Statistical Analysis Plan (SAP): Feasibility

PROState Pathway Embedded Comparative Trial

IP3-PROSPECT

19CX5601

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Document version history log:

Version	Date	Author	Summary of changes made
v0.1	21/04/2021	Emily Day	Initial draft taken from protocol
v0.2	07/06/2021	Emily Day	Inclusion criteria wording updated to correspond to protocol v4.0 and updates following review from Prof Hashim Ahmed
v0.3	09/06/2021	Emily Day	Updated following review from Mr Brian Birch and Prof Adrian Mander
v1.0	11/04/2022	Matyas Szigeti	No changes since v0.3. Finalised version.

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1. Abbreviations

AE	Adverse Event
cmRCT	Cohort Multiple Randomised Control Trial
CRF	Case Report Form
CTA	Clinical Trials Agreement
CTCAE	Common Terminology Criteria for Adverse Events
DMEC	Data Monitoring and Ethics Committee
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report Form
EOS	End of Study
EQ-5D-5L	European Quality of Life Instrument (5 dimensions, 5 levels)
GCP	Good Clinical Practice
HRQoL	Health-Related Quality of LIfe
ICTU	Imperial Clinical Trials Unit
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
IQR	Interquartile Range
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NHS	National Health Service
PROMS	Patient Reported Outcome Measures
PSA	Prostate Specific Antigen
QoL	Quality of Life
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SD	Standard Deviation
TMG	Trial Management Group
TSC	Trial Steering Committee
TWiCS	Trials Within Cohorts
VAS	Visual Analogue Scale

2. 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
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. 2. 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. 3. An understanding of the English language sufficient to understand written and verbal information about the trial and consent process. 4. Estimated life expectancy of 5 years or more. 5. 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; - Recruitment to cohort. - 0-6, 6, 12, 18 & 24 months from recruitment to cohort - Yearly questionnaires thereafter during inclusion in the cohort and provided the study is open. • 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

	○ 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.

3. Study Outcomes and Endpoints

3.1. 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.[1] 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 1.1c.[1] 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.

[1]These are semi-structured transcribed qualitative interviews with thematic extraction of broader aspects of acceptance and non-acceptance and will be analysed by the clinical research team. These analyses are not part of the Statistical Analysis Plan (SAP).

3.2. 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[1]**:** 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 (EQ-5D-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.

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).

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.

[1]These are semi-structured transcribed qualitative interviews with thematic extraction of broader aspects of acceptance and non-acceptance and will be analysed by the clinical research team. These analyses are not part of the Statistical Analysis Plan (SAP).

4. Design

4.1. Study 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 4.3, 4.4).

4.2. Consent

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

4.2.1. 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.

