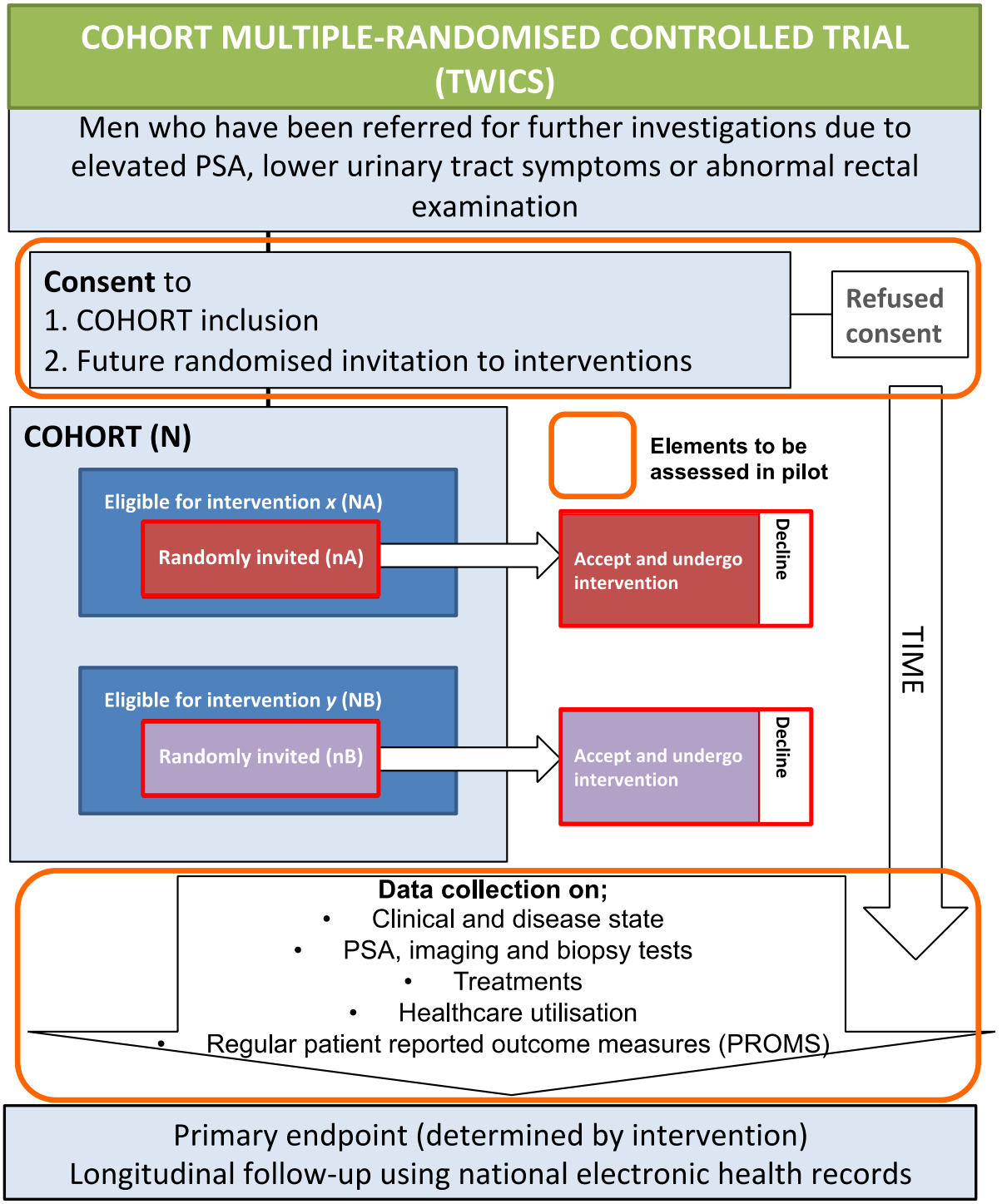
The second stage of PROSPECT will be to investigate and evaluate in a similarly careful manner the feasibility and acceptability of randomising men from our cohort of eligible men to interventions or changes in management that require evaluation, following submission to REC. As part of the cmRCT design, these men randomly selected are re-approached and invited to consider undergoing the intervention of interest. Patients who are randomly allocated to the control arm will also receive standard of care, and are not informed about their participation in the control arm. This additional consent will be obtained at the time of consent for the cohort study.

3.3. PROSPECT cmRCT OVERALL FLOWCHART



Primary analysis: unmodified intention-to-treat approach.
Group 'nA' and 'nB' (intervention) will be compared to Group 'NA-nA' and NB-nB'(control) respectively.

3.4. AREAS TO BE INVESTIGATED BY PROSPECT



Primary analysis: unmodified intention-to-treat approach.
Group 'nA' and 'nB' (intervention) will be compared to Group 'NA-nA' and NB-nB'(control) respectively.

4. PARTICIPANT ENTRY

4.1 STUDY SETTING AND POPULATION

We wish to include all men referred for investigation of prostate cancer. The inclusion criteria for our cohort are deliberately broad.

4.2 INCLUSION CRITERIA

1. Men aged 18 years old and over who are referred for investigations for urinary symptoms or elevated serum prostate specific antigen (PSA) levels or other risk factors for possible prostate malignancy OR Men aged 18 years or older with a diagnosis of prostate cancer on active surveillance or referred from another centre for consideration of surgery, radiotherapy or ablative therapy to the prostate
2. An understanding of the English language sufficient to understand written and verbal information about the trial and consent process.
3. Estimated life expectancy of 5 years or more.
4. Signed informed consent.

4.3 EXCLUSION CRITERIA

1. Men who are unable to give informed consent.

5. PROCEDURES AND MEASUREMENTS

5.1 IDENTIFICATION AND RECRUITMENT OF PATIENTS

No participant will be paid to participate in the study. All men who meet the eligibility criteria for inclusion in the cohort will be contacted by the dedicated Research Team Recruitment Officer (e.g., Research Nurse / Clinical Trial Practitioner, Research/Clinical Fellow) in each participating centre.

Potential participants will be men who are referred to the respective centre for investigation of their prostate for possible malignancy as part of the NHS suspected cancer referral system. The NHS clinical team will make contact with each man as normal, to organise their first appointment and inform them that the study recruitment may approach them to discuss the trial.

The dedicated Research Team Recruitment Officer will contact the eligible men remotely before the patient is seen in clinic. The patient will be asked for permission to send him the literature pertaining to the PROSPECT study including REC approved PIS, ICF and contact information for the research team along with the patient invitation letter. All men will have the opportunity to discuss all aspects of the study with their GP, family members, and their Recruitment Officer prior to the clinic appointment at their participating centre.

On the day of appointment at the participating centre patients will be seen by a member of the research team (Clinical Research Fellow, Clinical Research Nurse, Clinical Trial Practitioner) either in person or remotely, where they meet the clinical team who will lead the usual care investigation for their prostate. At this point, the PROSPECT study will be

described to them again and the patient will be asked whether they would like to participate. If they agree to participating, they will be given the option to consent to the study remotely using e-consent or through the more traditional paper-based approach.

The patient will be asked to sign the REC approved ICF. The fully signed original copy will be kept in the Investigator's Site File, a copy will be provided to the patient and a further copy will be placed in the patients' medical notes and the consent process documented. Consent will be obtained by one of the research team who has been trained to GCP standards and delegated to this task. The patient will also be given the quality of life questionnaires to complete. This can be in one of three ways. First, via a link to the questionnaire via the participant's email address that input directly into the eCRF. Second, the questionnaire is filled out on a university tablet device which inputs directly into the eCRF. Third, on paper if neither of the first options is possible. Paper questionnaires can either be completed in clinic and given straight to the research team or taken home and returned by post.

5.2 SCREENING EVALUATIONS

Potential participants will be men who are referred to the respective centre for investigation of their prostate for possible malignancy. The dedicated Recruitment Officer will contact the eligible men remotely before the patient is seen in clinic. The patient will be asked for permission to send him the literature pertaining to the PROSPECT study including REC approved PIS, ICF and contact information for the research team. All men will have the opportunity to discuss all aspects of the study with their GP, family members, and their Recruitment Officer prior to the clinic appointment at their participating centre.

