PROTOCOL

The FINESSE Study: A randomised phase 3 trial evaluating the role of Finasteride in increasing compliance with Active surveillance, in men with a new diagnosis of low and intermediate risk prostate cancer, when compared with usual care.

SHORT TRIAL TITLE / ACRONYM:

FINESSE (FINasteride Evaluation in active Surveillance for low and intermediate risk prostate cancer) Study

This protocol has regard for the HRA guidance and order of content

RESEARCH REFERENCE NUMBERS

REC Reference:	21/SC/0349
IRAS Number:	1004290
Sponsor Reference Number:	STH 21032
ISRCTN Number:	ISRCTN16867955
EudraCT Number:	2021-004004-17
Funder Number:	Yorkshire Cancer Research ID: **RA/2019/R1/005**
University of Sheffield Project Code:	**162209**

PROTOCOL VERSION NUMBER AND DATE

Version 4.0

Date 19th June 2023

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Name: Dr. Dipak Patel Position: Research & Innovation Manager	
Signature: DocuSigned by: Dipak Patel 256DFD85A397464...	Date: Jul 3, 2023 | 06:17 PDT

Name: Professor Jim Catto Position: Chief Investigator	
Signature: DocuSigned by: James WF Catto 7F6518067BAE4AF...	Date: Jul 3, 2023 | 06:10 PDT

Name: Professor Peter Sasieni Position: Co- Lead Applicant & Trial Statistician	
Signature: DocuSigned by: Peter Sasieni 2D5B00FC78CC4FE...	Date: Jul 4, 2023 | 10:16 BST

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i. Key Trial Contacts

Chief Investigator	Professor Jim Catto University of Sheffield Email: J.catto@sheffield.ac.uk Phone: + 44 (0)114 215 9002
Co- Lead Applicant & Trial Statistician	Professor Peter Sasieni Kings College London, Cancer Prevention Trials Unit Email: peter.sasieni@kcl.ac.uk Phone: +44 (0)207 188 4484
Co- Investigator	Mr Marcus Cumberbatch University of Sheffield Email: m.g.cumberbatch@sheffield.ac.uk Phone: +44 (0)114 215 9235
Trial Manager	Miss Roseann Kealy Kings College London, Cancer Prevention Trials Unit Email: roseann.kealy@kcl.ac.uk Phone: +44 (0)207 848 9705
Sponsor	Sheffield Teaching Hospital NHS Foundation Trust (STHNFT) Email: sth.researchadministration@nhs.net Phone: +44 (0)114 271 2572
Funder(s)	Yorkshire Cancer Research Email: Research@ycr.org.uk Phone: +44 (0)1423 877 231
Clinical Trials Unit	Cancer Research UK & Kings College London Cancer Prevention Trials Unit (CPTU) Kings College London Email: finesse@kcl.ac.uk Phone: +44 (0)207 848 9706
Key Protocol Contributors	Professor Jim Catto, Chief Investigator Professor Peter Sasieni, Co - Chief Investigator, KCL CPTU Mr. Marcus Cumberbatch, Co-Investigator Mr. Alastair Lamb, Consultant Urologist, Oxford University Hospitals NHS Trust Mr. William Cross, Consultant Urologist, Leeds Teaching Hospitals NHS Trust

	Miss Roseann Kealy, Trial Manager, KCL CPTU Dr Jessica Barnes, Research Fellow, KCL CPTU Dr Sam Smith, Associate Professor, University of Leeds Dr. Dorota Juszczyk, KCL. CPTU. Dr Bernard North, Statistician, KCL CPTU Dr Steven Kennish, Lead Radiologist, Sheffield Teaching Hospitals NHS Foundation Trust (STHNFT) Dr Selina Bhattarai, Lead Pathologist, Leeds Hospital NHS Foundation Trust
Independent Trial Statistician	Dr Bernard North Kings College London, Cancer Prevention Trials Unit Email: Bernard.north@kcl.ac.uk Phone: +44 (0)289 091 3975
Lead Radiologist	Dr Steven Kennish Sheffield Teaching Hospitals NHS Foundation Trust (STHNFT) Department of Medical Imaging Northern General Hospital Herries Road Sheffield S5 7AU Email: Steven.kennish@nhs.net Phone: +44 (0)114 226 8860 (Office) +44 (0)114 2268926 (Secretary)
Lead Pathologist	Dr Selina Bhattrai Leeds Teaching Hospital NHS Foundation Trust Consultant Urological Pathologist Leeds Teaching Hospital NHS Foundation Trust Level 5, Bexley Wing St James' Institutes of Oncology Leeds, United Kingdom. Email: Selina.Bhattari@nhs.net Phone: +44 (0)796 972 0717
Committees	Trial Steering Committee: Independent members: • Prof Caroline Moore, Professor of Urology, University College London (Chair) – caroline.moore@ucl.ac.uk

	• Dr Tristan Barrett, Consultant Radiologist, University of Cambridge School of Clinical Medicine – tb507@medschl.cam.ac.uk • Ms. Phyllis Goodman, Statistician, Southwest Oncology Group –pgoodman@fredhutch.org • Professor Rakesh Heer, Urology consultant, Newcastle upon Tyne Hospitals NHS Foundation Trust – • Mr Ray Monk, PPI representative – rl.monk@yahoo.co.uk • Prof Matt Sydes, Statistician, University College London – m.sydes@ucl.ac.uk • Mr Jeff Willmot, East Suffolk Prostate Cancer Support Group, PPI representative – jeff.willmot@icloud.com Independent Data Monitoring Committee: • Prof Emma Hall (chair), The Institute of Cancer Research – Emma.Hall@icr.ac.uk cc in tara.thorneycroft@icr.ac.uk • Prof Chris Parker, The Royal Marsden NHS Foundation Trust – chris.parker@icr.ac.uk • Dr Peter Albertsen, UConn Health – albertsen@uchc.edu • Dr Sam Merriel, University of Manchester – samuel.merriel@manchester.ac.uk Trial Management Group: • Prof Jim Catto - Chief Investigator, University of Sheffield • Prof Peter Sasieni – Co-CI, KCL CPTU • Mr. Marcus Cumberbatch – Co-investigator, University of Sheffield. • Roseann Kealy – Trial Manager, KCL CPTU, Roseann.kealy@kcl.ac.uk • Sarah Bottomley – Project Coordinator, University of Sheffield, s.e.bottomley@sheffield.ac.uk • Dr Bernard North – Statistician, KCL CPTU Bernard.north@kcl.ac.uk • Samuel Smith – Associate Professor, University of Leeds, s.smith1@leeds.ac.uk

	• Mr Simon Faulkner, Metro Charity PPI representative, simon.faulkner@metrocharity.org.uk

ii. List of abbreviations

AE	Adverse Event
AR	Adverse Reaction
ADT	Androgen Deprivation Therapy
AS	Active Surveillance
bpMRI	Bi-Parametric Magnetic Resonance Imaging scan.
CA	Competent Authority
CCO	Central Co-ordinating Office
CI	Chief Investigator
CPTU	Cancer Research UK & King's College London Cancer Prevention Trials Unit
CRF/eCRF/pCRF	Case Report Form/electronic CRF/paper CRF
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DGH	District General Hospital
DRE	Digital Rectal Examination
DSUR	Development Safety Update Report
EC	European Commission
ED	Erectile dysfunction
EDC	Electronic Data Capture
EMEA	European Medicines Agency
EoT	End of Trial
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice

HES	Hospital Episode Statistics
HSM	Hub and Spoke Model
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
KCL	King's College London
KCTU	King's Clinical Trials Unit
LATP	Local Anaesthetic Transperineal Prostate Biopsy
LCO	Local Coordinator
LPLV	Last Patient Last Visit
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
mpMRI	Multi-parametric Magnetic Resonance Imaging scan
MS	Member State
NCRAS	National Cancer Registration and Analysis Service
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PET	Positron Emission Tomography
PI	Principal Investigator
PIC	Participant Identification Centre
PIL	Patient Information Leaflet
PIN	Patient Identification Number
PIS	Participant Information Sheet
PSA	Prostate Specific Antigen
PSMA	Prostate Specific Membrane Antigen
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person

RARP	Robot-assisted laparoscopic radical prostatectomy
RCT	Randomised Control Trial
REC	Research Ethics Committee
RT	Radiotherapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SoC	Standard of Care
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
STHNFT	Sheffield Teaching Hospitals NHS Foundations Trust
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Trial Co-ordinator/Monitor
TM	Trial Manager
TMF	Trial Master File
TMG	Trial Management Group
TRUS	Trans-rectal Ultrasound Guided
TSC	Trial Steering Committee
UoS	University of Sheffield
URS	User Requirement Specification
WUCC	Within Usual Care Competence

iii. Trial Summary

Trial Title	**A randomised phase 3 trial evaluating the role of Finasteride at increasing compliance with active surveillance in men with a new diagnosis of low and intermediate risk prostate cancer, when compared with usual care.**
Internal ref. no. (or short title)	FINESSE Study
Clinical Phase	Phase III
Trial Design	Open label, prospective, two arm, randomised CTIMP.
Trial Participants	Men aged 50 to 75 years diagnosed with low/intermediate risk localised prostate cancer in the 6 months preceding their date of randomisation.
Planned Sample Size	550
Treatment duration	2 years
Follow up duration	3 to 5 years dependent upon randomisation date.
Planned Trial Period	6 years; comprising 12 months set-up, 24 months recruitment, 24 months treatment and 3 to 5 yrs. follow-up from the date of randomisation.
Investigational Medicinal Product(s):	Finasteride
Formulation, Dose, Route of Administration:	Finasteride 5mg Tablets, taken orally, once daily.

iv. Hypotheses, aims, objectives and outcomes.

Hypotheses: We hypothesise that the addition of Finasteride to usual care, in men receiving active surveillance for prostate cancer, will increase adherence to surveillance. In turn, this will reduce the rates of radical and palliative treatment. We hypothesise this will occur through reduced PSA values (in absolute terms) and reductions in benign PSA fluctuation.

Aims:

1. To understand whether the addition of finasteride to active surveillance increases adherence in men with low/intermediate risk prostate cancer.