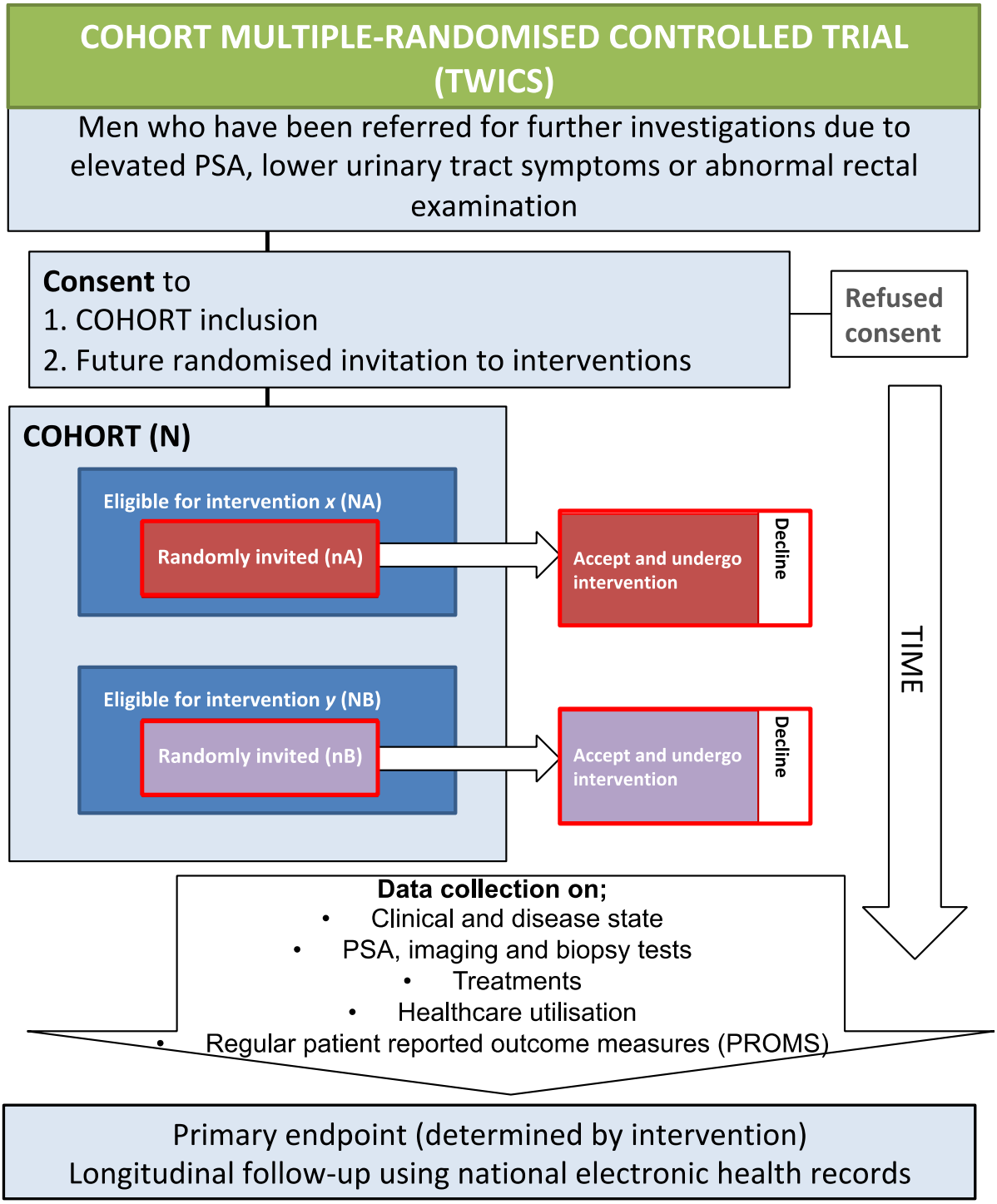
4.2.2. Point of Consent Two

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.

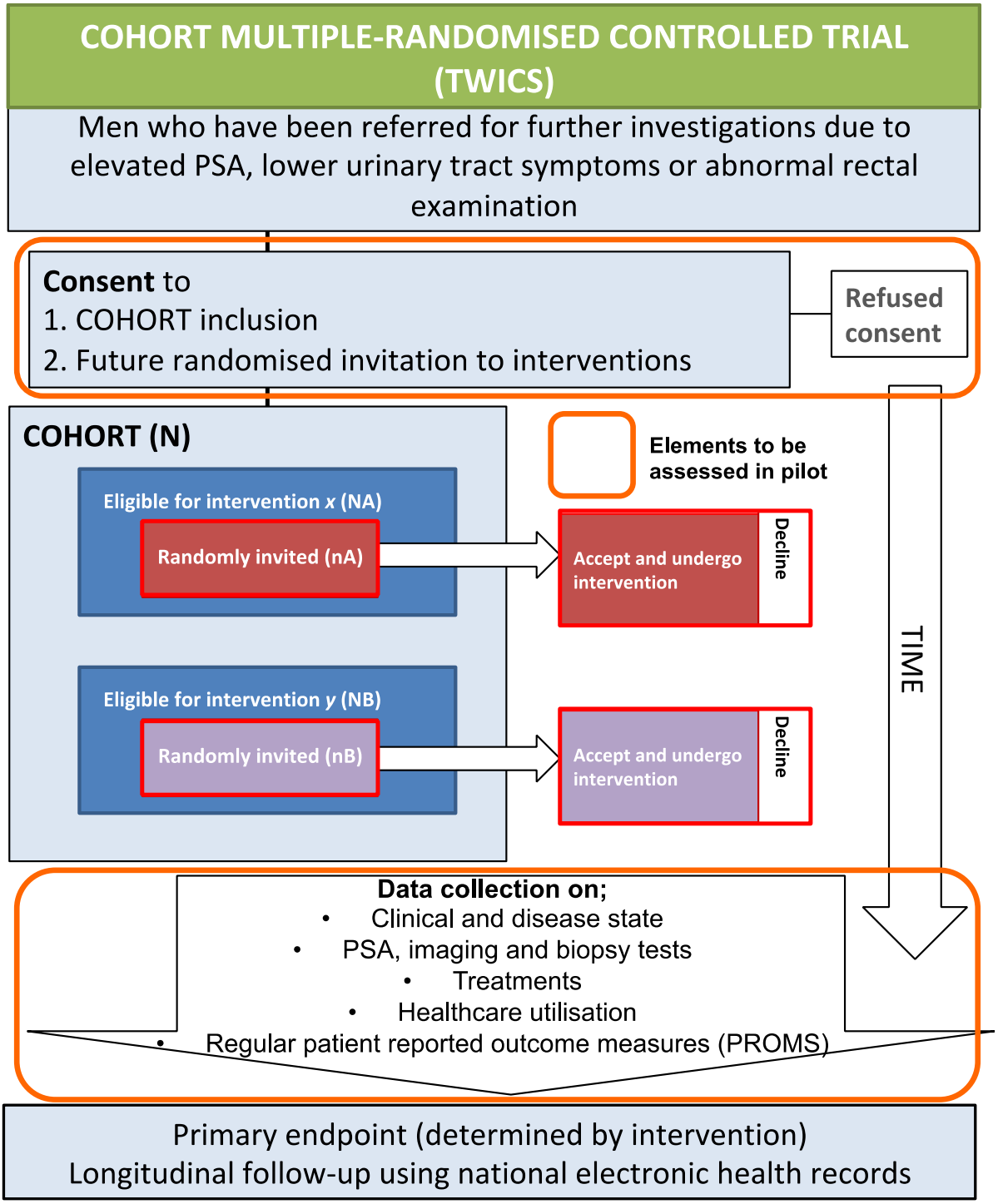
The second stage of PROSPECT will be to investigate and evaluate in a similarly careful manner the feasibility and acceptability of randomising men from our cohort of eligible men to interventions or changes in management that require evaluation, following submission to REC. As part of the cmRCT design, 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.