5.3 BLINDING & OTHER MEASURES TAKEN TO AVOID BIAS

5.3.1 BLINDING

In the pilot stage of PROSPECT no interventions are being tested. Nonetheless, there are a number of measures that will minimise the interference of bias in the collection of our data. The following are features that are inherent in the structure of a cmRCT and will also be evident in PROSPECT.

- PROSPECT participants are included prior to receipt of treatment, whether this is usual standard of care or intervention. This has two beneficial corollaries for the quality of patient data we receive. Initial questionnaires and quality of life data will represent a baseline, and this can also be compared to participants who have no prostate cancer moving forward. Furthermore, baseline data will be collected about PROSPECT participants and their prostate disease before investigators know whether they will be randomised to intervention or whether they remain in the standard of care control. This is in effect a form of blinding as in other trial formats, the randomisation status of the patient may already be known to researchers as this important pre-intervention disease and subject data is being collected.

- The inclusion criteria for our cohort are deliberately very broad. We will include all patients referred for investigation of prostate cancer. The decision to invite a patient to the cohort will not rest with the clinicians who treat the men with disease. Consequently, PROSPECT allows for highly equitable access to inclusion in clinical trials. This will also maximise the external validity of the PROSPECT cohort thereby minimising subject sampling bias. Our patient group feedback was particularly positive about this aspect.

5.3.2 OTHER MEASURES TO AVOID BIAS

The following methodological techniques, which are not unique to the cmRCT study design, will also be employed to ensure minimisation of bias in PROSPECT.

- Standardisation of patient quality of life assessment using validated questionnaires at pre-determined timepoints, from recruitment to the cohort/point of referral and eventually post-treatment or longitudinal surveillance. Use of participant self-completed questionnaires will avoid interviewer bias in the follow-up assessment.

- Collation of patient quality of life questionnaires will be performed by researchers who are blinded to the intervention the man has undergone as all participants will be assigned a confidential personal number that does not reveal whether the participant has been randomly selected to undergo intervention or control.

- All staff involved in the collection of objective outcomes and/or other data on the men included in the cohort will receive training to ensure the standardisation and consistency of the measurement and collation of patient data.

5.3.3 CODEBREAKING / UNBLINDING

Not applicable.

5.4 INTEGRATED QUALITATIVE OUTCOME MEASURES

5.4.1 TRIAL PARTICIPANTS

The integrated qualitative component of the PROSPECT trial will explore patients who;

- Consented to inclusion in the cohort study,

- Declined to enter into the cohort,

- Consented to inclusion in the cohort initially but who subsequently requested to leave the cohort,

We will perform structured thematic interviews. Initially, we will aim to interview at least five men who consent to participate in PROSPECT and at least 5 men who decline to participate in PROSPECT. We will also ask to interview any men who initially agree to participate in

PROSPECT who subsequently ask to be withdrawn. Recruitment for qualitative interviews will continue until no further themes emerge.

Interviews will be conducted by the researchers who will follow the Interview Questionnaire Template whilst allowing for some flexibility in the direction and emphasis of the discussion. The interviews will be recorded and transcribed in house before analysis and theme-based extraction of the reasons behind men's decision regarding inclusion in the cohort. Direct quotes may be used in subsequent publications, but these will always be non-identifiable to the individual interviewed. If during the course of the five interviews feedback demonstrates new emerging themes, then consideration will be given to interviewing more men in order to give a broad and fully representative picture of the reasons behind men's decisions. Results from the thematic interrogation of these interviews will be formally fed back to the TMG as well as put into writing for peer-reviewed publication.

5.4.2 HEALTHCARE PROFESSIONALS

The opinions of healthcare professionals who regularly look after men with prostate cancer will be sought. We will interview at least 5 doctors and nurses and up to 10 if necessary and up to 5 research and managerial staff. We will conduct interviews at 6 and 12 months from the opening of PROSPECT. We will perform semi-structured interviews that focus on ethics, implementation, practicality and efficiency of PROSPECT. There will be a different Interview Questionnaire Template for interviews with healthcare professionals.

5.5 STUDY DURATION

The currently funded study allows for 10 months of recruitment to PROSPECT. We estimate that each participating centre receives 15-20 new referrals for assessment of possible prostate cancer each month. Therefore, we estimate that 180-250 men will be approached to consider entering PROSPECT a year. If the pilot phase of the study is successful and further funding is awarded to extend PROSPECT, then we will submit a substantial amendment for a 6 month transition phase, to extend the recruitment and follow-up of the study to 10 years longitudinal follow-up.

5.6 ANALYSIS AND STATISTICAL CONSIDERATIONS

We wish to assess the acceptability and feasibility of this trial design in men undergoing evaluating and subsequently potentially being treated for prostate cancer and other benign disease of the prostate. We will be testing the acceptability of the trial format to patients as well as the levels of data return and the quality of data return. As such, for these endpoints we have no formal power calculations for the qualitative aspects. As part of the feasibility objectives for this pilot phase, we will measure the numbers of men approached and numbers saying yes to point of consent one. Analysis of the consent and participation rates will be

around a precision estimate of 30% acceptance to initial consent to the cohort and future randomised interventions or change in management.

Acceptability of initial consent sample size

75 patients are needed to show that 30% of the eligible patients will accept initial consent with a 95% CI of ±10%. If we consider a loss to follow up of 5%, then 80 patients will be approached. In the less optimistic rate of 10 eligible patients per month, it would take about 8 months to prove acceptability.

The actual cohort sample will not be restricted as the overall number needed will be dependent on future randomised interventions and therefore there is no maximum number. if the feasibility number is met then we will continue recruitment for the entire recruitment period with no upper limit on numbers and continue beyond existing recruitment period if further funding allows and pending formal application and approval by REC.

Qualitative Sub Study

An inductive, thematic content analysis will be used. Common themes will be identified on a constant basis, organically throughout the whole data set. This analysis is highly dependent on the quality of transcription. Thus, all interviews will be recorded and transcribed in the manner set out in section 12.5/6

5.7 CONFIDENTIALITY AND DATA STORAGE

Information regarding study participants will be kept confidential and managed in accordance with the GDPR, NHS Caldecott Guardian, the UK policy framework for Health and Social Care, and Research Ethics Approval.

Responsibility for data collection will be taken by a nominated individual at each centre, likely to be the Clinical Nurse Specialist/Recruitment Officer.

Individual patient data from the original visit at the point of recruitment will be collected. Data will be collected on electronic Case Record Forms (eCRFs), including baseline, follow-up and safety data. Each participant will be given a unique subject number and subject identifier which will be used on all of their study records i.e., pseudonymised. The eCRFs will be held on Imperial College London's secure RedCap server.

This data will be sent to Imperial College London via one of two routes: (1) a secure online database portal (RedCap), (2) on paper through the post in the exceptional case of PROMs questionnaires. Once the questionnaires are uploaded to the site's NHS patient administration service data base, AND subject to monitoring these paper documents will be destroyed. Note that the PROSPECT study group can only accept responsibility for the data after it has arrived in their custody.

Structured interviews are to be conducted as part of the qualitative sub study. These will either be conducted remotely or in the field i.e. at a site. In the case of the former, the interview will be recorded on a University dictaphone and stored in secure University cabinets. In the case of the latter the interview will be recorded on a University laptop with encrypted hard drive. The recordings will be deleted as soon as it is transcribed in-house and checked for accuracy. The transcription is held in secure University Cabinet until 10 years after close of study.

Imperial College London and each participating site (NHS Trust) recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at ICTU-Surgery for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents for 10 years and in line with all relevant legal and statutory requirements.

The data will be retained by Imperial College London until 10 years after the final publication from the trial according to Imperial College London guidelines. Specific details regarding data storage and destruction are covered in a separate document available from ICTU on request.

5.8 PARTICIPANT IDENTIFIABLE INFORMATION

Only authorised individuals will have access to person identifiable data. The Trial Management Group makes a commitment to maintaining the confidentiality, safety, security and integrity of all confidential and sensitive data, which is held under its guardianship. Staff in pilot study are obliged to fully comply with The Data Protection Act 2018, together with all relevant rules of the sponsor organisation (Imperial College, London).