2. To understand the tolerability and compliance with finasteride within an active surveillance regimen.

3. To understand whether the addition of finasteride to active surveillance reduces disease progression in these men.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
Primary Objective: To compare adherence with active surveillance in men with low or intermediate prostate cancer with and without 2 years of finasteride during follow up of between 3 and 5 years from randomisation Adherence is defined as men who have received neither radical nor palliative treatment, and have remained under surveillance, at each timepoint.	• Rate of either radical prostatectomy, radical radiotherapy, brachytherapy or prostate-cancer targeted treatment. • Rate of use of systemic therapies. • Rate of use of androgen deprivation therapy.	All cessation from AS events from participants during follow up of between 3 and 5 years from randomisation, will be included in the first analysis.	Rates in each arm will be measured by patient self-reporting and national clinical registries, e.g., NCRAS. Participants who are lost to follow up, or who die of a cause unrelated to prostate cancer will be taken as censored.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
	• Rate of other treatment for prostate cancer. • Rate of participant death from prostate cancer • Rate of men discontinuing AS for any other reason.		
Secondary Objectives:			
1. To compare between Finasteride with AS and AS alone, the rates of cessation of AS due to initiation of i. ADT and/or chemotherapy ii. Radical Prostatectomy or iii. Radical Radiotherapy	Time until cessation of AS due to initiation of: i. ADT and/or chemotherapy ii. Radical Prostatectomy or iii. Radical Radiotherapy	All occurrences of cessation from AS events due to ADT initiation, chemotherapy, Radical Prostatectomy or iii) Radical Radiotherapy during participant follow-up, 4 years on average, will be included in the analysis. The listed reasons for AS cessation will	

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
		be treated as competing risks. Cumulative incidence plots will be presented with a curve for overall AS cessation and for cessation for the individual post AS treatment.	
2. To measure prostate cancer progression	Progression will be defined by the presence of one or more of the following: • An increase in bpMRI/mpMRI stage from either T2a to ≥T2c, T2b to ≥T2c, or T2x to ≥T3b • An increase in biopsy grade from Gleason 3+3 to ≥3+4 or 3+4 to ≥4+3 • RARP histology revealing either	All progression occurring during the 3-5 follow-up of the study will be recorded and analysed.	

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
	Grade ≥4+3 or stage ≥T3a • PSA progression defined as a ≥25% increase from the highest pre-randomisation PSA value. • Radiological confirmation of metastatic prostate cancer including identification via bone and/or PSMA PET scans. • Clinical record of cancer progression • Clinical record of the initiation of palliative care. • Participant death from prostate cancer • Clinical DRE deterioration * • Extra prostatic disease		

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
	And compared by Kaplan-Meier curves and log-rank tests *DRE results alone will not be considered a definitive endpoint.		
3. To measure prostate cancer mortality.	• Participant death from prostate cancer	All deaths from prostate cancer occurring during the 3-5 years follow-up of the study will be recorded and analysed.	
4. To study the changes in bpMRI/mpMRI appearances of the prostate over time in men with/without finasteride.	bpMRI/mpMRI scan results at baseline, i.e., diagnostic MRI, 12 and 36 months. Please note, a 36-month MRI scan is strongly recommended.	Baseline, 12 and 36 months. Please note, a 36-month MRI scan is strongly recommended.	Specifically, we will record: • Prostate volume: Site radiologists will use callipers on MRI images to take measurements in 3 planes (height, width, length) • Prostate cancer stage – This will be done using

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
			the Prostate Imaging Reporting and Data System (PI-RADS, version 2) and TNM (Tumour, Nodes, Metastasis staging system). • Prostate cancer size: This will be taken as a single measurement of maximum diameter on an axial slice from the MRI acquisitions. • Prostate vasculature will not be assessed. 100% of the bpMRI/mpMRI images will be quality controlled centrally by the Lead radiologist, and any discrepancies will be discussed with the local radiology team. Full details can be found in the FINESSE Radiology Manual.
5. To understand the views of patients and healthcare professionals regarding the use of finasteride within active surveillance for this disease.	Semi-structured one to one interviews led by a trained interviewer, with selected individuals during the follow-up phase, (months 48-60 inclusive).	Months 48 to 60 inclusive.	

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
6. To measure the rate of intervention for symptoms related to benign prostate enlargement (defined as the use of oral medication (such as alpha blocker, PDE5 inhibitor or anti-cholinergic) or endoscopic prostate surgery (such as TURP, Urolift, Green light laser TURP, steam treatment, HOLEP or other).	Patient self-reporting and national registries.	All symptoms during the follow up of between 3 and 5 years until trial end.	This will be determined by a new prescription for an oral medication (such as alpha blocker, PDE5 inhibitor or anti-cholinergic) or the participant undergoing a prostate surgery for benign enlargement. (such as TURP, Urolift, Green light laser TURP, steam treatment, HOLEP or other).
7. Overall (all-cause) mortality.	• Death eCRF completed by sites • Registries	All deaths during the follow up of between 3 and 5 years until trial end.	Cause of death will be decided by note review (and CRF completion) and death certificates.
Explanatory Objectives:			
1. To compare QOL in men with and without finasteride in AS regimens	The results of the following questionnaires completed at baseline 3, 6, 12, 18, 24, 36, 48 and 60 months will be summarised by counts of each level for the individual dimensions or subscales and	QOL questionnaires completed at baseline, 3, 6, 12, 18, 24, 36, 48 and 60 months will be assessed.	**a) EQ5D5L questionnaire** A 25-item, self-assessed, health related quality of life questionnaire. The scale measures quality of life on a 5-

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
	compared between Finasteride and AS alone. a. EQ-5D-5L b. EORCT QLQ 30 c. EPIC d. EORTC QLQ FA12 e. Memorial Anxiety Scale PC f. DASS 21		component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. **b) European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30** A 30-item, patient report tool to assess health-related quality of life in cancer patients. 24 items make up nine multi-item scales; containing five functioning subscales; (physical, role, cognitive, emotional, and social), three symptoms' subscales (fatigue, pain and nausea/vomiting), and one global health status scale. The other six single items assess symptoms. **c) Expanded Prostate Cancer Index Composite (EPIC)** The Expanded prostate cancer Index Composite (EPIC) is a

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
			comprehensive instrument designed to evaluate patient function and bother after prostate cancer treatment. It contains 32 items assessing urinary function, bowel habits, sexual function, hormonal function, and overall satisfaction with treatment. **d) European Organisation for Research and Treatment of Cancer (EORTC) QLQ FA12** A 12-item, patient report tool to assess fatigue in cancer patients. **e) Memorial Anxiety Scale Prostate Cancer** A 18-item questionnaire designed to provide a brief method for detecting anxiety in men with prostate cancer. It can be used to calculate an overall score, but includes three subscales assessing prostate

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
			cancer anxiety, PSA anxiety and fear of recurrence. **f) Depression Anxiety Stress Scales (DASS)-21** A 21-item self-report measure of negative emotional states. It contains three subscales; depression, anxiety and stress, all of which consist of 7 items each.
2. To monitor adherence to finasteride treatment in men on AS, and to identify factors affecting adherence.	• Adherence to treatment: ○ Voils' DOSE Non-adherence measure-Extent scale. ○ Pill count	• Voils' DOSE Non-adherence measure-Extent scale to be completed at the 3, 6, 9, 12, 15, 18, 21 & 24 months timepoints. Tablet returns at the 3, 6, 9, 12,	• **Voils DOSE-Non-adherence measure-Extent Scale :** A 3-item patient report scale to assess the extent of nonadherence. Responses are measured on a 5-component scale. An additional 15 items are included in a sub-scale to ascertain the reasons for non-adherence.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
		15, 18, 21 & 24 mths clinic visits will be tabulated.	• **Pill count:** An assessment of the number of finasteride pills remaining at designated appointments will enable a calculation of the proportion of days covered, an indicator of adherence to finasteride.
3. To compare satisfaction and quality of decision-making in men with and without finasteride in AS regimens.	• Decision-making quality: a. Decisional Conflict Scale b. Subjective decision quality scale c. Decisional regret scale d. Decisional involvement	Decision making questionnaires completed at baseline, 12, 24, 36, 48 and 60 months will be assessed.	**a) Decisional conflict scale** A 16-item scale that measures perceptions of uncertainty in choosing options, modifiable factors contributing to uncertainty, and affective decision making. **b) Subjective decision quality** A 6-item scale that measures perceptions of the quality of decision-making. It comprises items for access to information, time, involvement, regret,

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
			satisfaction, and the perceived appropriateness of the decision for the individual. **c) Decisional regret** A 5-item scale that measures distress or remorse after a healthcare decision. **d) Decisional involvement** A single-item measure that assesses the extent to which the individual perceives their views were considered when discussing their treatment.
4. To measure side effects of finasteride within AS regimen.	• Assessment of the side effect rate, via Finasteride AE reporting and patient self-reporting.	All adverse events occurring during the 3-5 years follow-up of the study will be counted and tabulated.	The quality-of-life assessments cover a wide-range of generic and specific patient reported outcomes relevant to this population. Trial case report forms (CRFs) will specifically question common side effects such as: decreased sex drive, trouble getting or keeping an erection, ejaculation disorder,

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
			increase in breast size and tenderness and skin rash.

v. Funding and support in kind

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Yorkshire Cancer Research (Registered Charity: 516898). Jacob Smith House, 7 Grove Park Court, Harrogate HG1 4DP	Primary funders (Research costs part A)
National Institute for Health Research (NIHR)	Service support costs, Research costs (Part B)
NHS Commissioners	Excess treatment costs

vi. Role of trial Sponsor and funder

The Sheffield Teaching Hospitals NHS Foundations Trust (STHNFT) will act as sponsor for this Trial. Whilst they will retain overall responsibility for the study in line with signed collaboration agreement, certain activities will be delegated to the Cancer Research UK & King's College London Cancer Prevention Trials Unit (CPTU). These will be defined in the Log of Duties Delegation document, agreed and signed by all relevant parties. Access to data and Intellectual Property Rights will be governed by the Yorkshire Cancer Research (YCR) grant conditions.

The YCR will act as funder and collaborative working partner with the University of Sheffield, (project grant holders), for delivery of this project.

The CPTU will be responsible for trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results on behalf of the Sponsors.

vii. Roles and responsibilities of trial management committees/groups and individuals.

Trial management committees

An **Independent Data Monitoring Committee** (IDMC) will review the trial data and advise the sponsor (directly or indirectly) on the future management of the trial. It will comprise at least one independent statistician, and one independent clinician.

The IDMC will review quality and compliance data, as well as safety and efficacy. They will be privy to interim comparisons by arm and see data in a format that will not be shared beyond its independent members.