4.3. 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.

4.4. 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.

4.5. 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.

4.6. Eligibility Criteria

4.6.1. 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, orMen 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.

4.6.2. Exclusion Criteria

1. Men who are unable to give informed consent.

4.7. 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.

4.8. 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.

4.9. 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.

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.

4.10. Schedule of Time and Events

4.10.1. 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.

	Screening	**Baseline**	**0-6 months**	**6 Month intervals up to 24 months** (+/- 4 weeks)
Informed Consent	✓			
PSA		✓		✓ *
Medical history (from medical records and		✓	✓ MRI, biopsy	✓ Treatment given if cancer

questionnaires to patients)			Grade and stage if cancer	Other diagnostic tests carried out if not
Quality of Life (QoL) Questionnaires sent directly to patients		✓	✓	✓

*

Collected if carried out in standard care practice

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.

4.10.2. Patients (Qualitative Sub study)

Face-to-face or telephone 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.

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

4.10.3. 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 telephone 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.

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

4.11. Follow-Up

The minimum length of follow-up for the feasibility phase of PROSPECT is 6 months.

5. Populations of Analysis Sets

5.1. Evaluable Population

Analysis will be carried out for the evaluable population. This is defined as those individuals who meet the eligibility criteria and are approached for inclusion in PROSPECT.

6. Variables of Analysis

6.1. Acceptability Outcomes Variables

- Number of men who consented to PROSPECT cohort
- Number of men approached for inclusion in the PROSPECT cohort

6.2. Feasibility Outcomes Variables

- Number of men who were approached for inclusion in PROSPECT cohort
- Number of men referred to the participating centres for investigation of prostate cancer (available from the clinical NHS departments)
- EQ-5D-5L (Appendix 2)
- EPIC-26 (Appendix 2)
- IPSS (Appendix 2)
- IIEF-15 (Appendix 2)
- Subject Data collected at 0 Months Visit:
    - Age at enrolment
    - Medical History/Comorbidities
    - WHO Performance Status
    - Ethnicity
    - Family history of prostate cancer
    - Family history of breast cancer
- Disease Characteristics collected at 0-6 Months Visit (and updated at consecutive visits):
    - PSA
    - MRI prostate volume
    - MRI score:
        - PIRADS

        - Likert
    - Biopsy type
    - Biopsy findings
    - TNM stage if cancer evident
- Treatment Data collected at 6 Month Visit (and updated at consecutive visits):
    - Modality
    - Follow-up
    - Adjuvant/salvage treatments
- Mortality collected via EOS or SAE forms.

6.3. Safety Variables

An adverse event (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.

A serious adverse event (SAE) is defined as any event that:

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's 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 admission that were planned before study inclusion or visits to casualty (without admission).

AE reporting will utilise NCI CTCAE v4.0 terminology, providing a grading (severity) scale for each AE term. The expected adverse events that may require hospitalisation and serious adverse events that will not require reporting as SAEs, but that will be collected, are listed in Appendix 1.

All protocol deviations and violations will be recorded throughout the study and reported.

6.4. Demographic Variables

After obtaining informed consent and registering the patient in PROSPECT, the following clinical and baseline assessments will be undertaken:

- Demographics: age at enrolment, ethnicity
- Family history: family history of prostate cancer, family history of breast cancer
- Presenting clinical parameters: BMI, Presenting PSA, DRE and result, WHO Performance Status
- Urological History
- Medical History.

7. Statistical Methodology

7.1. Baseline Demographics

Patient characteristics will be summarised. Summaries of continuous variables will be presented as means and standard deviations if approximately normally distributed, and as medians and inter-quartile ranges for skewed data; categorical variables will be presented as frequencies and percentages.