All electronic personal identifiable data will be kept separate from pseudonymised data. The study database is held on a dedicated Imperial College London database server. Access to server and the network is password & access right controlled. Access to identifiable data is controlled by staff roles and passwords. Patient data will be allowed linkage to national registries.

5.9 MATERIAL / SAMPLE STORAGE

Prostate biopsies taken will be stored by local site (NHS Trust) pathology departments. Blood and urine will be analysed / stored and disposed of as for all other clinical blood samples at local site (NHS Trust). Only members of the Trust's pathology staff have access to the samples. Patients will be consented to the possibility of stored biopsy samples being used for future research. No blood will be stored longer than standard of care and will not be subject to future use. Any future study involving use of the tissue samples for research would only be carried out with Research Ethical Approval by an Ethics Committee

5.10 SAFETY REPORTING (INTERVIEWS)

It has been deemed unlikely by the study team that participants may be adversely affected by taking part in the interviews. However, it is possible that as a result of taking part in the interviews participants may experience distress regarding their condition and the effect it has on their lives. To ensure the study team become aware of this, participants will be provided with a contact card, which contains the contact details of the qualitative researcher to report any issues arising from taking part in the interview. Any such contact made will be recorded on the adverse event form and reported to the PROSPECT trial management team, relevant R&D department and ethics committee (if deemed appropriate). Participants will also be directed to hospital based and independent support agencies as per local practice.

5.11 PRESENTATION / DISSEMINATION OF RESULTS

Real time data will be used throughout the duration of the study. Final results will be triangulated with other study data towards the end of the study and prepared for submission as part of the end of study report.

5.12 INTEGRATED HEALTH ECONOMIC ANALYSES

The aim of the economic analysis nested alongside the main trial uses the NHS perspective to determine the cost per QALYs (CUA), cost per PFS/FFS (CEA) and cost and consequences (CCA) to inform the decision regarding which interventions are most health-economically beneficial. Data on resource-use, FFS and quality-of-life (as measured by EQ-5D-5L) collected alongside the trial are used for the analysis. CRFs validated in the pilot study will be used to collect patient NHS resource usage. Alongside CUA and CEA we also propose the use of cost and consequences analysis to account for any important aspect of care that might emerge from the qualitative analysis and not captured via EQ-5D-5L or PFS/FFS (e.g. burden of treatment routine). A series of one-way, multi-way and probabilistic sensitivity analyses will be carried out to test the robustness of results.

Alongside CUA and CEA we also propose the use of cost and consequences analysis to account for any important aspect of care that might emerge from the qualitative analysis and not captured via EQ-5D-5L or PFS/FFS (e.g. burden of treatment routine). A series of one-way, multi-way and probabilistic sensitivity analyses will be carried out to test the robustness of results.

5.14 VISIT SCHEDULE

5.14.1.PATIENTS (Main Study)

The design and number of visits mirror the standard of care pathway for patients undergoing either focal therapy or radical therapy, so that additional patient burden is minimal.

Following enrolment, all patients will undergo a standard follow-up regimen in the cohort. If they undergo an MRI and biopsy, these usually occur within 6 months of enrolment under standard care. The results of these tests will be collated directly from patient records. If the patient has a cancer diagnosis then the biopsy laterality, Gleason grade and clinical and radiological stage details will be collated in the CRFs. Follow-up information (PSA blood tests, treatments given) will be collated from each follow-up visit directly from the patient records into CRFs. Specific treatment types (active surveillance, surgery, radiotherapy, minimally invasive therapies) or further diagnostic tests (MRI, biopsy) will be recorded into CRFs. Performance status will be collected. Further, patients will be sent out questionnaires asking about any prostate tests or treatments they might have undergone as well as patient reported outcome measures. The table below shows each participant's schedule of activities. Data will be collected via the GP and/or hospital practices if necessary.

NB - Once the primary outcome measures are reached (approx. 80 patients), the follow up period will be reduced to 3 months.

* *Collected if carried out in standard care practice*

	Screening	**Baseline**	**0-6 months**	**6 Month intervals up to 24 months** (+/- 4 weeks)
Informed Consent	✓			
PSA		✓		✓ *
Medical history (from medical records and questionnaires to patients)		✓	✓ MRI, biopsy Grade and stage if cancer	✓ Treatment given if cancer Other diagnostic tests carried out if not
Quality of Life (QoL) Questionnaires sent directly to patients		✓	✓	✓

Time window for each visit will be +/- 4 weeks

By virtue of asking men to join PROSPECT prior to their investigation for prostate cancer we will have the consent of men who go on not to have prostate cancer. We would still like to include these men in our cohort of patients. The non-prostate cancer participants will provide valuable age and comorbidity matched control cohort to participants with prostate cancer. Many of these patients will receive repeat referrals for investigation of prostate cancer again in the future and as such it may be valuable to ask questions of this population in the future. They will receive questionnaires at the same intervals as men with prostate cancer. The inclusion and observation of men without prostate cancer in PROSPECT will also be valuable because it will afford us the opportunity to implement methods for the arrangement and follow-up of large numbers of patients. For instance, fluidic or imaging biomarkers as alternative follow-up strategies for these men who might still harbour or develop cancer in

future. These would be tested as randomised interventions in PROSPECT in the normal manner.

An overall CONSORT flowchart for the PROSPECT cmRCT model and a flowchart demonstrating the potential for further embedded RCTs can be found in Appendix A

5.14.2 PATIENTS (Qualitative Sub study)

Face-to-face or remote semi-structured interviews will be performed in at least five men who agree to, and five who do not agree to a randomised intervention. As these are therefore dependent on the timing of that intervention, it could occur at any point in the trial. Whilst the aim is to interview five of each interview type, that is the minimum. We will continue to invite participants to interview until no further qualitative themes emerge from the interviews. We will use purposive sampling to ensure our sample relates to the UK population in terms of wealth / income, ethnicity and age. Men will continue to be approached for interview until the qualitative sample is representative of these factors. How the interviews are performed is outlined in section 6.8.

	Screening	**At randomisation**
Informed Consent	✓	
Semi-structured interview (Entry)		✓
Semi-structured interview (Exit)		✓

5.14.3 HEALTHCARE PROFESSIONALS

Healthcare professionals i.e. doctors and nurses, who are involved in prostate cancer care and research will be approached by the clinical trial coordinator by email to take part In PROPSECT by giving an interview as to their thoughts on the study design. Face-to-face or remote semi-structured interviews that focus on ethics, implementation, practicality and efficiency of PROSPECT will be performed of at least 5 but up to 10 doctors and nurses and up to 5 research and managerial staff involved in prostate cancer care and research. We will use purposive sampling to ensure our sample relates to the direct healthcare workforce for urological oncology, in terms of appropriate spread for age and job type. Healthcare professionals will continue to be approached for interview until the qualitative sample is representative of these factors. We will conduct interviews at 6 and 12 months from the opening of PROSPECT. There will be a different Interview Questionnaire Template for interviews with healthcare professionals. We will continue to invite participants to interview until no further qualitative

themes emerge from the interviews. How the interviews are performed is outlined in section 6.8.

	Trial Commencement	6 Months	12 Months
Informed Consent	✓		
Semi-structured interview		✓	✓

6 NON-TREATMENT STUDY INTERVENTIONS

6.1 INFORMED CONSENT PROCEDURE

Informed consent may be taken via the traditional paper-based approach or via electronic methods through the REDCap database for seeking, confirming and documenting informed consent.

It is the responsibility of the Investigator, who may be a medical or nursing professional, or a clinical research practitioner, but who must be GCP certified to obtain written or electronic informed consent from each patient prior to participation in the study. This follows adequate explanation of the aims, methods, anticipated benefits and possible risks of the study. A minimum of 24 hours must be given for consideration by the patients before taking part. The researcher must record when the PIS has been given to the patient. It must be explained to the patient that they are in no manner obligated to take part in the study and further, that they may withdraw at any time during the study and are not required to give a reason for doing so. No clinical study procedures may be performed prior to obtaining written or electronic informed consent from the participant. Consent is not a denotation of enrolment into the study. A copy of the signed ICF must be given to the patient for their records. If paper-based consent has been taken, the original form with the wet signature will be retained at the study site. If consent has been taken remotely, a printed copy of the completed document must be retained at site. A copy of the completed informed consent must also be placed in the patients' medical notes. If at any time during the study new safety information results in significant changes in the risk/benefit assessment, the consent form is to be reviewed and updated as necessary and if appropriate, patient will be consented again. Patients will be consented to provide their full contact details including name, address and email address where appropriate to the trial team based at Imperial so that the trials team can send out PROMS and questionnaires on health status.