The IDMC will meet once before the trial starts and at appropriate intervals as determined by the committee, but at least six monthly.

The committee will review the data within the reports produced by the Independent Trial Statistician at the CPTU. They will advise the Trial Steering Committee (TSC) and the discontinuation of any research arm, temporary cessation or early closure of the trial as deemed necessary will be at the discretion of the Sponsor and TSC.

A **Trial Steering Committee** (TSC) will be set up to provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder, and to ensure that the trial is conducted to the rigorous standards set out in the Guidelines for Good Clinical Practice. The TSC will concentrate on trial progress, adherence to the protocol, patient welfare, and consider new information of relevance to the research question. The TSC will relay advice from the IDMC, through its chair, to the Chief Investigator (CI), Trial Sponsor, Trial Funder, and any relevant contractor(s) on all appropriate aspects of the trial. Membership of the TSC will include an independent Chair, at least two other independent members and one patient representative. Representatives of the Trial Sponsor and the Trial Funder will also be invited to all TSC meetings. The final decision regarding whether or not the trial may continue is the responsibility of the TSC.

A **Trial Management Group** (TMG) will be formed to oversee the progress of the trial and act on the decisions of the TSC. It will include amongst its members the lead investigators (clinical and non-clinical), trial co-ordinators, staff from the CPTU and at least one patient representative. The TMG will be responsible for the day-to-day running and management of the trial.

An Independent Progression Review Panel will be established. Ideally this will consist of three members, ideally urologists, who will be responsible for evaluating the relevant pseudo-anonymised patient information, (PSA values, MRI scans, biopsy pathology), for all patients who have 'progressed'. The committee will decide whether progression has occurred or not, and their decision will be communicated as advice to the local sites by a member of the FINESSE central coordinating office (CCO) within CPTU. Ultimately, the treating clinician makes the treatment decision with the participant. However, it will mean we are able to determine if there has been any selection bias in either arm, in favour of, or against the intervention at the point of analysis.

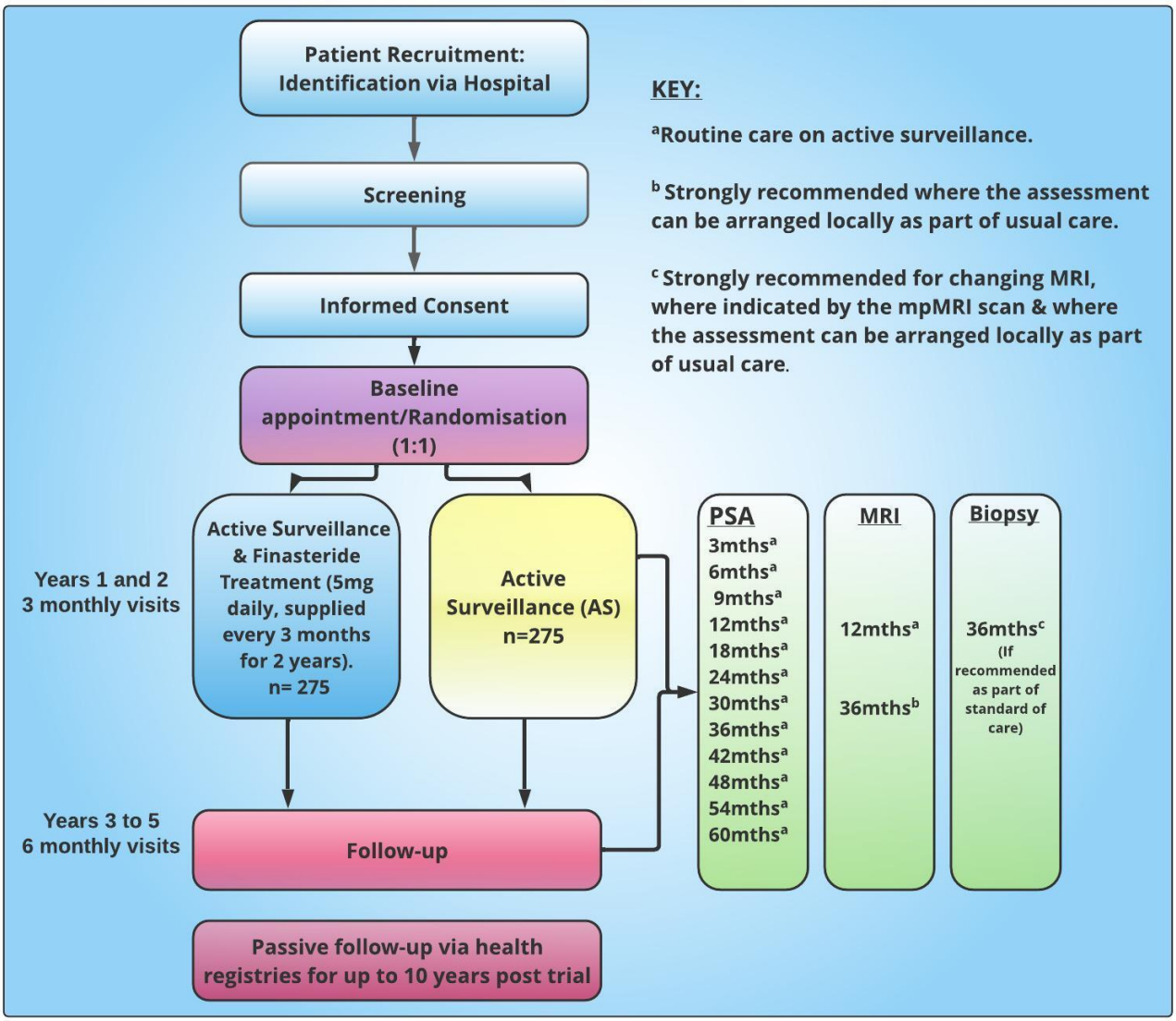
viii. Protocol contributors

A range of stakeholders have contributed to the development of this protocol including academic and research management staff at The University of Sheffield (UoS), STHNFT, KCL Cancer Prevention Group, CPTU team members, research delivery and management staff at the National Institute of Health Research, and the charity YCR. Protocol design has taken account of the view of patients and the public via several rounds of reviews, focus groups and one to one interviews.

ix. Key words

Prostate Cancer, Active Surveillance, Finasteride, Secondary care, Disease Progression, Radical Treatment, bpMRI/mpMRI and Biopsy.

x. Flow chart of the overview of the FINESSE study.



xi. Protocol surveillance (patients may be randomised up to 24 months after diagnosis)

Regimen:

Year 1: PSA 3 monthly. MRI at 12 months

Year 2-3: PSA 6 monthly. A year 3 bpMRI/mpMRI scan and subsequent prostate biopsy where indicated by the mpMRI scan, are strongly recommended where the assessment(s) can be arranged locally, as part of usual care.

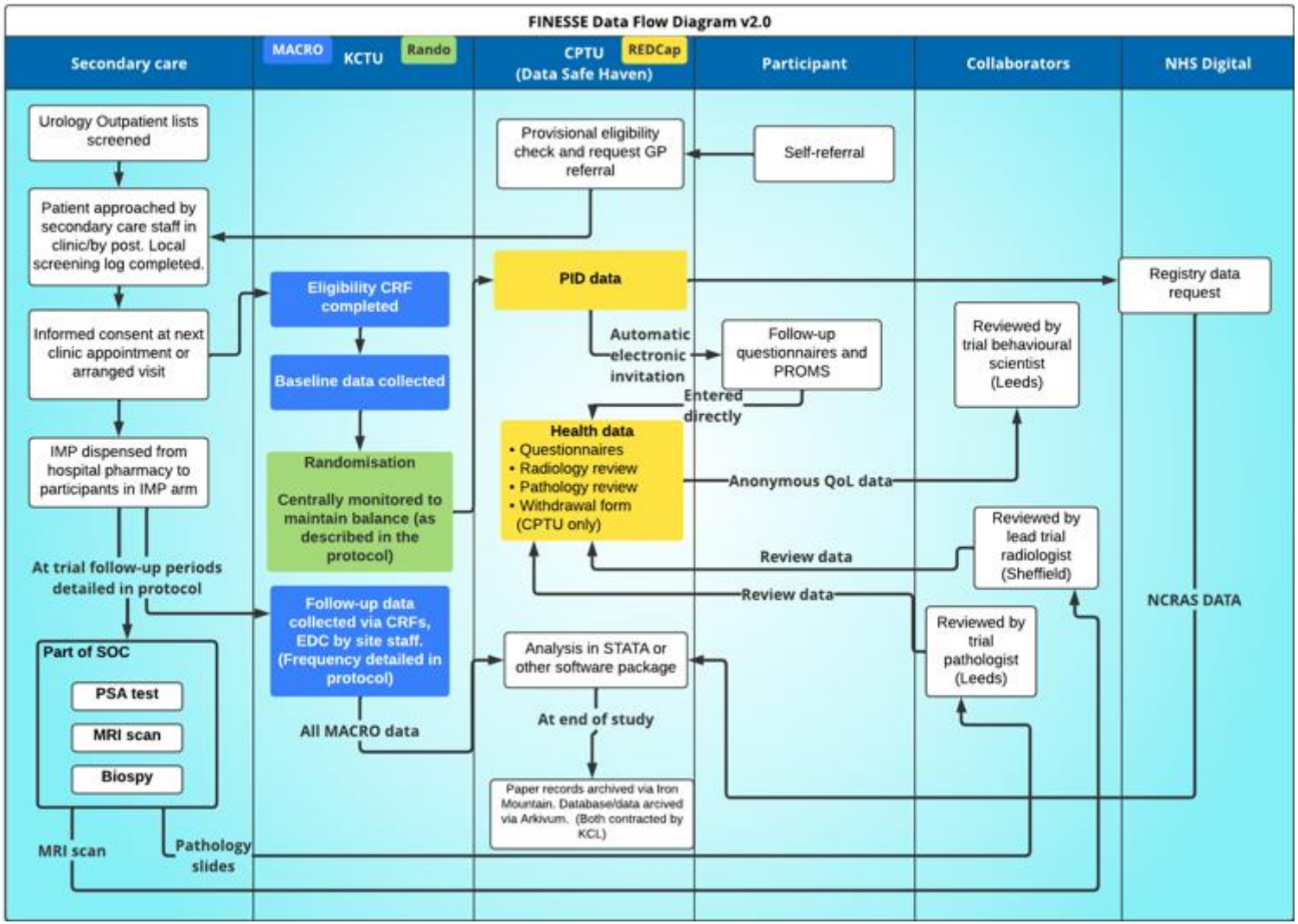
Year 4 onwards: PSA 6 monthly

Off protocol MRI for rapidly rising PSA or changes in DRE strongly recommended where the assessment can be arranged locally, as part of usual care.