7.2. Endpoint Analysis

Outcome	Variables	Analysis	Population
Acceptability			
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.	• Number of men who consented to PROSPECT cohort • Number of men who were approached for inclusion in PROSPECT cohort	Proportion of patients who consented to participate in PROSPECT out of those approached for inclusion	Patients who were approached for inclusion in PROSPECT
Feasibility			
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.	• Number of men who were approached for inclusion in PROSPECT cohort • Number of men referred to the participating centres for investigation of prostate cancer	Proportion of men approached to enter PROSPECT out of number of men referred to the participating centres for investigation of prostate cancer	Men who were referred to the participating centres for investigation for 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.	• EQ-5D-5L	• Proportion of patients who responded to the questionnaires at each visit • Proportion of completed questionnaires at each visit • Proportions of missing data for each question at each visit	Patients who consented to PROSPECT cohort
All participants will be asked to complete PROMS 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 and provided the study is open. PROSPECT will calculate the rates of response from participants with these questionnaires.	• EPIC-26 • IPSS • IIEF-15	• Proportion of patients who responded to the questionnaires at each visit • Proportions of patients who completed the questionnaires at each visit • Proportions of missing data for each question at each visit	Patients who consented to PROSPECT cohort

Feasibility of collecting data from the participating centres evidenced by the completeness of data for cohort participants including: • *Subject Data*: age, co-morbidities, ECOG/WHO Performance Status, ethnic risk, family history • *Disease Characteristics*: PSA, MRI (prostate volume, MRI score), biopsy type and findings, TNM stage if cancer • *Treatment Data*: modality, follow-up, adjuvant/salvage treatments, mortality 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.	• Subject Data: •Age at enrolment •Medical History/Comorbidities •WHO Performance Status •Ethnicity •Family history of prostate cancer •Family history of breast cancer • Disease Characteristics: •PSA •MRI prostate volume •MRI score: ▪ PIRADS ▪ Likert •Biopsy type •Biopsy findings •TNM stage if cancer evident • Treatment Data: •Modality •Follow-up •Adjuvant/salvage treatments •Mortality (EOS or SAE form)	• Proportions of missing data	Patients who consented to PROSPECT cohort

[1]These are semi-structured transcribed qualitative interviews with thematic extraction of broader aspects of acceptance and non-acceptance and will be analysed by the clinical research team. These analyses are not part of the Statistical Analysis Plan (SAP).

7.3. Acceptability Analysis

The proportion of patients who consented to inclusion in the PROSPECT cohort out of the total number approached will be calculated, along with the 95% confidence interval.

7.4. Feasibility Analysis

The proportion of men approached to enter PROSPECT out of the total number of men referred to the participating centres for investigation of prostate cancer.

Questionnaire response rates will be assessed as part of the feasibility analysis. EQ-5D-5L, EPIC-26, IPSS and IIEF-15 will be collected at recruitment, 0-6, 6, 12, 18, 24 months from recruitment and yearly thereafter. The minimum length of follow-up for the feasibility phase of PROSPECT is 6 months. The proportions of patients who responded to the questionnaires out of

the total number of patients consented to the trial will be calculated. The proportions of patients who completed the questionnaires out of those who responded will also be calculated. A questionnaire is considered to be complete if there are no missing values for any of the questions. The proportions of missing data for each question of each questionnaire will also be tabulated. Proportions will be calculated along with 95% confidence intervals.

Proportions of missing subject data, disease characteristics and treatment data will be calculated for all patients consented to inclusion in the PROSPECT cohort.

7.5. Missing Data

A specific missing data mechanism is not required for the feasibility phase of PROSPECT.

7.6. Outliers

No formal method will be used for handling outliers in the feasibility phase of PROSPECT.

7.7. Safety Analysis

Adverse and serious adverse events should be reconciled on the eCRF. Reported adverse events (AEs) and serious adverse events (SAEs) will be listed and summarised separately.

7.8. Protocol Deviations

Protocol deviations, and violations, are to be listed and summarised. If necessary, by category and site.