6.2 DOCUMENTATION OF SCREEN FAILURES

A screening log will include information on all patients who have voluntarily given informed consent to participate in the study and whether or not the patient was then enrolled. The screening log will include the patient initials, date of birth, the date of signing the ICF, and, if failed screening, the reasons why.

6.3 DEMOGRAPHICS, MEDICAL AND UROLOGICAL HISTORY

A complete medical and urological history will be obtained at the Screening visit. Demographic information will include date of birth and ethnicity. All patients in this study are men. Medical history will include, and significant prior and concurrent conditions, diseases and procedures not related to urology. Urological history will include all conditions and procedures related to urology. The World Health Organisation performance status will also be documented.

6.4 LABORATORY TESTS

Biologic assessment will include blood tests, as drawn by venipuncture, including:

- Prostate specific antigen (PSA), a test often used to screen for prostate cancer but used here as a surrogate objective marker of tumour load.

6.5 MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING (mpMRI)

MpMRI will be performed with either 1.5 or 3.0 Tesla scanners with a pelvic phased array coil. The patient will be supine and contrast administered by use of a power injector. As per consensus guidelines setting out minimum requirements, T2-weighted, diffusion-weighted (DWI), +/- dynamic contrast enhanced (DCE) sequences (Intravenous Gadolinium) will acquired. The images will be reported by a dedicated specialist uro-radiologist.

6.6 PROSTATE BIOPSY

In participants in which a lesion scoring 3-5 is identified a transperineal or transrectal targeted biopsy with concomitant systematic biopsies will be performed and performed by operators experienced in each approach.

6.7 VALIDATED PATIENT QUESTIONNAIRES

International Prostatic Symptoms Score (IPSS) a validated questionnaire made up of seven questions to ascertain the severity of lower urinary tract symptoms. [54]

EPIC bowel and bladder questionnaire (EPIC-26), a validated questionnaire used to measure urinary incontinence, urinary irritation, bowel, sexual and hormonal health related quality of life. [55]

IIEF-5, a validated, multi-dimensional, self-administered investigation that has been found useful in the clinical assessment of erectile dysfunction and clinical trials [56]

The EuroQol (EQ-5D-5L) will be used in the study as a generic measure of health-related quality-of-life which can be linked to public preferences. [57]

7 FOLLOW-UP

7.1 SCHEDULE OUTLINE

Follow-up will not be dictated by the study within the cohort. It will be standard of care for that patient. This will differ, as some will have no cancer, some have cancer treated whilst others will have surveillance for low risk cancer. Clinical outcomes such as presence or absence of cancer on biopsy, TNM stage, risk, grade and type of treatment with any future failure and adjuvant/salvage treatment will be recorded. Those not having a cancer diagnosis will have future tests and outcomes and future prostate cancer diagnosis recorded if appropriate. Health status and PROMs will be collected at regular intervals during study duration.

7.2 PATIENT RELATED OUTCOME MEASURES (PROMS)

The PROMS as described in 6.7 will be used. Questionnaires should be self-administered, although it is recommended that a key person (e.g. research nurse) at each centre be responsible for the data collection to optimise compliance and completeness of the data.

The patients should complete the quality of life and the resource use data questionnaires independently without discussion with friends or relatives and all questions should be answered. The member of the study team should check each questionnaire and query any missing or incorrect data with the patient. Checks should also take place for date and identifiers. Patients should be approached at appropriate visits to complete the questionnaires.

7.3 FOLLOW-UP CONSULTATIONS

Collection of data at each time point will be permissible via postal, electronic, remote or face-to-face communication. Unless the patient requests face-to-face visits they will only require attendance for hospitals visits that are defined by the local hospitals follow-up protocol within standard care. In certain circumstances it may be appropriate to replace hospital visits with telephone, remote or email consultations providing that it is still possible to collect all the necessary follow-up information. In order to maintain confidentiality during email consultations these episodes will be conducted via the local site practitioner's protected NHS email account. Such remote consultations are undertaken frequently in routine clinical care and in these instances, it is acceptable to perform appointments with telephone, remote or email consultations providing the required blood results, such as PSA tests are available to the research team (can be performed at local hospital or GP practice as per patients request and the GP's discretion). In any instance the hospital will carry out these tests if the GP was

to refuse. All necessary information required to complete the follow-up case report form (CRF) is still required. All details on the telehealth consultations must be recorded in the patients' notes.

7.4 STUDY VISITS – SPECIFIC TESTS

7.4.1 PROSTATE SPECIFIC ANTIGEN (PSA)

Blood sample for PSA can be collected during a scheduled hospital visit or at a hospital local to the patient or at a community/primary care facility, whichever is more convenient for the patient provided the result is available to the research team.

7.4.2 PATIENT RELATED OUTCOME MEASURES (PROMS)

PROMS questionnaires can be completed or returned during a scheduled hospital visit or via post/electronic communication.

7.4.3 FURTHER FOLLOW-UP IMAGING

Follow-up imaging will not be protocol led, with appropriate imaging chosen as per the local hospital resources and policies (may include any of prostate MRI, nuclear medicine bone scan, PET-CT/MRI, Whole body MRI or CT chest/abdomen/pelvis).

7.4.4 FURTHER FOLLOW-UP BIOPSIES

Some patients will undergo further biopsies due to ongoing suspicion of cancer or following treatment as part of their standard care.

7.4.5 FURTHER NON-TRIAL INTERVENTIONS

Some patients will also undergo secondary non-cancer related procedures to manage adverse events from the therapy such as, but not limited to, transurethral resection of prostate, bladder neck incision, urethral dilatation, optical urethrotomy, male-sling or other continence procedures as well as penile implant surgery for impotence. Endoscopic tests or interventions of the lower bowel may also be required. These rates of interventions will be collected.

7.4.6 FUTURE FOLLOW-UP

Patients will be consented for their names to be linked to national registries for survival information such as NHS Information Centre/Office of National Statistics (ONS) in England/Wales and General Register Office in Scotland, Hospital Episode Statistics (HES).

7.5 LABORATORY EVALUATIONS

7.5.1 BLOOD TESTS:

PSA will be measured as per standard care and using local laboratory processes and assays. Centralised measure of PSA will not be used. No additional haematology or biochemistry tests will be mandated by the trial. It is envisaged that standard of care haematological and biochemical tests will be ordered by the treating clinician to monitor for pre-assessment requirements for anaesthetic fitness or for assessing treatment related toxicity.

7.5.2 URINALYSIS:

No additional urinalysis test will be mandated by the trial.

7.6. SAMPLE STORAGE AND ANALYSIS

7.6.1 STANDARD OF CARE SAMPLES

The standard care urine samples taken as part of routine clinical care will be stored for 7 days post analysis and then auto disposed in tiger stripe (offensive waste) bag as per the Trust Clinical Waste Management Policy.

Blood for standard care tests in clinical care will be via peripheral venepuncture and placed in a plastic tube containing SST (serum separating tube). This will be processed in a local laboratory. The blood samples will be stored for 4 days post analysis and then auto disposed to bio-bins and incinerated off site according to the Trust Clinical Waste Management Policy.

7.6.3 HEALTH STATUS

At the screening visit, patients will also be asked to give optional consent for identifiable data to be linked with the national databases (ONS and HES database). The identifiable fields (NHS number) required for linkage will be encrypted using a one-way encryption algorithm. We will ask patients if they are happy to give consent for their health status to be followed up over time. This will be done by linking the patient's name and NHS number with records held by the NHS and maintained by the NHS Information Centre and the NHS Central Register, or any applicable NHS information system. This will allow us to track what happens after the study finishes and observe if anyone gets cancer in future and about the type of cancer and the treatment they have had.