Off protocol biopsy for changing MRI where indicated by the bpMRI/mpMRI scan, are strongly recommended where the assessment(s) can be arranged locally, as part of usual care.

	Protocol	Routine care
PSA	Years: 1: 3-monthly; up to 2 PSA tests will be research costs as patients may be in year 2 of their AS protocol 2 to 5: 6-monthly	1: 3 to 4-monthly 2-5: 6-monthly
MRI	Years: 1 +/-6M 3 +/-6M. Strongly recommended where the assessment(s) can be arranged locally, as part of usual care.	1: 12 to 18 months from diagnosis 3: N/A
Biopsy	Year 3: Transperineal biopsy strongly recommended where indicated by the bpMRI/mpMRI scan, and can be arranged locally, as part of usual care.	N/A

xii. FINESSE Data Flow Diagram and the EDC System Defined.



Three systems will be used to collect data for the FINESSE trial.

1) **The randomisation system:** used to randomise participants and allocate a PIN.
2) **The FINESSE EDC,** (also referred to as simply the EDC within the protocol): a web-based EDC system designed, using the InferMed Macro 4 system for the collection of trial eCRFs.
3) **REDCap:** used to collect patient identifiable data, participant surveys, and PROMs data.

   A library of study documents will also be available within REDCap. It is here that site staff will access blank SAE Report CRFS.

NB: 1) and 2) will be used by site staff and FINESSE CCO personnel only. 3) will be used by site staff, FINESSE CCO personnel AND FINESSE participants. Please see section 10, Data Management, for full details.

1 BACKGROUND

1.1. Prostate cancer

Prostate cancer is the commonest male malignancy in the western world, and the commonest cause of male cancer deaths in the UK in 2016 [1] , it accounted for 1 in 4 cancers in British men. Prostate Specific Antigen (PSA) screening of asymptomatic men has been used in an attempt to reduce mortality from the disease. However, most men diagnosed through PSA testing have clinically localised disease and may not benefit from treatment (as their cancers may be either indolent with a long natural history or metastatic at diagnosis[2]. The detection and radical treatment of prostate cancer that would not impact the patient during their lifetime represents overdiagnosis and overtreatment, respectively [3]. One solution to overtreatment is the use of active surveillance (AS)[4]. This strategy selects men with indolent appearing cancers and monitors tumour growth without radical treatment. Subsequently, radical treatment is reserved for men whose tumours progress biochemically, clinically, or radiologically.

In men with low-risk prostate cancer undergoing AS, the risk of prostate cancer specific mortality is small and lower than that from other diseases (e.g., 0.3% at 8 years [5]). AS is popular amongst men with localised prostate cancer [6, 7] and recommended by NICE [https://www.nice.org.uk/guidance/ng131]. However, there are concerns regarding the accuracy of prostate cancer risk stratification and the reliability of monitoring tools [4,[8-10]. Clinicians and patients fear that deferring radical treatment could reduce the chance of cure and lead to higher morbidity [3, 10, 11]].

Between 50-70% of men starting AS will receive either radical or palliative treatment over the following 10 years [[12-14]]. In most men, radical treatment is initiated due to either a rising PSA or changes in Gleason grade on biopsy. Both are surrogate measures for disease progression. Many men are reluctant to undergo multiple biopsies, and so most AS programmes are heavily reliant on PSA kinetics. For example, 25% of men in the Gothenberg screening trial [14] and 43% of men in Toronto who started AS received radical treatment due to a rising PSA alone [4]. PSA values reflect benign enlargement and inflammation within the prostate [13], as well as cancer growth. So many men with rising PSA values may not have disease progression and therefore may not need radical treatment. In another example, 65% of men within the PRIAS study [13] and 72% in a large US series [15] had favourable histology at Radical Prostatectomy after a period of AS. Within the ProtecT RCT, 50% of men randomised to monitoring received radical treatment with a <2% mortality rate at ten years [12].

Various approaches have been tried, of which pharmacological attenuation of PSA kinetics appears promising. The REDEEM study randomised 302 men with low-risk prostate cancer to 0.5mg daily Dutasteride or placebo [16]. At 3 years, the Dutasteride group had 10% fewer men with disease progression (defined as increasing cancer burden on biopsy or undergoing radical treatment). REDEEM recruited men with low-risk prostate cancer with very low risks of cancer progression.

1.2. Contemporary Prostate cancer

bpMRI/mpMRI as a diagnostic tool for prostate cancer is changing the spectrum of cancers seen in the UK [17, 18]. Many men with small, low risk prostate cancers are no longer diagnosed (by either not having a biopsy or avoiding random prostate sampling) [19, 20]. For example, within the PRECISION trial, 38% of men with bpMRI/mpMRI guided biopsy (versus 24% in USS guided-biopsies) had Gleason

3+4 prostate cancer [17, 18]. an der Leest et al. found bpMRI/mpMRI guided biopsy reduced the rate of insignificant prostate cancer diagnosis from 25% to 14% [19]. As such, contemporary UK practice includes a higher proportion of men with intermediate risk prostate cancer than in the pre-bpMRI/mpMRI era. Therefore, the focus to improve the care of men with prostate cancer is shifting to using AS in men with intermediate risk prostate cancer[21-26] . This population is common and includes a number of men with lethal cancer [5]. Thus, AS regimens need to combine safety with tolerability and adherence. Improving AS was the highest research priority selected in the recent NICE guidelines for prostate cancer management [Question #1: What is the most suitable surveillance protocol? https://www.nice.org.uk/guidance/ng131].

Given the high proportion of men still unnecessarily experiencing the harms associated with prostate cancer therapy, and the positive signals from the REDEEM trial, this study aims to address the NICE identified need to improve AS. In particular, we aim to test if the drug Finasteride can increase the adherence of men to surveillance programmes and reduce radical treatment rates. Many men opt for treatment because of their rising PSA levels, which usually reflects non-cancerous enlargement of the prostate, rather than progressive/advancing cancer.

1.3. Finasteride

Finasteride is a 5 alpha reductase inhibitor that stops/slows the metabolism of testosterone to its more active metabolite; dihydrotestosterone. In clinical trials, Finasteride has been shown to slow prostate growth and reduce serum PSA levels [27].

In general, Finasteride is well tolerated with few side effects[28]. The most important side effect, is related to Quality of Life. It is impact on sexual desire and sexual function. For example, a review suggests between 2.1% and 3.8% of men receiving finasteride complain of erectile dysfunction (ED), ejaculatory dysfunction and loss of libido[29]

In the FINESSE trial, 550 men with newly diagnosed low/intermediate risk localised prostate cancer will be randomised to AS with finasteride, or usual care. Patients will receive finasteride for 2 years and will be followed up for an average of 4 years. Active surveillance will include PSA, re-biopsy and bpMRI/mpMRI as per usual NHS care, (PSA testing: 3 monthly in year 1, and 6 monthly in years 2/3, and bpMRI/mpMRI scanning 12 to 18 months from diagnosis). A year 3 bpMRI/mpMRI scan and subsequent prostate biopsy where indicated by the bpMRI/mpMRI scan, are strongly recommended where the assessment(s) can be arranged locally, as part of usual care.

The primary outcome is adherence with active surveillance in both arms. It is predicted that finasteride will reduce the number of men receiving radical treatment from 20% to 10% at 4 years.

2. RATIONALE

Prostate cancer is the most common cancer in men in the UK and now accounts for more deaths than breast cancer [1]. Improvements in survival can be made through the use of PSA screening. However, screening dramatically increases the rate of over-diagnosis, over-treatment and harm to some men. This offsets any survival benefits and so screening has not been introduced in most countries. active surveillance (AS) offers a solution to over-treatment. Most men diagnosed with localised prostate cancer are suitable for AS. However, current AS regimens are ineffective at preventing men from receiving radical treatment. More than 50% of men receive radical treatment, and as a result are exposed to the risks of radical therapy toxicity including urinary and bowel dysfunction together with

sexual dysfunction. One of the commonest reasons for radical treatment is concern over a rising PSA. For example, 25% of men in the Gothenberg screening trial [14]and 43% of men in Toronto who started AS received radical treatment due to a rising PSA alone [4]

The identification of well tolerated adjuvant therapy that may potentially modify a man's risk of prostate cancer progression while on active surveillance could enable durable surveillance programmes. If such a therapy was found to reduce progression, it is likely that more men would choose active surveillance as a treatment option rather than opting for radical therapy at the outset. Furthermore, it may prevent men from subsequently requiring radical therapy due to disease progression while on active surveillance. This would reduce the harm to men diagnosed with localised prostate cancer, allow PSA based screening to continue and reduce the cost of managing this cancer.

Evidence from clinical studies on therapies that may modify a man's risk of either being diagnosed with prostate cancer or developing clinically significant prostate cancer while on active surveillance are largely lacking. This is in part due to the huge cost of performing chemoprevention studies, needing to expose large populations of healthy men to the agent and then subsequently following them up for many years. To date there have been only three studies on prostate cancer chemoprevention in those without a previous diagnosis of prostate cancer, whilst there are two studies in men on active surveillance.

The SELECT trial evaluated selenium and vitamin E supplementation in 35,000 men.[27, 28] The study identified that, after 7 years of follow-up, disease rates were higher in men taking the supplements, but none were statistically significant. The study was stopped prematurely for futility. Two other large-scale chemoprevention trials have been performed (Prostate Cancer Prevention Trial [29] and the REDUCE trial)[30]. Both reported 5-alpha reductase inhibitors reduced prostate cancer risk in the treatment arms.

As mentioned previously, the REDEEM trial [16] Is the only known study to evaluate a chemopreventive agent in men with low to intermediate risk prostate cancer on surveillance. Fleishner and colleagues randomised 302 men to either placebo or dutasteride, a 5-alpha reductase inhibitor. At 3 years, 38% of men had progressed in the dutasteride arm, while 48% of men progressed in the placebo arm, a difference which was statistically significant. However, many have questioned the primary endpoint of the REDEEM trial that was histological progression of prostate cancer on repeat prostate biopsy and/or therapeutic progression, defined as the clinical decision to proceed to radical therapy.