7.9. Tables to present

7.9.1. Baseline Characteristics

Table 1. 1: Baseline Characteristics

Variable	Statistics	Total
Age	N Mean (SD) Median (IQR) Missing from eCRF – n(%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx.x%)
Ethnicity – n (%)	N White Mixed/Multiple Ethnic Groups Asian/Asian British Black/African/Caribbean/Black British Other Ethnic Group Unknown Missing from eCRF	xxx xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)
Family history of PCa – n (%)	N Yes No Unknown Missing from eCRF	xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)
Family history of breast cancer – n (%)	N Yes No Unknown Missing from eCRF	xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)
BMI	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx.x%)
Presenting PSA	N Mean (SD) Median (IQR) Missing from eCRF – n (%)	xxx xx.xx (xx.xx) xx.xx (xx.xx, xx.xx) xx (xx.x%)
DRE – n (%)	N Yes: T1 (Normal) T2 (Abnormal) T3+ (Evidence for Locally Advanced/Metastatic Disease) No Missing from eCRF	xxx xx (xx.x%): xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)
WHO Performance Status – n (%)	N 0 1 2 3 4 5	xxx xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)

	Missing from eCRF – n (%)	xx (xx.x%)

Table 1. 2: Urological History

Variable	Statistics	Total
Has there ever been treated for a prostate condition? – n (%)	N Yes No Missing from eCRF	xxx xx (xx.x%) xx (xx.x%) xx (xx.x%)
Is the patient taking medication for symptoms of an enlarged prostate? – n (%)[1]	N Yes: Alpha blocker 5 ARI PDE Inhibitor No Missing from eCRF	xxx xx (xx.x%): xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)
Has the patient ever taken hormones for prostate cancer? – n (%)[1]	N Yes No Missing from eCRF	xxx xx (xx.x%) xx (xx.x%) xx (xx.x%)
Has the patient ever had a surgical procedure for an enlarged prostate? – n (%)[1]	N Yes: TURP Laser PVP Laser Enucleation Open Prostatectomy Urolift Rezum Other No Missing from eCRF	xxx xx (xx.x%): xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)

[1]Only for those patients who have ever been treated for a prostate condition (Question 1 is answered "Yes")

Table 1. 3: Medical History[1]

Variable	Statistics	Total
Does the participant/subject have a history of any medical problems/conditions? – n (%)	N Yes No Missing from eCRF	xxx xx (xx.x%) xx (xx.x%) xx (xx.x%)
Number of medical problems/conditions reported – n (%)[2]	N 1 2 3 4 5 6 7 8	xxx xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)

	9 10 Missing from eCRF	xx (xx.x%) xx (xx.x%) xx (xx.x%)
Body System Code – n (%)[2]	N Constitutional symptoms (e.g. fever, weight loss) Eyes Ears, Nose, Mouth, Throat Cardiovascular Respiratory Gastrointestinal Genitourinary Musculoskeletal Integumentary (skin and/or breast) Neurological Psychiatric Endocrine Hematologic/Lymphatic Allergic/Immunologic Missing from eCRF	xxx xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)
Medical History Term – n (%)[2]	N … … … Missing from eCRF	xxx xx (xx.x%) xx (xx.x%) xx (xx.x%) xx (xx.x%)

[1]All summaries at patient level

[2]Only for patients who reported having a history of medical problems/conditions

7.9.2. Acceptability Endpoints

Table 2. 1: Proportion of patients who consented to inclusion in PROSPECT cohort out of total number of patients approached

Consent rate
xx.x% (xx.x% to xx.x%)

7.9.3. Feasibility Endpoints

Table 3. 1: Proportion of men approached to enter PROSPECT out of number of men referred to the participating centres for investigation of prostate cancer

Approached rate
xx.x% (xx.x% to xx.x%)

Table 3. 2: Proportions of patients who responded to[1], and completed[2], the questionnaires (EQ-5D-5L, EPIC26, IPSS, IIEF-15)

Visit	Questionnaire	Responded	Completed
0 Months	**EQ-5D-5L**	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
	EPIC26	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
	IPSS	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
	IIEF-15	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
0-6 Months	**EQ-5D-5L**	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)

	EPIC26	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
	IPSS	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
	IIEF-15	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
6 Months	**EQ-5D-5L**	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
	EPIC26	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
	IPSS	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
	IIEF-15	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
12 Months	**EQ-5D-5L**	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
	EPIC26	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
	IPSS	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)
	IIEF-15	xx.x% (xx.x% to xx.x%)	xx.x% (xx.x% to xx.x%)

[1]Proportions of patients who responded to the questionnaires out of the total number of patients consented to the trial

[2]Proportions of patients who completed the questionnaires out of those who responded

Table 3. 3: Proportions of missing data for each question in EPIC16, IPSS, IIEF-15 and EQ-5D-5L[1]