We will also ask patients whether or not they give permission to be contacted by a member of the central / local study research team within 10 years of signing their consent form, after the study has ended to assess their willingness to complete a questionnaire about their health status (including details of any other tests and treatment they have had since the study) and quality of life. If the patient decides to take part a member of the study research team may send this request to the patient's home address. This will only occur if the trial progresses to main phase.

As prostate cancer is often a slow-growing disease which may not progress for many years we will also ask patients if they are happy to keep personal data be stored or accessed for an additional 10 years on the NHSCR (National Health Service Care Register). This is an optional part of consent.

8 STUDY COMPLIANCE AND PARTICIPANT WITHDRAWAL

8.1 PARTICIPANT WITHDRAWAL FROM STUDY

Withdrawal from the study refers to discontinuation of study treatment and study procedures and can occur for the following reasons:

- Subject decision
- Loss to follow-up

Withdrawal of patients from the cohort is an important outcome in itself for PROSPECT to evaluate the acceptability of the study structure and design to participants.

Men may decide to opt out of PROSPECT at any time. This is entirely within their right to do so. Such cases will be reported to the Research Team Office so that no further data are entered onto the database, as specified in the patient information leaflet and appropriate Standard Operating procedure. Data captured before consent was withdrawn will be used in the study, but no further data, beyond this date will be collected or used in any analysis. The right to opt out of PROSPECT at any point, without reason and with no effect on the treatment received by the patient will be made clear to men in the PIS.

It is the patient's right to request discontinuation of their participation in the study. If this request is made, it will be respected and will not affect the patient's ability to receive medical care from the investigators now or in the future. This will also be made clear in the Patient Information Sheet and in the Informed Consent Form. It will be very helpful for the investigators to know the reasons men who decide to withdraw from the trial have for their decision. We will ask these patients who request to opt out of the cohort whether they would consent to an interview with one of the researchers to investigate the reasons behind their withdrawal. We will make it clear to patients who withdraw from the study that their medical records will no longer be used for data collection.

8.2 DISCONTINUATION OF PARTICIPANT ATTENDANCE AT INVESTIGATION SITE

Efforts should be made to maintain the study schedule and continue follow-up. If a patient moves out of the geographical area of the cohort the patient will still be able to complete the health and quality of life questionnaires. Important clinical and follow-up details such as biochemistry, treatment modality, mortality can be sought by direct request of the researchers from the patient's treating urology team, GP and by correlation with national registries.

8.3 NON_RESPONDERS TO PATIENT QUESTIONNAIRES AND ATTEMPTS TO OBTAIN UP TO DATE INFORMATION ON PARTICIPANTS

Completeness of data and patient questionnaire response rates is an important outcome in PROSPECT as it informs our analysis of feasibility. Where possible we will prompt men to complete the questionnaires sent to them by telephone reminder or by email which will be coordinated by the Lead Investigator and Recruitment Officer at the respective participating centres. If a patient continues to not return or complete the QoL and symptom questionnaires sent to him, efforts will be made to contact the patient via telephone and by email in order to encourage the patient to respond. The researchers at the participating centres may also co-ordinate with the departmental clinic appointments in order to hand the questionnaires to the patient personally.

In the case of the study moving to its main phase, patients who do not complete the questionnaires for five consecutive years will no longer receive communication from the PROSPECT research team. However, in the absence of a direct request from the participant to be removed from PROSPECT, the research group will continue to collect and store information pertaining to the individual's health and prostate cancer status.

8.4 PROCEDURES FOR PARTICIPANT WITHDRAWAL FROM STUDY

Every effort should be made to follow-up all patients who have been randomised. Patients should, if possible, remain under the care of an oncologist or urologist for the duration of the trial. If care of a patient is returned to the GP, it is the responsibility of the responsible clinician who obtained the patient's consent to participate in the trial to ensure that all relevant data collection forms are completed. Nurse-led follow-up is permitted and should be conducted in line with local practice and procedures.

If the patient moves away from the local area, arrangements should be made for trial follow-up to be undertaken by their new local centre. Details of other participating centres can be obtained from the Study Manager. If the responsible clinician moves, appropriate arrangements should be made to arrange for trial follow-up to continue at the centre.

All efforts should be made to preserve the patient's initial consent for long-term survival information to be flagged through national registries, for example NHS Digital (previously the Health and Social Care Information Centre); Office of National Statistics (ONS) in England/Wales; General Register Office in Scotland; Hospital Episode Statistics (HES) or Public Health England.

In order to do this, we will provide all patients an optional consent to provide identifiable information for us to trace the patient on the National Health Service Care Register (NHSCR) for an additional 10 years.

We will also ask patients whether or not they give permission to be contacted by a member of the study research team within 10 years of signing their consent form, after the study has ended to assess their willingness to complete a questionnaire on their health status and quality of life. This will allow us to track what happens after the study finishes to observe if anyone gets cancer in future and about the type of cancer and the treatment they have had. Results of the optional health status check will also help us to refer to any future upcoming studies. If the study does not continue after the pilot, each patient will be contacted and informed as such when the study ends.

9 PHARMACOVIGILANCE/ ADVERSE EVENT REPORTING

The Common Terminology Criteria for Adverse Events (CTCAEv4.0) will be used to report adverse events. Please refer to for further details: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

9.1 ADVERSE EVENT (AE)

An AE is any untoward medical occurrence in a patient or clinical trial subject undergoing a trial intervention and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial interventions, whether or not considered related to the interventions being evaluated.

9.1.1 ADVERSE EVENT RECORDING

For the purposes of the study, AEs will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is the sooner. All AEs and SAEs will be recorded throughout the study and all SAES should be reported to the sponsor. Any unexpected and related SAES should also be reported to the REC (as per attached RGIT SOP – appendix 3).

9.1.2 SEVERITY OF ADVERSE EVENTS

Mild: Awareness of event but easily tolerated

Moderate: Discomfort enough to cause some interference with usual activity

Severe: Inability to carry out usual activity

9.1.3 CAUSALITY OF ADVERSE EVENTS

- *Unrelated:* No evidence of any causal relationship

- *Unlikely:* There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after trial interventions). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

- *Possible:* There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial interventions). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

- *Probable:* There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- *Definite:* There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

9.1.4 ABNORMAL LABORATORY TEST RESULTS

All clinically important abnormal laboratory test results (apart from PSA) occurring in participants will be recorded as adverse events. The clinically important laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made.

9.2 SERIOUS ADVERSE EVENTS (SAE)

9.2.1 DEFINITION OF SAE

An SAE is defined as any event that:

- Results in death;

- Is life-threatening*;

- Requires hospitalisation or prolongation of existing inpatient hospitalisation**;

- Results in persistent or significant disability or incapacity;

- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).

Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

9.2.2 LIST OF EXPECTED ADVERSE EVENTS:

There are number of expected potential adverse events after interventions that may occur and require hospitalisation but will not require reporting as SAEs but will be collected. These include:

- Urinary retention and any admission required for this
- Urinary tract infection and any admission required for this
- Epididymo-orchitis and any admission required for this
- Dysuria
- Debris in urine and any admission required for this
- Haematuria and any admission required for this
- Erectile dysfunction and any other sexual sequelae side-effects such as dry orgasm, lack of orgasm, poor libido
- Urinary incontinence
- Rectal discomfort, bleeding, diarrhoea
- Recto-urethral fistula and any operations required for this
- Lethargy, tiredness, poor appetite
- Urethral stricture and any operations required for this
- Transurethral resection of prostate and any operations required for this
- Operations required for symptoms of bladder outlet obstruction
- Any expected complication related to post-operative course from radical prostatectomy i.e. lymphocoele, bowel injury, haematoma needing percutaneous drainage
- Expected toxicity from systemic therapy such as neutropenia, neutropenic sepsis, weight gain, decreased libido, breast tenderness, metabolic syndrome, lethargy, fatigue, osteoporosis, nausea and vomiting, diarrhoea, constipation, muscle/joint pains and hair loss.

- Bowel stricture post radiotherapy, and procedures required for this

9.2.3 REPORTING OF SAEs

Rapid reporting of all SAEs i.e. within 24 hours, occurring during the study must be performed as detailed in SAE reporting instructions. If the investigator becomes aware of safety information that appears to be study related, involving a subject who participated in the study, even after an individual subject has completed the study, this should be reported to the Sponsor.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (CRF/electronic case report form [RedCap]).