Finally, the PROVENT trial, (Cuzick et al, currently in submission), tested the feasibility of a randomised controlled trial to examine the clinical effectiveness of aspirin and/or Vitamin D3 to prevent disease progression in men on active surveillance for low to intermediate risk prostate cancer. However, whilst the trial demonstrated that men were keen to join the trial thereby potentially supplementing their AS with an IMP, the sample size was insufficient to assess efficacy.

In the FINESSE study we aim to compare adherence with active surveillance in men receiving standard care alone (AS only), or AS with 2 years of finasteride treatment. The active surveillance only arm will be the control arm. This agent was chosen since it has been demonstrated to slow prostate growth and reduce both PSA levels and a man's risk of developing prostate cancer [31]. Furthermore, the drug has few side-effects.

2.1 Assessment and management of risk

This trial has been determined as Type A on the basis of MHRA risk adaptation guidance since there is extensive clinical experience with the product, and no reason to suspect a different safety profile in this trial population. Please see Appendix 1 for a full justification and risk details.

Up to half of men with low to intermediate risk prostate cancer entered into an active surveillance programme experience prostate cancer progression within three to five years of diagnosis. Disease progression often results in the recommendation that the patient undergo radical therapy with its associated toxicity. Furthermore, historic data demonstrate that between 40 - 60% of men with low to intermediate risk prostate cancer in the UK have received radical therapy for their disease. Many of these men will have chosen radical therapy due to the possibility of prostate cancer progression on active surveillance.

The standard of care for men entering an active surveillance programme is careful disease monitoring, including serial serum PSA analysis and repeat prostate biopsies, together with repeat prostate imaging. In the FINESSE study we aim to compare adherence with active surveillance in men receiving standard care alone, or active surveillance with 2 years of 5mg daily finasteride treatment. This is the dose currently used to treat a benign enlarged prostate. Although finasteride has known side effects, (see section 1.3) it is generally well tolerated. As such, we believe that for men on surveillance, the benefits of taking this agent to potentially prevent unnecessary radical treatment and prostate cancer progression would outweigh the side effects caused by the medication.

The Quality Assurance (QA) and Quality Control (QC) considerations for FINESSE have been based on a formal risk assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This risk assessment has been reviewed by the CPTU QA Manager CTU and CI.

3. TRIAL DESIGN

FINESSE is a multicentre, open label, prospective, two-armed randomised controlled CTIMP, to test the superiority of finasteride and active surveillance over active surveillance alone, in men with newly diagnosed low/intermediate risk localised prostate cancer.

We will randomise (1:1), 550 patients to active surveillance with or without once daily finasteride, (5mg). Eligible participants will receive finasteride for 2 years and will be followed up for an average of 4 years. Active surveillance will include PSA, re-biopsy and bpMRI/mpMRI as per usual NHS care. In addition, a year 3 bpMRI/mpMRI scan and subsequent prostate biopsy where indicated by the bpMRI/mpMRI scan, are strongly recommended where the assessment(s) can be arranged locally, as part of usual care.

The primary outcome is adherence with active surveillance in both arms.

There are no placebo treatments for the following reasons:

- The PSA levels in men treated with finasteride will almost halve. Since it is necessary to monitor PSA (for AS) this would unblind both arms unless clinicians and participants were blinded to the PSA results.
- Blinding PSA data would be impractical, since men may actively seek PSA tests outside the study.
- It is ethical that control participants experiencing any side effects, e.g., erectile dysfunction, ejaculatory problems, or a rash, know they are independent of the treatment.
- Participants unaware they are taking finasteride may opt for radical treatment earlier. This is a pragmatic trial designed to see whether knowing that they are being treated and that the treatment is having a positive impact on PSA levels would reassure men and enable them to continue with active surveillance for longer, rather than seeking radical treatment even though their disease may not have progressed.
- The prohibitive costs and logistics associated with placebo-controlled trials

4. TRIAL SETTING and SET-UP

Summary

- FINESSE is a multi-centre prospective randomised non-placebo-controlled trial
- The study will recruit from NHS hospitals. Most patients will be recruited from cancer centres and surrounding district general hospitals (DGHs) may be used as Participant Identification Centres (PICs) for their neighbouring cancer centre, and / or to conduct standard of care procedures (SoC), and those within usual care competence (WUCC), for the FINESSE trial. DGHs may either act as 'spoke' trial sites to a main hospital's 'hub' investigator site or become investigator sites in their own right. See in Appendix 2 for a full list of planned participating centres and potential PIC/spoke sites. See Appendix 3 for a diagram explaining the 'Hub and Spoke' model (HSM).
- The HSM is possible due to the guidance for setting up interventional trials and working with sites in unconventional ways released by the HRA in 2021. The guidance allows for reduced investigator oversight of some or all activity, and for the inclusion of locations performing some trial activity, without the need to act as formal investigator sites.
- Under the HSM arrangement, activities that require only some level of PI oversight are undertaken at a spoke site which does not employ (substantively or via honorary contract) the PI, under the delegation of a PI employed at the hub site. In such a circumstance, the spoke site being overseen from a distance is part of the hub site, as oversight of the activities is still required from a PI. The spoke site does not have its own PI. A PI may oversee several spoke sites without being based in any of those locations. [IRAS Help - Preparing & submitting applications - Interventional Research (myresearchproject.org.uk)]

- A centre eligibility is defined as having:
  - A Urological surgeon as site PI
  - Sufficient Research support

  - Ability to offer both active surveillance and provide in-house, or work within a network that can provide radical/advanced prostate cancer treatment
  - Availability of bpMRI/mpMRI prostate and biopsy (TRUS or transperineal)
- Participants will be recruited from Urology Outpatient Clinics, reviews of suitable patients lists or other local approaches, once they have decided upon active surveillance, or are already undergoing active surveillance.
- Participants identified at PICs and / or spoke sites will be recruited at the hub investigator site, and therefore considered as the hub's recruitment numbers, even if further trial activity continues at the spoke site, as per the model.

4.1 Trial set up

The trial has been adopted onto the NIHR portfolio and will therefore have network support for identifying and setting up study sites. Since the trial is funded by Yorkshire Cancer Research, a charity whose remit is to fund research which will save lives in Yorkshire, the Yorkshire and Humber LCRN will assist and the main sites will be established within the Yorkshire region. However non-Yorkshire centres will be included to expedite recruitment. It is anticipated 2 to 8 sites will be required to reach target accrual within the allocated two-year randomisation period.

Site set up will be staggered, with additional sites being opened one month after the principal site. This will provide the opportunity to identify any initial problems before wider launch of the study.

Trial Site Selection, Initiation and Activation will be conducted in line with CPTU SOPs.

The study Trial Manager and/or Trial Coordinator/Monitor (TC) will perform the Site Initiating Visits; full details regarding procedures and schedules can be found in the FINESSE Monitoring Plan.

Before sites are given the green light to begin recruitment, the following will be required by the trial team from sites prior to opening to recruitment:

- Confirmation of capability and capacity
- Organisation information document or signed model Non-Commercial Agreement
- Updated delegation log
- Signed CVs and GCP certificates of site staff listed on the delegation log
- Source data agreement, listing all source document locations, signed off by the PI
- Study documents such as the Patient Information Sheet (PIS), Patient Information Leaflet (PIL), Informed Consent Form (ICF), GP Information sheet etc. localised for the site and copies collected for filing in the TMF.
- Completed training log
- Completed checklists confirming that all essential documents are filed in the ISF and PSF.
- EDC, randomisation system and REDCap access confirmed, and local user account holder requirements identified and authorised.

- Confirmation that pharmacy is ready for the trial to start e.g., sufficient IMP stock held, any local changes to the IMP labels, prescriptions, accountability logs, checked and approved by the Sponsor.

The trial will not be allowed to commence at the site until all necessary approvals have been granted, all essential documentation is present in the ISF, and the IMP management and accountability procedures have been confirmed and approved by the site pharmacy representative.

DGHs will be used on a case-by-case basis, as and when required, for example, if an NHS cancer centre is having recruitment difficulties, which alternative strategies have been unable to address.

4.2 Active recruitment

4.2.1 Secondary care recruitment:

A total of 550 men will be recruited over 24 months. Participants will be recruited from urological clinics within Leeds, Sheffield, Oxford, Wakefield, and Bradford and referring District General Hospitals A full list of planned participating centres and potential PICs/spoke sites is in Appendix 2.

Using prior trial recruitment data and eligible patient estimates was projected that the 25% recruitment target will be reached within 12 months and 100% within 24 months. However, since opening to recruitment, we have experienced slower-than-anticipated recruitment rates. Sheffield Teaching Hospital, for example, has recruited an average of 2 participants per month, where the reported expected rate at feasibility assessment was 5-10 per month. This is predominantly because fewer than expected numbers of low-intermediate grade disease are being referred from local District General Hospitals (DGHs).

The introduction of the ‘hub and spoke' (H&S) model, will allow us to access the low/intermediate risk patients whose active surveillance care is being delivered by DGHs. In addition, we have amended the eligibility criteria, extending the time since diagnosis, to increase the pool of potentially eligible participants.

The TMG will continue to monitor recruitment in real time and will recommend further action if slower than expected.

PPI representatives and behavioural scientists will be involved from the outset to tailor patient facing literature and to facilitate effective recruitment.

4.3 Follow-up

Note re: Hub & Spoke Sites - Post randomisation standard of care activities (PSA, bpMRI/mpMRI and diagnostic biopsy), will be conducted at either the hub or spoke depending upon the patient’s decision to continue their active surveillance at spoke sites, or transfer to the hub sites. Post randomisation research follow-up will be delivered by the hub site either remotely or in person, depending on the participant’s willingness to travel.

4.3.1 Clinical follow up

Follow up is shown in appendix 4. According to the schedule, patients will be reviewed by a member of the clinical team (doctor or specialist nurse according to local usual practice). According to schedule they will receive a serum PSA, symptom review and rectal examination (according to local practice).

A repeat bpMRI/mpMRI scan will be performed at 12months (+/- 6mths) from the date of the diagnostic bpMRI/mpMRI scan. Biopsy may be offered if the bpMRI/mpMRI suggests disease progression.

A 36mth (+/-6mths from the date of randomisation) bpMRI/mpMRI scan is strongly recommended, where the assessment can be arranged locally, as part of usual care. Biopsy may be offered if the bpMRI/mpMRI suggests disease progression and the assessment can be arranged locally as part of usual care.