Question Number	Question Verbatim	Missing from eCRF – n (%)
EPIC26		
1	Over the past 4 weeks, how often have you leaked urine?	xx (xx.x%)
2	Which of the following best describes your urinary control during the last 4 weeks?	xx (xx.x%)
3	How many pads or adult diapers per day did you use to control leakage during the last 4 weeks?	xx (xx.x%)
4a	How big a problem, if any, has each of the following been for you during the last four weeks? Dripping or leaking urine	xx (xx.x%)
4b	How big a problem, if any, has each of the following been for you during the last four weeks? Pain or burning on urination	xx (xx.x%)
4c	How big a problem, if any, has each of the following been for you during the last four weeks? Bleeding with urination	xx (xx.x%)
4d	How big a problem, if any, has each of the following been for you during the last four weeks? Weak urine stream or incomplete emptying	xx (xx.x%)
4e	How big a problem, if any, has each of the following been for you during the last four weeks? Need to urinate frequently during the day	xx (xx.x%)
5	Overall, how big a problem has your urinary function been for you during the last 4 weeks?	xx (xx.x%)
6a	How big a problem, if any, has each of the following been for you? Urgency to have a bowel movement	xx (xx.x%)
6b	How big a problem, if any, has each of the following been for you? Increased frequency of bowel movements	xx (xx.x%)
6c	How big a problem, if any, has each of the following been for you? Losing control of your stools	xx (xx.x%)
6d	How big a problem, if any, has each of the following been for you? Bloody stools	xx (xx.x%)
6e	How big a problem, if any, has each of the following been for you? Abdominal/Pelvic/Rectal pain	xx (xx.x%)
7	Overall, how big a problem have your bowel habits been for you during the last 4 weeks?	xx (xx.x%)
8a	How would you rate each of the following during the last 4 weeks? Your ability to have an erection?	xx (xx.x%)

8b	How would you rate each of the following during the last 4 weeks? Your ability to reach orgasm (climax)?	xx (xx.x%)
9	How would you describe the usual quality of your erections during the last 4 weeks?	xx (xx.x%)
10	How would you describe the frequency of your erections during the last 4 weeks?	xx (xx.x%)
11	Overall, how would you rate your ability to function sexually during the last 4 weeks?	xx (xx.x%)
12	Overall, how big a problem has your sexual function or lack of sexual function been for you during the last 4 weeks?	xx (xx.x%)
13a	How big a problem during the last 4 weeks, if any, has each of the following been for you? Hot flashes	xx (xx.x%)
13b	How big a problem during the last 4 weeks, if any, has each of the following been for you? Breast tenderness/enlargement	xx (xx.x%)
13c	How big a problem during the last 4 weeks, if any, has each of the following been for you? Feeling depressed	xx (xx.x%)
13d	How big a problem during the last 4 weeks, if any, has each of the following been for you? Lack of energy	xx (xx.x%)
13e	How big a problem during the last 4 weeks, if any, has each of the following been for you? Change in body weight	xx (xx.x%)
IPSS		
1	Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	xx (xx.x%)
2	During the past month or so, how often have you had to urinate again less than two hours after you finished urinating?	xx (xx.x%)
3	During the past month or so, how often have you found you stopped and started again several times when you urinated?	xx (xx.x%)
4	During the past month or so, how often have you found it difficult to postpone urination?	xx (xx.x%)
5	During the past month or so, how often have you had a weak urinary stream?	xx (xx.x%)
6	During the past month or so, how often have you had to push or strain to begin urination?	xx (xx.x%)
7	Over the past month, how many times per night did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	xx (xx.x%)
8	Quality of life: How would you feel if you had to live with your urinary condition the way it is now, no better, no worse, for the rest of your life?	xx (xx.x%)
IIEF-15		
1	How often were you able to get an erection during sexual activity?	xx (xx.x%)
2	When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	xx (xx.x%)
3	When you attempted intercourse, how often were you able to penetrate (enter) your partner?	xx (xx.x%)
4	During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	xx (xx.x%)
5	During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	xx (xx.x%)
6	How many times have you attempted sexual intercourse?	xx (xx.x%)
7	When you attempted sexual intercourse, how often was it satisfactory for you?	xx (xx.x%)
8	How much have you enjoyed sexual intercourse?	xx (xx.x%)
9	When you had sexual stimulation or intercourse, how often did you ejaculate?	xx (xx.x%)

10	When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax?	xx (xx.x%)
11	How often have you felt sexual desire?	xx (xx.x%)
12	How would you rate the level of sexual desire?	xx (xx.x%)
13	How satisfied have you been with your overall sex life?	xx (xx.x%)
14	How satisfied have you been with your sexual relationship with your partner?	xx (xx.x%)
15	How do you rate your confidence that you could get and keep an erection?	xx (xx.x%)
EQ-5D-5L		
1	Mobility	xx (xx.x%)
2	Self-care	xx (xx.x%)
3	Usual activities	xx (xx.x%)
4	Pain/Discomfort	xx (xx.x%)
5	Anxiety/Depression	xx (xx.x%)

[1]Repeated for questionnaires at visits 0 months, 0-6 months, 6 months and 12 months

Table 3. 4: Proportions of missing subject data, disease characteristics and treatment data