9.2.4 RELATED SAEs

Related: results from administration of any research procedures

9.2.5 UNEXPECTED SAEs

Unexpected: type of event is not listed in the protocol as an expected occurrence

9.2.6 REPORTING OF SAEs THAT ARE RELATED AND UNEXPECTED

An SAE form should be completed on the Redcap eCRF within 24 hours. However, relapse, death and/or hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the REC where in the opinion of the Chief Investigator, the event was:

• 'Related', i.e. resulted from the administration of any of the research procedures; and

• 'Unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the *NRES SAE form for non-IMP studies*. The Chief Investigator must also notify the Sponsor of all SAEs. Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details of sponsor for reporting SAEs are as follows:

Research Governance and Integrity Team (RGIT):

Imperial College London and Imperial College Healthcare NHS Trust

E-mail: rgit@imperial.ac.uk

Chief Investigator:

Professor Hashim Uddin Ahmed

Imperial College London, Charing Cross Campus

E-mail: hashim.ahmed@imperial.ac.uk or prospect@imperial.ac.uk

Tel: 020 7589 5111 (Mon to Fri 09.00 –17.00)

9.3 ANNUAL PROGRESS REPORTS

Annual Progress Reports will be submitted to the Research Ethics Committee, the Regulatory Authority and the Sponsor in accordance with local requirements. The Annual Progress Reports will detail all SAEs recorded.

9.4 PREGNANCY

Not applicable as the study population is male.

9.5 CHILDREN

Not applicable as the study population is over 18 years of age.

9.6 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken and give written notice to the HRA, the relevant research ethics committee (REC) as well as the sponsors of the measures taken and the circumstances giving rise to those measures. The sponsor in any case should also be informed of urgent safety measures.

10. STATISTICAL ANALYSES

10.1 SAMPLE SIZE AND POWER CONSIDERATIONS

Acceptability to initial consent sample size

We will measure the precision around a conservative 30% anticipated acceptance to participate in the study.

80 patients are needed to show that 30% (95% CI of ±10%) of the eligible patients will accept initial consent with a 95% CI of ±10%, assuming 5% loss to follow up.

10.2 PLANNED RECRUITMENT RATE

We propose to recruit to PROSPECT over 18 months with each man followed for at least 6 months within the current funding envelope. The study may be extended if further funding is awarded and this will require approval by REC. We estimate that each participating centre receives 15-20 new referrals for assessment of possible prostate cancer each month. Therefore, we estimate that 180-250 men will be approached to consider entering PROSPECT a year per centre. The actual cohort sample will not be restricted as the overall number needed will be dependent on future randomised interventions and therefore there is no maximum number. if the feasibility number is met then we will continue recruitment for the entire recruitment period with no upper limit on numbers and continue beyond existing recruitment period if further funding allows and pending formal REC approval.

10.3 STATISTICAL ANALYSIS

As outlined in section 5.7 we wish to assess the acceptability and feasibility of this trial design in men undergoing evaluating and subsequently potentially being treated for prostate cancer and other benign disease of the prostate. We will be testing the acceptability of the trial format to patients as well as the levels of data return and the quality of data return. As such, for these endpoints we have no formal power calculations for the qualitative aspects.

As part of the feasibility objectives, we will measure the numbers of men approached and numbers saying yes to each point of consent. We will measure the precision around our estimate of 30% acceptance to the first point of consent.

All the statistical analyses will be outlined in a Statistical Analysis Plan (SAP) which will be signed by the CI, Senior Statistician and TSC ahead of seeing the data.

11. REGULATORY, ETHICAL AND LEGAL ISSUES

11.1 DECLARATION OF HELSINKI

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

11.2 GOOD CLINICAL PRACTICE

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

11.3 CLINICAL TRIALS AUTHORISATION

Not applicable as cohort study and not CTIMP.

11.4 INDEPENDENT ETHICS COMMITTEE APPROVAL

11.4.1 INITIAL APPROVAL

Prior to the enrolment of subjects, the Research Ethics Committee (REC) and Human Research Authority (HRA) must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Patient Information Sheet and Consent Form, any other written information that will be provided to the subjects, any advertisements that will be used and details of any subject compensation.

11.4.2 APPROVAL OF AMENDMENTS

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval as instructed by the Sponsor. Amendments requiring REC approval may be implemented only after a copy of the REC approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

11.4.3 ANNUAL PROGRESS REPORTS AND END OF TRIAL NOTIFICATION

The REC will be sent annual progress reports in accordance with national requirements and will also be informed about the end of the trial, within the required timelines.

11.5 HRA APPROVAL

Health Research Authority (HRA) approval will be obtained prior to starting the study.

The HRA also needs to be notified of all protocol amendments.

11.6 OTHER REQUIRED APPROVALS

PROSPECT itself requires no additional approvals for the cohort element. Further approvals may be necessary, dependant on interventions offered after point of consent 2. As appropriate, the Chief Investigator will ensure that the procedures are compliant with regulatory bodies.

11.7 NON-COMPLIANCE AND SERIOUS BREACHES

All protocol deviations and protocol violations will be reported via the eCRF and reviewed by the Chief Investigator and reported to the ICTU QA Manager on a monthly basis. Protocol violations will be reported to the Sponsor.

An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the UK trial subjects; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to HRA and REC within 7 days of becoming aware of the serious breach.

11.9 INSURANCE AND INDEMNITY AND SPONSOR

11.9.1 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

11.9.2 SPONSOR

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

11.9.3 FUNDING

Wellcome trust are funding this study.

11.10 TRIAL REGISTRATION

The study will be registered on the trial database ClinicalTrials.gov in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations.

11.11 INFORMED CONSENT

All subjects must sign and personally date the REC approved Informed Consent Form after having received detailed written and verbal information about the reason, nature and possible risks associated with the research study. This will apply for both our initial invitation to participate in the PROSPECT cmRCT, and any subsequent intervention(s) we seek to evaluate by inviting cohort participants to undergo. PROSPECT will be the first time that the cmRCT design has been piloted for the evaluation of interventions in the prostate pathway. Although the trial design is no longer controversial given its increasingly widespread adoption by clinical researchers worldwide in benign and cancer disease spaces as well as complex interventions, the innovative features of the cmRCT design warrants further consideration of its specific ethical matters.

11.11.1 Patient information about future interventions at Point of Consent 1

The Patient Information Sheet and the Consent Form should not need to include details on the proposed interventions to which the patient may be randomly selected in the future. This is what other ethics committee approved studies have done and the reasons are listed below.

- The exact disease status and risk of a disease once diagnosed are not known at the first point of consent for a man.
- It is not possible to provide information on all of the possible interventions that might be evaluated that a man may be invited to participate in because we do not yet know what they all are. Further treatments may become available in the future which we are not currently able to predict and inform the patient about.
- To give prospective participants information about all the possible novel interventions

or changes in management for evaluation as embedded randomised interventions to which they may or may not be randomly selected may represent excessive information for the patient. The idea of 'patient-centred consent' is central to the attribute of the cmRCT. Therefore, we would not like to provide patients who we are seeking to recruit to the cohort an excess of information on all possible future interventions as we do not want to overwhelm them, potentially causing confusion and thereby reducing recruitment rates.

- Point of Consent 1 gains consent only to collect patient information prospectively and the permission to re-contact in the future if they are eligible for an intervention. PROSPECT participants categorically cannot undergo any embedded novel interventions or changes in management strategies for evaluation without being approached again by the researchers at Point of Consent 2. The consent process at Point of Consent 2 will be in a patient-centred manner that will include comprehensive information on the risks and benefits of the intervention in question. So that the procedure is clear to the patient who will undergo the intervention if he agrees to it.

- The principle of consent-for-consent in which patients are asked to consent to a future approach to participate in research (which in itself is subject to further patient information and informed consent) is now being used in a number of disease areas and networks (e.g., DH funded DCRIS; BioResource funded by NIHR).

- The level of information that is given to men in the cohort is not yet defined. As this protocol also seeks to assess the acceptability and feasibility of the cmRCT design we will interview patients and healthcare professionals to determine the level of information that should be given to patients at Point of Consent One as part of our qualitative work. We will change our patient documentation, subject to substantial amendments, if necessary based on this qualitative work.