Concern around PSA kinetics or clinical examination (DRE) may prompt clinical review and either a repeat PSA (at a suitable interval) or an additional bpMRI/mpMRI scan. Biopsy may be performed if the bpMRI/mpMRI suggests disease progression.

4.3.2 Pharmacological follow up

Participants randomised to the finasteride arm, will receive finasteride for 2 years, and all pharmacovigilance reporting will continue until the LPLV. However, where a participant withdraws from both IMP treatment and follow-up prematurely, the LCO is responsible for checking their AE status at least 30 days after the date the participant states they have stopped their IMP dose. This may be done via a telephone call.

Individual participant clinical follow-up length will depend on the point at which they are enrolled and will range from 3 to 5 years.

4.3.3 Passive long term follow up

On joining the trial, participants consent to long term follow-up (up to 10 years post recruitment), and to the FINESSE CCO receiving relevant healthcare data. They will have cancer stage/progression confirmed via NCRAS and HES data registries. This is detailed on the Patient information sheet (PIS).

5 PARTICIPANT ELIGIBILITY CRITERIA

5.1 Population and Recruitment:

Eligible men aged 50 – 75 years with low or intermediate risk prostate cancer diagnosed within the last 6 months will be invited to join the trial. Men must give informed consent and be willing to take part in the study. Although the trial is being funded by Yorkshire Cancer Research, participants will be recruited from urological centres within and beyond Yorkshire.

Low risk cancers are those defined in the PRIAS study [https://www.prias-project.org] namely: Gleason 6 (grade group 1), cT1c-T2, PSA ≤10ng/ml, PSA Density ≤0.2ng/ml, and any bpMRI/mpMRI biopsy features or blinded/saturation biopsies with <15% cores involved.

Intermediate risk cancers are defined by the presence of either Gleason 4 components (≤3+4) (grade groups 1 and 2), cT2b on bpMRI/mpMRI, PSA ≥ 10ng/ml or the presence of ≥ 5mm cancer on biopsy [27].

In 2016, there were 3,642 men diagnosed with prostate cancer in Yorkshire [Yorkshire Cancer Research own data]. The 2018 National Prostatectomy Cancer Audit reported 60% of new diagnosis had localised (stage T1 or T2) cancer (60% of 3,642 = 2,185 men) [https://www.npca.org.uk/]. In the ProtecT RCT (using PSA screening), most men with localised disease were low or intermediate risk (T1-T2 and Gleason 3+3 (77%)/3+4 (15%)) [12]. Thus, it is estimated 90% of 2,185 are suitable for this improved pathway (i.e., 1,966 men in Yorkshire per annum).

Study eligibility must always be confirmed by a medical practitioner designated the responsibility on the trial delegation log. This must be prior to randomisation, and fully documented in the participant's medical notes.

This study aims to randomise 550 men who have opted for active surveillance as their preferred prostate cancer therapy. Participants must fulfil all of the inclusion criteria and none of the exclusion criteria. All patients who meet the eligibility criteria and are randomised will be included in the intention to treat (ITT) analysis. 225 men will be randomised into each of the two study arms (1:1).

Please note, whilst the terms 'men' and 'male' are used throughout the protocol, the trial is open to anyone with prostate cancer regardless of gender (including transgender /non-binary persons), providing they satisfy the inclusion and exclusion criteria).

5.1.2 Inclusion criteria

1) Male participants:
   a) Aged 50 to 75 years
   b) With an estimated life expectancy of 10 years or more
   c) Who have opted for Active Surveillance as their preferred prostate cancer therapy.

2) Willing and able to provide written informed consent or if appropriate, have an acceptable individual capable of giving consent on their behalf

3) Fit enough and suitable for radical treatment

4) Eastern Oncology Performance (ECOG) status ≤ 1 (See figure one below)

5) Histopathological diagnosis of low or intermediate risk adenocarcinoma of the prostate in the last 24 months (from the date of histology to the date of the patient's randomisation)

6) Gleason grade group ≤ 2 (i.e. Gleason grade ≤ 3+4=7)

7) Radiological stage ≤T2c cN0 cM0 as defined by bpMRI/mpMRI imaging within the last 12 months (from the date of the bpMRI/mpMRI scan to the date of the patient's randomisation). A copy of the bpMRI/mpMRI scan, and report confirming eligibility will be required. In this study, MX will be treated as M0, and NX will be treated as N0.

8) PSA ≤20ng/ml. The result must be within 3 months of the date of the patient's randomisation.

9) PSA Density ≤0.2 ng/ml. The result must be within 3 months of the date of the patient's randomisation
10) Biopsy criteria (route can be trans-rectal or trans-perineal, but must have been within the last 24 months of the patient's randomisation date) **Regardless of biopsy strategy**:
    - Maximum cancer core length is ≤ 10mm
    - ≤3cores involved with cancer.

Figure One: Eastern Cooperative Oncology Group (ECOG) performance status

Performance status	Definition
0	Fully active; no performance restrictions.
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work.
2	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair >50% of waking hours.
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

Adapted from: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649.

5.1.3 Exclusion criteria

Ineligible men will be:

1) Those who have previously received treatment for prostate cancer (including radiotherapy, hormone therapy, brachytherapy or surgery). Men who have received medical or surgical treatment for benign prostate enlargement are eligible.

2) Either current or recent (≤12 months ago) treatment with finasteride or dutasteride

3) Currently enrolled or has been a participant within the last 30 days, in any other investigational drug or device study.

4) Men not willing to comply with the procedural requirements of this protocol

5) Known allergy/sensitivity to, or intolerance of, finasteride or other 5-alpha reductase inhibitors, e.g., dutasteride.

6) Known allergy to any excipients of finasteride. Please refer to section 16, appendix 5.

7) Any malignancy (other than non-melanoma skin cancer and/or prostate cancer) that has not been in complete remission for five years

8) Any serious co-existent medical condition that would make repeat prostate biopsy hazardous

9) All contraindications to finasteride including concomitant therapy with any medication that may interact with finasteride.
10) Any rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption

11) Men trying for a baby or with a pregnant partner

6 TRIAL PROCEDURES

All procedures are summarised in the Schedule of Assessments table, (see appendix 3).

6.1 Recruitment/ Patient Identification

Participants will predominantly be recruited via urology clinics at each site, and PICs/spoke sites in the following ways:

a) New patient approach: Potentially eligible patients who have been recently diagnosed with prostate cancer will be identified by the clinical team in the outpatient clinic of recruiting hospitals and PICs/spoke sites, having recently undergone bpMRI/mpMRI scanning and systematic and/or targeted prostate biopsy. The clinical care team at each site will be responsible for informing the patient of his diagnosis and discussing the available treatment options, including (if appropriate) active surveillance. Patients for whom active surveillance is a treatment option will be assessed by a clinician for study eligibility and, if suitable, will be given a PIS and a shorter trifold PIL, explaining the FINESSE study to take away for consideration. Potential participants may wish to read the shorter leaflet first to get a feel for the trial before investing time in reviewing the longer PIS. This will be documented in the patient's notes.

   Assuming the patient is willing and eligible, they will be consented, randomised and dispensed IMP, if applicable at their next clinic visit, or asked to attend specifically a trial appointment.

b) Prior active surveillance populations: Recruiting hospitals can assess their databases to identify potentially eligible patients already managed by active surveillance, diagnosed within the last 6 months. Suitable candidates will be contacted by invitation letter, (template provided by the FINESSE CCO), with the PIS and PIL included. Assuming the patient is willing and eligible, they will be consented, randomised and dispensed IMP, if applicable at their next clinic visit, or asked to attend a trial appointment specifically.

Where patients have been mailed the trial details, PIS and PIL in advance, e.g., existing AS patients, the consent visit may be their first trial specific appointment.

Where patients have been identified by PICs/spoke sites they will be referred to the nearest recruiting main hospital known in this model as the 'hub'. The hub research staff will be responsible for obtaining informed consent, conducting the baseline and eligibility assessments, and t for the randomisation of the participant.

Prior to randomisation, men will be given the choice of transferring their active surveillance care to the main hospital (investigator site, and hub) or not. Post randomisation standard of care activities (PSA, bpMRI/mpMRI and diagnostic biopsy) may be conducted at either the DGH or the hub depending upon the patient's decision. However, IMP must be prescribed, dispensed, collected at, and returned to the hub, therefore participants choosing to retain their AS at the DGHs must be willing to travel to their nearest hub to collect and return their IMP, if they are randomised to the trial arm. Collection will be on a three-monthly basis during the two-year treatment phase only.

During the active follow-up phase, all men will be given regular consultations with a hub investigator. This will be to ensure clinical oversight of their IMP by a trial trained clinician and/or delegated trial team member, for men randomised to take finasteride, and for the purpose of collecting adverse event data in both standard care and active treatment arms. These appointments will be three monthly during the treatment phase, and reduced thereafter. They may be conducted remotely.

Where hub sites have the capacity for staff to run spoke based clinics, collection of the IMP on behalf of the participant by a hub research nurse, and is permitted, providing an IMP chain of custody form is completed. There are no special carriage conditions for Finasteride.

The possibility of appointments at the hub, and the potential to change the location of their active surveillance care, will be clearly communicated in the patient facing documents and at the point of consent. Further training will be provided to hub staff. Participants travelling to Sheffield may claim travel expenses of up to £25 per visit.

The HSM will be driven by the Lead Research Nurse employed by STHNFT, thereby keeping activities at the DGHs to a minimum beyond SoC and WUCC procedures.

Patients contacting the FINESSE CCO directly expressing interest in the trial will be advised to request a referral to the nearest recruiting site, from their GP.

6.1.1 Screening

Recruitment will take place primarily in specialist urological clinics at participating centres, and the locally held site screening log will be completed for each potentially eligible patient who is given copies of the PIS and PIL. The log will be completed with the screening date, patient's initials, year of birth, (YYYY) and ethnicity. If a patient is found to be ineligible, or does not wish to participate, the reason for non-participation will be added to the screening log. If a patient wishes to participate and is found to be eligible, the screening log must be updated with the Patient Identification Number (PIN), once consent has been taken and the participant has been successfully randomised.

Where the HSM is used, spokes will not be expected to collect screening data on behalf of sites. It is expected information regarding the number of potentially eligible participants will be available via the hubs' multi-disciplinary teams network.