Variable	Missing from eCRF – n (%)
Subject Data[1]	
Age at enrolment	xx (xx.x%)
Medical History/Comorbidities	xx (xx.x%)
WHO Performance Status	xx (xx.x%)
Ethnicity	xx (xx.x%)
Family history of prostate cancer	xx (xx.x%)
Family history of breast cancer	xx (xx.x%)
Disease Characteristics[2]	
PSA	xx (xx.x%)
MRI Prostate Volume	xx (xx.x%)
MRI PIRADS score	xx (xx.x%)
MRI Likert score	xx (xx.x%)
Biopsy type	xx (xx.x%)
Biopsy findings	xx (xx.x%)
T Stage (if cancer present)	xx (xx.x%)
N Stage (if cancer present)	xx (xx.x%)
M Stage (if cancer present)	xx (xx.x%)
Treatment Data[3]	
Modality	xx (xx.x%)
Follow-up	xx (xx.x%)
Adjuvant/salvage treatments	xx (xx.x%)
Mortality[4]	
Mortality	xx (xx.x%)

[1]Collected at 0 months visit

[2]Collected at 0-6 months visit and checked for any updates at each consecutive visit

[3]Collected at 6 months visit and checked for any updates at each consecutive visit

[4]Collected using EOS and SAE forms

7.9.4. Safety Reporting

Table 4. 1: Listing of all Adverse Events

Subject ID	Site	AE Description	Onset Date	End Date	Severity	Relationship to Study Treatment	Action Taken with Study Intervention	Other Action Taken	Outcome	SAE?

Summary of Adverse Events[2] by Severity Grade (v4.0 CTCAE)

	Subjects with AEs[1]					
	1 - Mild	2 - Moderate	3 - Severe	4 – Life-threatening	5 – Fatal or Death	Total
Total	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

	All AEs					
Treatment	1 - Mild	2 - Moderate	3 - Severe	4 – Life-threatening	5 – Fatal or Death	Total
Total	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

[1]Where subjects have more than one AE, the highest severity grade has been used

[2]Expected adverse events which will not be reported are listed in Appendix 1

Table 4. 2: Listing of all Serious Adverse Events

Subject ID	Site	SAE number	SAE Description	Date of notification	Why was the event serious?	Date of onset	Where did the SAE take place?	Severity

Table 2. 2: Summary of Serious Adverse Events by Category, by Treatment Arm*

	Subjects with SAEs					
	Resulted in death	**Life threatening**	**Required inpatient hospitalisation or prolongation of existing hospitalisation**	**Resulted in persistent or significant disability/incapacity**	**Resulted in congenital anomaly/birth defect**	**Other medically important event**
Total	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

	All SAEs					
	Resulted in death	**Life threatening**	**Required inpatient hospitalisation or prolongation of existing hospitalisation**	**Resulted in persistent or significant disability/incapacity**	**Resulted in congenital anomaly/birth defect**	**Other medically important event**
Total	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)	xxx (xx%)

7.9.5. Protocol Deviations

Table 4. 3: Listing of Protocol Deviations and Violations*

Subject ID	Site	Deviation or violation	Description	Classification	Date deviation /violation occurred	Date ICTU notified	Serious breach?	Study Manager comments	PI comments

Table 4. 4: Number of Protocol Deviations and Violations by Site

Type of Deviation/Violation	…	…	…	Total
Inclusion/exclusion criteria	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Study drug administration	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Sampling/laboratory measurements	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Consent issue	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Study visit windows	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
NIMP administration	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Study drug prescription	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Dispensing	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Accountability	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Compliance	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Missed study visit	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Study measurements/assessments:	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Device	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Equipment	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Prohibited medication/substance(s)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
AE/SAE reporting	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Blinding/unblinding	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Randomisation:	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Implementation of document prior to research approval	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Licence/certification/calibration/servicing (labs and equipment)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Delegation log/authorisation	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Dose interruptions/modifications not specified in protocol	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Variation in clinical management of participant	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Withdrawal issue	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Falsifying research or medical records	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Repeated protocol deviations (of same type)	xx (xx%)	xx (xx%)	xx (xx%)	xx (xx%)
Total	**xx (xx%)**	**xx (xx%)**	**xx (xx%)**	**xx (xx%)**

7.10. Figures to present

8. Imperial Prostate Trial Steering Committee

A combined TSC and DMEC is in place to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of Good Clinical Practice (GCP) and the relevant regulations. The TSC should agree the trial protocol and any protocol amendments and provide advice to the investigators and the Trial Management Group (TMG), via Imperial Clinical Trials Unit (ICTU) on all aspects of the trial.

The TSC should meet at least annually, although there may be periods when more frequent meetings are necessary.

9. Amendments to Version 1.0

10. References

1. Tomita N., Oze I., Shimizu H., Yoshida M., Kimura K. et al. International Prostate Symptom Score (IPSS) change and changing factor in intensity-modulated radiotherapy combined with androgen deprivation therapy for prostate cancer. Nagoya J Med Sci. 2015; 77(4): 637-646.