11.11.2 Participants Consented for possibility of future intervention who are not approached for embedded randomised studies

All PROSPECT participants will have been consented at Point of Consent 1 for the possibility of being selected in the future for an intervention. Many of these men will not be invited to participate in embedded randomised studies.

- Through the consent process and the PIS we will make clear the structure of the PROSPECT cmRCT, such that participants are aware that they may might not be approached for an embedded intervention as they may be ineligible for interventions being trialled, or they may be eligible but not approached due to the randomized process.

- Through the consent process and the PIS we will make clear that the treatments and interventions being trialled are not of proven benefit to patients. This is why we as researchers are seeking information on the embedded interventions. Interventions trialled within the cmRCT format should only be interventions around which there is clinical equipoise. Therefore, it must be clear to patients that the usual care

management and treatment they receive will under no circumstances be sub-optimal or compromised as a result of their participation in PROSPECT within the longitudinal cohort element of the study.

- Through the consent process and the PIS we will make clear that patients who are not selected to embedded randomised interventions in PROSPECT will continue to experience the standard of care management according to their treating doctors and multi-disciplinary medical team.

- Patients in our focus groups emphasised the fact that participation in the cohort was something in of itself that they might derive benefit from. For instance, access to researchers and additional patient reported outcome measures reporting, and that such participation might help others through outcomes measures that might not otherwise be collected and reported.

The right of the patient to refuse to participate in the study without giving reasons must be respected. After the patient has entered the study, the clinician must remain free to manage the patient however s/he feels fit to suit the best interest of the patient, regardless of the protocol.

An Independent Ethics Committee must approve the protocol, the patient information sheet, the content of the informed consent form and any promotional materials used for the recruitment of subjects before the accrual of any patients. If legally required, the protocol and informed consent must be submitted to the country regulatory authorities

Participants should be made aware and agree that their personal information may be scrutinised during monitoring and audit by competent authorities and properly authorised persons. However, the personal information will be treated as strictly confidential and will not be publicly available.

11.12 CONTACT WITH GENERAL PRACTITIONER

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

Every six months, the trial management team or investigator will contact each participant's General practitioner for updates on the participant's medical or procedural history, as well as any changes to the participant's regular medications. Full informed consent from each participant will be required for this.

11.13 PARTICIPANT CONFIDENTIALTY

The investigator must ensure that the subject's confidentiality is maintained. On the CRF or other documents submitted to the Sponsors, subjects will be identified by a subject ID

number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to subjects' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS and regulatory authorities.

For trial follow-up purposes, the trial management team are required to contact each participant every six months. To allow for this, the team will require the names, addresses - and email address where applicable – of each participant. These details, i.e., the names address and email address will be housed separately to the electronic CRF and pseudonymised, i.e., linked by the participant's unique trial identifier and will be stored, securely walled off on Imperial College London University computers with access only granted to the study research team.

11.14 DATA PROTECTION

The investigator will preserve the confidentiality of all participants taking part in the study, which will be conducted in accordance with GDPR and the Data Protection Act 2018. Furthermore, all investigators and study staff must comply with the requirements of the Data Protection Act with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

11.15 END OF TRIAL

The end of the trial will occur at the point of database lock or at the request of the Trial Steering Committee.

12. DATA MANAGEMENT, STUDY DOCUMENTATION AND DATA STORAGE

12.1 PERSONAL IDENTIFYING DATA:

The study investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

All research documentation and information will undergo a process of pseudonymisation where possible. Whilst within the study, patients will be identified by a unique study number, and the data in the CRF will be linked to this number. Research data will be entered onto a dedicated, secure, encrypted trial database, specifically constructed for this purpose. The study team will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given

explicit consent for data transfer. Data within the NHS system such as patient notes, and reports will remain confidential in accordance with NHS confidentiality code of practice.

Personal identifying data will be kept electronically on NHS computers at participating sites and in paper format stored in NHS premises within secure offices only accessible by authorised trained personnel. The central research team will also keep patient identifiable names and contact details separate from the main trial database and linked with trial identifiers in order to send health status questionnaires and PROMS directly to patients in the post or via email or online links via the RedCap eCRF database.

12.2 REDCAP ELECTRONIC CASE REPORT FORM DATABASE:

Database Data and remote informed consent will be entered onto a trial database application electronic Case Report Form (eCRF) known as RedCap. E-consent will be documented using eSignatures traced with a finger, mouse or a stylus.

The database is stored on an Imperial College network protected by a firewall. Access to the database is restricted to the research team by login and password for user. All RedCap users will be trained and certified in the usage of the database. Desktop security is maintained through user names and frequently update passwords. On this eCRF or other documents submitted to the coordinating centre or sponsor, documents will not be labelled with any patient identifiable information, but instead by a unique patient identification number (study number). Therefore all identifying information will be removed.

12.3 SITE FILES AND SOURCE DATA:

The investigator at each participating site must ensure that patients' anonymity will be maintained and that their identities are protected from unauthorised parties. Manual files of source data and consent forms will be stored at each participating centre. This will also include the Investigator Site File (ISF), which will all be locked and secured in filing cabinets or rooms only accessed by authorised personnel.

12.4 TRIAL MASTER FILES (TMF):

This will be kept in a secured, locked Imperial College Office space in the Laboratory block at Charing Cross Hospital accessed only by appropriately trained study staff, people working on behalf of the Sponsor, and by representatives of Regulatory Authorities, where it is relevant to this research.

Storage and handling of confidential trial data and documents will be in accordance with GDPR and the Data Protection Act 2018 (UK). Embedded qualitative sub-study data:

12.5 QUALITATIVE SUBSTUDY DATA:

Qualitative data will be stored at Imperial College London and stored separately from recordings, transcripts and data analysis notes. A laptop may be used to store data temporarily when conducting fieldwork, but any data will be transferred securely, using an encrypted USB stick to a Imperial College PC and information held on the laptop and USB stick will be deleted. This will be recorded in data management records stored within the study site file. The laptop will be password protected and all files and documents pertaining to the study will also be password protected. All hard-copy data and study information will be kept secured in locked filing cabinets within Imperial College. All electronic data will be kept securely on a password protected computer and files and folders will also be password protected. Electronic files will be held on a University secured server. Only research staff will have access to the secure drive. Digital audio recordings of interviews will be uploaded to the secure drive at Imperial College and the originals deleted from the digital recorder. Audio recordings will be kept in a separate folder to any transcripts. Once transcribed and checked, interview transcripts will be stored in PDF format on the secured drive, which will ensure content cannot be altered. All transcripts will have identifiable information removed. Transcripts will be prepared in house and uploaded to the NVivo 11 qualitative software programme for efficient and rigorous data management. Anonymised transcripts will be stored securely for 10 years. No data will be transferred outside the EU.

12.6 VOICE RECORDINGS:

All voice data will be deleted after checking transcription accuracy. Anonymised transcripts will be stored securely for 10 years on secure Imperial College London computers. No data will be transferred outside the UK.

12.7 DESTRUCTION OF STUDY DOCUMENTS:

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study documents will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

12.1 SOURCE DATA

Source documentation is defined as the first time data appear, and may include original document, data and records (hospital records, clinical reports, MRI and Ultrasound reports, other procedure reports, laboratory notes, other data recorded at the pathology and biochemistry laboratories, etc.). Information in source documents (e.g. medical history) dated prior to the Informed Consent Form signature date may be used to verify patient suitability for the study.

Clinical records must be marked to indicate a subject has been enrolled into the clinical study.

The Investigator must ensure the availability of source documents from which the information on the eCRF was obtained. Where printouts and electronic medical records are provided as source documents, they should be signed and dated by a member of the adequately trained research team, to indicate that the data provided is a true reproduction of the original source document.

All study data may be inspected by the Sponsor and regulatory authorities by people working on behalf of the Sponsor, and by representatives of Regulatory Authorities, where it is relevant to this research.

13.2 LANGUAGE

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

13.3 DATABASE

The principal means of data collection from participant visits will be Electronic Data Capture (EDC) via the internet using the an eCRF database. Data is entered into the EDC system via site personnel. All source data will be recorded in the CRF and the completed case report book will be signed by the Investigator or his/her appropriate designee. All changes made at any time following the electronic signing will have an electronic audit trail with a signature and date. The completed case report book will then again be signed by the investigator or his/her appropriate designee. Specific instructions and further details will be outlined in the CRF manual.