Sites will be provided with a template study invitation letter, and poster advertising the trial, to assist with the recruitment process. In addition, there is a trial website. The site address, www.FINESSETRIAL.org is provided to participants in the PIS and PIL.

Once a patient has agreed to participate, and written informed consent has been obtained, the Investigator or a suitably trained member of the research team will be responsible for:

- Registering them within the EDC to generate a PIN via the Registration eCRF
- Completing the pre-randomisation Eligibility Assessment CRF to confirm the potential participant fulfils the eligibility criteria for the study
- Completing the additional baseline assessments & eCRFS, (see appendices 5a and 5b) .

The patient may be randomised, and the outcome added to the locally held site screening log.

6.1.2 Payment

Participants will be reimbursed reasonable travel expenses, (maximum £25 per visit), for any visits additional to normal care, where they are attended in person. For those in both study arms, this will be the baseline, 15 months and 21months visits.

For spoke identified participants randomised to finasteride but choosing to remain at the DGHs for their active surveillance care, these payments may be used to cover their travel to the hub to collect and return their IMP.

LCOs are responsible for informing participants of the local reimbursement procedure, and sites will be reimbursed by the UoS.

6.2 Consent

The Investigator, or a Research Nurse trained in taking informed consent and delegated by the PI (as documented in the Site Delegation Log), is responsible for obtaining written informed consent from each subject prior to participation in any study specific procedures. This follows a full explanation of the aims, methods, anticipated benefits, and potential hazards of the study. Participants will be reassured that they are free to refuse all involvement in the study, or may withdraw their consent at any time, and for any reason with no effect on their standard of care. Details of the consent visit can be found in section 6.5.

6.3 Randomisation

A web-based randomisation system will be designed, using the bespoke King's Clinical Trials Unit (KCTU) randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by KCTU for the duration of the project. It will be hosted on a dedicated server within KCL.

The CI or delegate will request usernames and passwords from the KCTU. System access will be restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the randomisation system are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g., Trial Manager (TM)) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., TM) in the first instance.

Participant initials and date of birth will be entered on the randomisation system, NHS number, email addresses, participant names, home addresses and full postcodes will not be entered into the randomisation system. No data will be entered onto the **randomisation system** unless a participant has signed a consent form to participate in the trial.

Randomisation will be undertaken by the recruiting site staff, by authorised staff logging onto the randomisation system via www.ctu.co.uk and clicking the link to access the randomisation system. A full audit trail of data entry will be automatically date and time stamped, alongside information about the user making the entry within the system.

The CI team will undertake appropriate reviews of the entered data for the purpose of data cleaning. No data can be amended in the system, however the CI or delegate (e.g., TM) may request KCTU to add notes against individual subject entries to clarify data entry errors.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

Randomisation will be at the level of the individual using the method of permuted block randomisation, with block sizes stratified by prostate cancer risk (low vs. intermediate), and participant age (<65 vs. ≥65 yrs.).

Please refer to section 5.1.2 for additional information regarding the randomisation risk groups.

6.3.1 Method of implementing the randomisation/allocation sequence

The EDC Eligibility Assessment eCRF will reaffirm patient eligibility. Eligible participants will be randomised in a 2-arm 1:1 design to receive one of the following:

1. Finasteride 5mg daily and active surveillance
2. Active surveillance only.

The participant will previously have been allocated a unique patient identification number (PIN), via completion of the EDC 'Registration eCRF'. The PIN will be of the format P010001, with 01 representing the site and 0001 representing the participant sequentially across the study.

Once the patient has been successfully randomised, this will be documented within the EDC by the Investigator or delegate. The FINESSE CCO, LCO, PI and local pharmacy department will be emailed a link to a PDF document confirming the participant's PIN, DOB, treatment allocation, and age and risk groups.

Sites will be notified in advance of any planned randomisation system outages. In the event of an unplanned outage, sites should contact the FINESSE CCO to trouble shoot the issue. in the first instance. There is no back-up randomisation facility available, which may mean, in rare circumstances, that the randomisation will need to be delayed. Therefore, sites should be vigilant of timelines and ensure they allow enough time to meet the windows stipulated in eligibility and study schedule.

6.3.2 Blinding

Whilst the FINESSE study is open label, meaning both the participant and their clinician will know which arm they have been randomised to, and test results e.g., MRI scans may make it obvious a participant is taking finasteride, the following will not be explicitly informed of the treatment allocation.

The:

1) Lead Trial Radiologist responsible for reviewing the MRI scans
2) Lead Trial Pathologist responsible for reviewing pathology.
3) The Independent Progression Review Panel, made up of three members, ideally urologists, will be responsible for evaluating the relevant pseudo-anonymised patient information, (PSA values, MRI scans, biopsy pathology), for all patients who have 'progressed'. The committee will decide whether progression has occurred or not, and their decision will be communicated on their behalf, as advice to the local sites by a member of the FINESSE CCO. Ultimately, the treating clinician makes the treatment decision with the participant.

6.4 Baseline data

At Baseline, data of participants who have consented to take part in the study will be entered into the eCRF within the FINESSE EDC before the participant is randomised. (Please see xii. FINESSE Data Flow Diagram at the beginning of the protocol, and section 10. Data Management),

The data collected will include:

- Confirmation of eligibility (Inclusion and Exclusion Assessment)
- Informed consent
- Medical History
    - Diagnosis name
    - Date of diagnosis (MM/YY)
    - Outcome of the diagnosis. Is it intermittent, ongoing or has it been resolved?
    - Where relevant, the grade.
- Demographics
    - Age
    - Ethnicity
    - Occupation
    - Highest education level
    - Height (cm) – taken as per site standard practice
    - Weight (–g) - taken as per site standard practice
- Eastern Oncology Performance (ECOG)
- Physical Examination (Digital Rectal Examination). The most recent DRE findings will be acceptable. It will not be necessary for the participant to undergo an additional physical examination, unless indicated.
- Concomitant Medication review of all current medication, including anything taken within 14 days prior to randomisation.
    - Name

  - Indication
  - Dose
  - Route
  - Start date and where applicable stop date, if no longer taking.

- Quality of life questionnaires (Completed in REDCap by the participants).
  - EQ-5D-5L [32]
  - EORTC QLQ C30 [33]
  - EPIC [34]
  - EORTC QLQ FA12 [35]
  - Memorial Anxiety Scale Prostate Cancer [36]
  - Depression Anxiety Stress Scales (DASS)-21 [37]
- Decision-making questionnaires (Completed in REDCap by the participants)
  - Decisional conflict scale [38]
  - Subjective decisional quality scale [39]
  - Decisional regret [40]
  - Decisional involvement [41]
- Clinical Examinations
  - PSA: An existing PSA result will be acceptable and entered into the eCRF if taken within 3 months prior to the randomisation date.
  - bpMRI/mpMRI: a copy of the bpMRI/mpMRI scan, taken within the last 12 months of randomisation date, and report confirming clinical or radiological stage ≤T2c cN0 cM0, will be requested by the local site staff from the relevant radiology department and where available, the scan will be transferred via an Image Exchange Portal, to STHNFT for central review by the Lead Radiologist. The corresponding report may be sent via NHS-to-NHS email. Details regarding the MRI results including prostate cancer volume, stage, and size will also be collected on the EDC via the Radiological Assessment eCRF. For this study MX and NX will be treated as M0 and N0, respectively. Biopsy: A 10% sample of all the biopsy samples confirming the histopathological diagnosis of adenocarcinoma of the prostate in the last 24 months of randomisation date will be requested by the local site staff from the relevant pathology laboratory and sent by post to Leeds Teaching Hospital NHS Trust for central review by the Lead Trial Pathologist. Corresponding anonymised pathology report forms will also be requested. Details regarding the prostate biopsy results including primary and secondary Gleason patterns will also be collected on the EDC via the Tissue Sample Collection eCRF.

Full details of the pathology and bpMRI/mpMRI scans, including reporting protocols are documented respectively in the FINESSE Study Pathology & Radiology Manuals.

6.5 Trial assessments

Please note, where patients have been identified by PICs/spoke sites they will be referred to the nearest recruiting main hospital known in this model as the 'hub'. The hub research staff will be responsible for taking fully informed consent, conducting the baseline and eligibility assessments, and potentially for the randomisation of the participant.

Prior to randomisation, men will be given the choice of transferring their active surveillance care to the main hospital (investigator site, and hub) or not. Post randomisation standard of care activities (PSA, bpMRI/mpMRI and diagnostic biopsy) may be conducted at either the DGH or the hub depending upon the patient's decision. However, since the finasteride IMP is prescribed, dispensed, collected at, and returned to the hub, therefore participants choosing to retain their AS at the DGHs must be willing to travel to their nearest hub to collect and return their IMP, if they are randomised to the trial arm. Collection will be on a three-monthly basis during the two-year treatment phase only.

Initial screening in routine clinic

Patients will normally attend a routine clinic to learn their diagnosis and treatment options. Those men identified as suitable candidates for active surveillance, and who appear to fulfil the inclusion criteria for the study, will be informed about the FINESSE study as an option within active surveillance. The clinic doctor will explain the study to the patient and a PIS and PIL will be given to him to take home for consideration. The screening date, patient's initials, year of birth, (YYYY) and ethnicity, will be recorded on the site-specific screening log.

A follow up appointment will be arranged for him to return to confirm his active surveillance treatment preference, giving sufficient time to read the PIS and consider his participation. If the patient wishes to join the trial, consent will be taken at this follow-up appointment, and he will be randomised into the study.

Consent Visit

The informed consent consultation should take place in a confidential appropriate environment. Neither the PI, nor any other trial staff should coerce or unduly influence a patient's decision to participate or continue to participate in the trial. All questions about the study should be answered to the satisfaction of the patient. This should occur prior to consent being obtained and the consent form signed.

For the consent to be valid, each box on the consent form should be initialled, and the consent form must be signed and dated by both the person obtaining consent and the person giving consent at the same occasion. Each person should clearly print their name by their signature and date only their own signature. Where consent is taken by someone other than an Investigator, a delegated investigator (clinician) must be readily available to ensure medical oversight and must countersign the consent form in a timely manner.

Once all parties have signed and dated the consent form, the original must be filed in the Investigator file. In addition, a copy of the form must be given to the participant, and a further copy must be filed in the participant's notes. A record of the discussion should be made by the Investigator in the medical notes.