2. EQ-5D-5L User Guide - Basic information on how to use the EQ-5D-5L instrument. 2019, EuroQol Research Foundation**.** *EuroQol - EQ-5D.* [Online] v3.0, September 2019. [Cited: 27 January 2020.] https://euroqol.org/wp-content/uploads/2019/09/EQ-5D-5L-English-User-Guide_version-3.0-Sept-2019-secured.pdf.

3. Rosen R, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): A multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49: 822-830.

4. Sanda MG., Wei JT., Litwin MS. Scoring Instructions for the Expanded Prostate cancer Index Composite (EPIC). University of Michigan, 2002.

11. Appendix 1 – 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

12. Appendix 2 - PROMS

12.1. IPSS

The International Prostate Symptom Score (I-PSS) is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. The responses to the questions concerning urinary symptoms range from 0 to 5, indicating increasing severity of the particular symptom. Thus, the overall score can range from 0 (asymptomatic) to 35 (very symptomatic). The total score for the questions concerning urinary symptoms can be categorised as follows (1):

- Mild – symptom score less than or equal to 7
- Moderate – symptom score range 8-19
- Severe – symptom score range 20-35.

The answers to the question concerning the patient's quality of life ranges from 0 "delightful" to 6 "terrible".

12.2. EQ-5D-5L

The EQ-5D family of instruments has been developed to describe and value health across a wide range of disease areas. The EQ-5D-5L comprises of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and each dimension has five response levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems (2).

12.2.1. EQ VAS

The EQ VAS records the respondent's overall current health on a vertical visual analogue scale, where the ends of the scale are labelled "The best health you can imagine" and "The worst health you can imagine" (2). The EQ VAS provides a quantitative measure of the patient's perception of their overall health. The EQ VAS is a continuous measure from 0 to 100.

12.3. IIEF-15

The 15-question International Index of Erectile Function (IIEF) Questionnaire is a validated, multi-dimensional, self-administered investigation that is useful in the clinical assessment of erectile dysfunction and treatment outcomes in clinical trials (3).

A score of 0-5 is awarded to each of the 15 questions that examine the 4 main domains of male sexual function: erectile function, orgasmic function, sexual desire and intercourse satisfaction (3).

Function Domain	Questions	Max score
Erectile Function	Q1, 2, 3, 4, 5, 15	30
Orgasmic Function	Q9, 10	10
Sexual Desire	Q11, 12	10
Intercourse Satisfaction	Q6, 7, 8	10
Overall Satisfaction	Q13, 14	10

12.4. EPIC-26

The Expanded Prostate Cancer Index Composite (EPIC) is a comprehensive instrument designed to evaluate patient function and bother after prostate cancer treatment. EPIC-26 was developed as a short-form version of the full EPIC. This version contains 26 items and 5 domains: urinary incontinence, urinary irritative/obstructive, bowel, sexual and hormonal. Response options for each EPIC item form a Likert scale, and multi-item scale scores are transformed to a 0-100 scale (4). Higher scores represent higher HRQoL.

Step 1: The response for each item is standardised to a 0 to 100 scale according to the table below (4):

Question Number	Item Number	Item Response Value	Standardised Value
1, 8a, 8b, 10, 11	23, 57, 58, 60, 64	1 2 3 4 5	0 25 50 75 100
2, 9	26, 59	1 2 3 4	0 33 67 100
3	27	0 1 2 3	100 67 33 0
4a, 4b, 4c, 4d, 4e, 6a, 6b, 6c, 6d, 6e, 13a, 13b, 13c, 13d, 13e	28, 29, 30, 31, 33, 49, 50, 52, 53, 54, 74, 75, 77, 78, 79	0 1 2 3 4	100 75 50 25 0
5, 7, 12	34, 55, 68	1 2 3 4 5	100 75 50 25 0

Step 2: Using the item groupings listed below for each HRQOL Domain Score, average the standardised values for all items within a group to create the summary or subscale score. If more then 20% of the items that comprise a domain summary score or subscale score are missing a response, the corresponding domain summary or subscale score cannot be calculated (4).

Domain	Question Number	Item Number	Number of non-missing items needed to compute the score
Urinary Incontinence	1, 2, 3, 4a	23, 26-28	4
Urinary Irritative/Obstructive	4b, 4c, 4d, 4e	29-31, 33	4
Bowel	6a, 6b, 6c, 6d, 6e, 7	49, 50, 52-55	5
Sexual	8a, 8b, 9, 10, 11, 12	57-60, 64, 68	5
Hormonal	13a, 13b, 13c, 13d, 13e	74, 75, 77-79	4