13.4 DATA COLLECTION

All study data will be entered into electronic Case Report (eCRFs) in a database provided by the Sponsor. All eCRFs will be completed using de-identified data.

CRF completion may be delegated by the Principal Investigator (documented on the Delegated Task List) to other study personnel though the Principal Investigator remains responsible for the accuracy and integrity of all data entered to eCRFs.

Further details of procedures for CRF/eCRF completion, including data review, database cleaning, issuing and resolving data queries, and identification of steps for creation, modification, maintenance and archiving of source data via any computerised systems will be provided in the study specific Data Management Plan (CRF manual).

13.5 ARCHIVING

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study. Subject files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved later. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 2018 (UK).

14. STUDY MANAGEMENT STRUCTURE

14.1 TRIAL STEERING COMMITTEE (TSC)

A combined Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) has been convened and included as a minimum an Independent Chair, Independent Clinician, Independent Statistician, and Patient Representative. The role of the TSC/DMC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

14.2 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be convened including the Chief Investigator (co-chair), lead co-investigator (co-chair) and other co-investigators and key collaborators, Study Coordinator, Study Statistician, Operations Manager and Study Manager. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate Terms of Reference.

When necessary, decisions will be referred to the TSC/DMC. Meetings will be scheduled in a risk-adapted manner to allow for the review of events during the trial.

14.3 DATA MONITORING COMMITTEE (DMC)

As mentioned in section 14.1, the DMC is combined with the TSC.

14.4 EARLY DISCONTINUATION OF THE STUDY

In case of early discontinuation of the study, the Follow-up Visit assessments should be performed for each subject, as far as possible.

14.5 RISK ASSESSMENT

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Study Manager and the result will be used to guide the Monitoring Plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

14.6 MONITORING

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan, developed in accordance with the risk assessment.

14.7 QUALITY CONTROL AND QUALITY ASSURANCE

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care (2nd Edition).

14.8 PEER REVIEW

This study has been peer reviewed by the funder Wellcome Trust and within the Urology Department at Imperial College London. It has also undergone review by the NCRI (UK) Prostate Clinical Studies Group.

14.9 PATIENT AND PUBLIC INVOLVEMENT

Lay people (including those who have undergone treatment for prostate cancer) have been involved in the design of the study, and will participate in the management of the research, and analysis and dissemination of the findings. This has been detailed in the introduction to the protocol.

14.10 PUBLICATION AND DISSEMINATION POLICY

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study in connection with the development of the ablative or radiotherapy or surgical techniques and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore, all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) is completed.

Permission from the Executive/Writing Committee is necessary prior to disclosing any information relative to this study outside of the Trial Steering Committee. Any request by site investigators or other collaborators to access the study dataset must be formally reviewed by the TMG.

The results may be published or presented by the investigator(s), but the Funder will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications are produced.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC.

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SIGNATURE PAGE 1 (Chief Investigator)

The signature below constitutes approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: PROState **P**athway **E**mbedded **C**omparative **T**rial

Protocol Number: 19CX5601

Signed: _____

Professor Hashim U Ahmed

Date: _____

SIGNATURE PAGE 2 (Sponsor)

The signatures below constitute approval of this protocol by the signatory.

Study Title: PROState **P**athway **E**mbedded **C**omparative **T**rial

Protocol Number: 19CX5601

Signed: _____

Name of Sponsor's Representative

Title

Sponsor name

Date: _____

SIGNATURE PAGE 3 (Statistician)

The signatures below constitute approval of this protocol by the signatory.

Study Title:PROState **P**athway **E**mbedded **C**omparative **T**rial

Protocol Number: 19CX5601

Signed: _____

Dr Francesca Fiorentino

Imperial Clinical Trials Unit and Division of Surgery

Date: _____

SIGNATURE PAGE 4 (Principal Investigator)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: PROState **P**athway **E**mbedded **C**omparative **T**rial

Protocol Number: 19CX5601

Address of Institution: _____

_____

_____

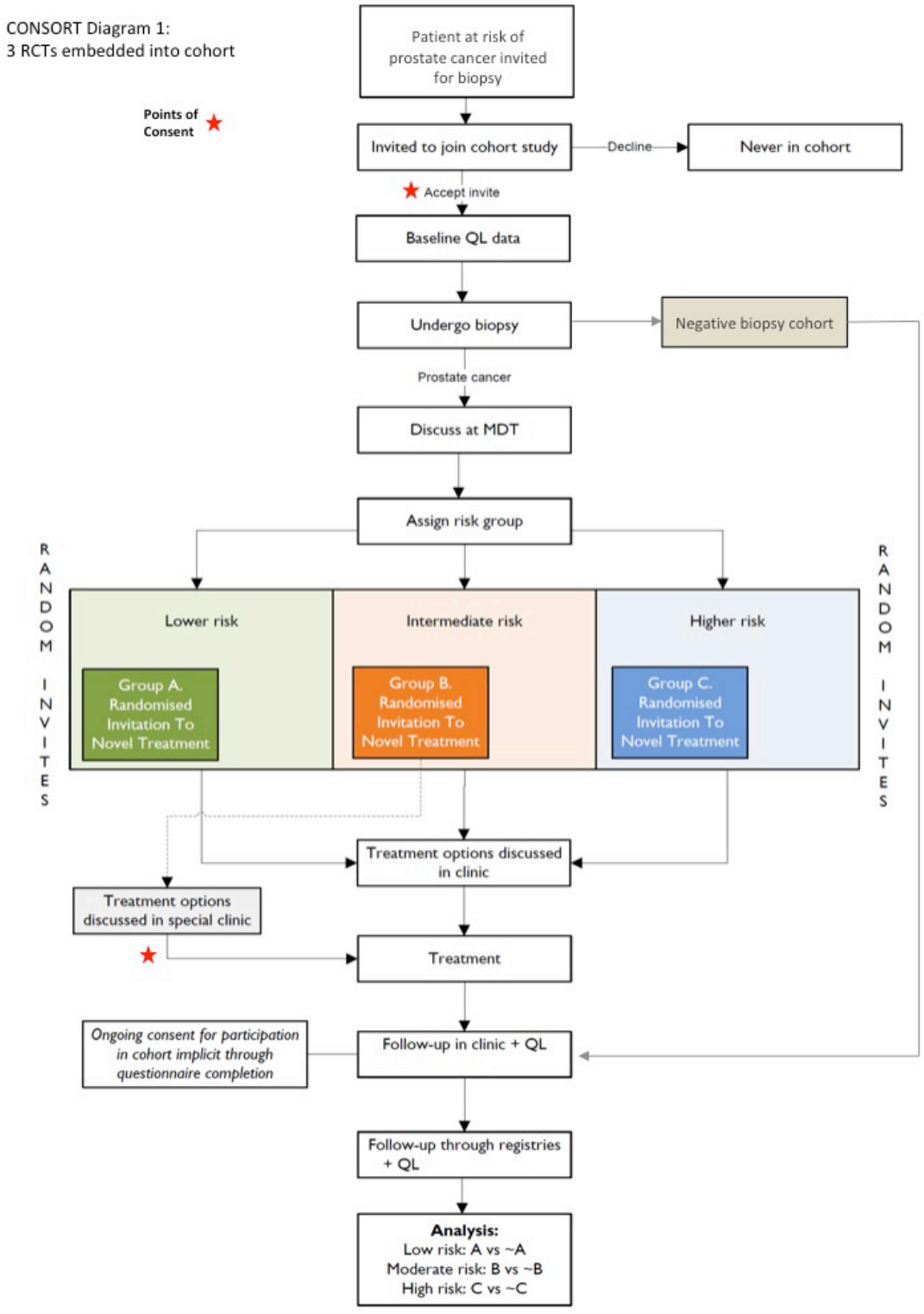
Signed: _____

Print Name and Title: _____

Date: _____

PROSPECT STUDY APPENDICES

Appendix A – Overall CONSORT Flowcharts for PROSPECT cmRCT



CONSORT Diagram 2:
Potential for further embedded RCTs