Both the PIS and CF should be printed on local trust headed paper for the trial site where the participant is consented and should show the date and version number. The contact details of the person/s to contact for further information about the study must also be given.

Should new safety information become available which may result in significant changes in the risk/benefit analysis, the PIS, PIL and Consent Form will be reviewed and updated accordingly. All participants actively involved in the trial will be informed of the updated information and given a copy of the revised PIS, PIL and the correspondingly revised consent form to sign, in order to confirm their wish to continue in the study.

E-consent

Obtaining written consent is a critical step in the clinical research process, but using paper forms may not always be possible, e.g., in the event of a pandemic, study visits to the hospital may be prohibited. The FINESSE REDCap EDC will offer a digital method to acquire and store subject consent forms through an e -Consent Framework and PDF Auto-Archiver. This functionality provides the ability to consent subjects remotely via computer, mobile phone, or tablet. Subjects will have the capability to sign electronically with a stylus, mouse, or finger. Once the consent form is signed and submitted, subjects will be able to print a paper copy, download a pdf, and/or receive an email with a PDF attachment of the signed consent form. Site staff will also be able to print copies which must be filed in the participant's notes and the ISF.

E-consent should only be used as a last resort, and site staff are required to obtain prior written permission from the FINESSE CCO before using this method. In addition, they must ensure that the person electronically signing the informed consent is the subject who will be participating in the research study, by conducting real-time identity verification prior to eConsent. In this approach, the presentation of valid photo ID, (current passport, current drivers' licence) will be necessary.

The study team could verify identity during a video conference by taking an image or screenshot during the conversation, or implement a post-process verification method, which requires the subject to upload a picture or scanned version of a specific identity document such as a passport or state issued ID card to accompany the e-Consent submission. This method would require manual document review by the study sites to ensure information matches what is expected.
Since this facility will be part of the REDCap electronic data capture (EDC) system (please see xii at the beginning of the protocol, and section 10. Data Management), the necessary information governance arrangements will be in place to ensure that participant confidentiality is protected with appropriate access and retention controls to the system.

PSA Testing and Digital Rectal Examination (DRE)

An existing PSA result will be acceptable if taken within 3 months prior to the randomisation date.

The most recent DRE findings will be acceptable. It will not be necessary for the participant to undergo an additional physical examination.

Randomisation Visit

The consent and randomisation can take place on the same day.

If eligibility is confirmed, patients will be randomised via the randomisation system , and a PIN allocated by the EDC. Relevant eCRFs (Appendices 5a, b and c) will be completed by the Investigator or a member of the research team, with paper-based backup CRFs available in case of system failure or for additional convenience. Where paper CRFs (pCRFs) are used, they should be kept in the ISF and will be reviewed alongside the corresponding source data during site monitoring. Within the EDC, participants will be identified only by initials, date of birth and trial number.

Finally, the local care team will schedule future AS visit to fit with the schedule of the randomisation date and protocol requirements. A prescription for **three months'** supply of study medication may be given and the IMP will be collected from the hospital pharmacy by the participant.

The Lead Trial Pathologist will review anonymised representative samples of 10% of all Gleason 3+4 tumours. This is for quality control, to monitor variation in reporting between centres. Where the participant has been diagnosed with a tumour having a Gleason grade of 3+4, site staff are responsible for collecting the pathology samples and corresponding reports. Ideally, a minimum of two formalin Haematoxylin and Eosin-stained slides, confirming the histopathological diagnosis of adenocarcinoma of the prostate in the last 24 months of the patient's randomisation date, will be requested by the local site staff from the relevant pathology laboratory, and sent to Leeds Teaching Hospital NHS Trust for central review. Corresponding anonymised pathology report forms will also be requested. It will be the responsibility of the FINESSE CCO to monitor and report to the TMG, the percentage of pathology reporting discrepancies per site. Should the Lead Pathologist report a higher rate of disagreement than expected, the TMG may consider increasing the proportion of biopsies to be centrally reviewed. However, at the time of writing this protocol, we envisage low levels of discord.

The 10% quota will be managed by the FINESSE Trial Coordinator/Monitor (TC) .

Local site staff will be responsible for liaising with the local Pathologist to collect the relevant anonymised pathology samples and thereafter shipment to the Lead pathologist. Sites must ensure all slides and corresponding reports are labelled in such a way they cannot be linked back to a participant by the Lead Trial Pathologist, but that they can be re-identified by the local pathologist once the slides are returned to them.

The LCO is also responsible for completing the associated Bio sample Collection Form for the samples. The local Pathologist is responsible for providing the relevant pathology samples and an anonymised copy of the original pathology report(s) for each participant's samples.

Pathology samples should be sent in the CCO provided padded envelope with the prepaid address label.

Centres will also be provided with slide mailers (80X25mm) to hold up to 5 slides each.

In addition, a copy of the bpMRI/mpMRI scan and corresponding report confirming clinical or radiological stage ≤T2c cN0 cM0, will be requested by the local site staff from the relevant radiology department. The scan must be transferred via an Image Exchange Portal to STHNFT for central review by the Lead Radiologist, but the corresponding report may be sent securely via NHS-to-NHS email. The radiologist will review 100% of the bpMRI/mpMRI scans., For this study MX and NX will be treated as M0 and N0, respectively.

Full details of the pathology and bpMRI/mpMRI scans, including reporting protocols are documented respectively in the FINESSE Study Pathology and Radiology Manuals.

Even though finasteride is not generally prescribed for women, and no women will be recruited into the FINESSE trial, it could still harm an unborn baby. Therefore, participants taking finasteride must be advised to:

a. Use a condom when having sex if there is a possibility their partner could become pregnant. This is because small amounts of finasteride pass into semen.
b. Inform their partners not to touch any crushed or broken finasteride tablets if there is any chance they could be pregnant. Finasteride can get into your bloodstream through your skin if you handle **broken** tablets. For this reason, the tablets come with a protective coating.

Follow-up Visits

Year One: Once randomised, participants will continue to attend routine active surveillance appointments every three months (+/- 14 days). FINESSE appointments will take place at the same time and where applicable, a prescription will be issued, and IMP dispensed on a 3 monthly basis. As is standard practice for men on active surveillance, blood samples for PSA testing will be taken at months 3, 6, 9 & 12, a repeat bpMRI/mpMRI scan will be carried out at month 12, and where it is local practice, a digital rectal examination (DRE) will be given.

The results of all these examinations will be captured in the FINESSE EDC, and copies of the bpMRI/mpMRI scan and report will be transferred to the Lead Radiologist, by the LCO for review. Full details regarding bpMRI/mpMRI scans, including reporting protocols will be documented in the FINESSE Study Radiology Manual.

Year Two: Whilst the frequency of routine active surveillance and blood samples for PSA testing will drop to 6 monthly, FINESSE study appointments will continue to be scheduled on a 3-monthly basis, (+/-14 days) to enable men randomised to the active arm of the trial to collect their prescription and IMP. This means participants will be required to attend two additional visits at months 15 and 21 during this period. Whilst these visits may be conducted virtually by telephone or video call, if necessary, and IMP dispatched by post, participants in the finasteride arm must ensure they return their remaining IMP for a pill count.

Participants may undergo a DRE at month 24 as per local practice. The results of this examination if conducted, will be recorded on the trial EDC, but it is not mandatory. Where applicable, dispensing of the IMP will stop at the end of year two.

Years three to five inclusive: Participants will continue to attend routine active surveillance appointments on a 6 monthly basis and all FINESSE study appointments will take place at the same time. A year 3 bpMRI/mpMRI scan, followed by a discussion of the findings in clinic, and a subsequent prostate re-biopsy where indicated by the bpMRI/mpMRI scan, are strongly recommended, where the assessment(s) can be arranged locally, as part of usual care.

Where conducted, the LCO will be responsible for transferring copies of the year 3 bpMRI/mpMRI scan and report to the Lead Radiologist and recording the results of the investigations in the trial EDC. The site may also be asked to send corresponding year 3 biopsy slides to the Lead Pathologist. Full details can be found in the FINESSE Study Pathology Manual.

Visit windows and additional follow-up visit information

For follow-up visits, a window of plus or minus 2 weeks either side of the scheduled time point is allowed, which gives 4 weeks in which to see the participant for their follow-up assessment. For example, if the participant was randomised on 17th December 2021 and their 3-month visit is due on 17th March 2022; the participant can be seen anytime from the 3rd of March to the 31st of March 2022 inclusive. However, it is important that the participants' medication regimen is not interrupted wherever possible. It is therefore necessary to ensure they have sufficient IMP supplies to cover any change in visit schedule.

For bpMRI/mpMRI scans and prostate biopsies, this window will be six months, which allows a year in which the assessments can take place. For example, if the participant was randomised on the 10th of November 2021 and their recommended 36mth bpMRI/mpMRI scan is due on 10th November 2024; the participant can be scanned anytime from the 10th of May 2024 to the 10th of May 2025 inclusive.

Follow-up CRFs will be completed at each visit (see appendix 6 Appendices 6a, b and c)), and the assessments required as part of AS and the protocol, conducted as scheduled (both detailed above and summarised in appendix 4).

Participants will be asked to return their unused medication three monthly at the 3, 6, 9, 12, 15, 18, 21 & 24 month time points for compliance evaluation. In addition, a FINESSE prescription will be issued three monthly, enabling a further supply of study medication to be dispensed by the pharmacy.

Any participant whose cancer has progressed but is still deemed suitable for continued surveillance by their treating clinician may continue on the study if authorised by the Principal Investigator (PI) at that centre. Participants with cancer progression, undergoing radical therapy, will discontinue study medication and trial follow-up appointments, but will be followed up in the long-term via NCRAS and HES registry data. Consent for this aspect of follow-up will have already been given at the time of registration.

Please refer to the objectives table for definitions of histopathological, radiological and biochemical progression.

Management of rising serum PSA during the study period

Participants may experience a rising serum PSA during the study period. It is at the clinician's discretion to either recommend a 'for cause' repeat prostate bpMRI/mpMRI or re-biopsy, or alternatively, recommend radical therapy. However, it is recommended that an off-protocol 'for cause' prostate biopsy only be performed if the participant's PSA doubling time is less than 12 months. In addition, it is recommended but not mandated that all participants undergo repeat biopsy for a rising serum PSA rather than undergo immediate radical therapy.

For participants who continue on the study for the full duration, annual surveillance in the community (by their GP), will be recommended for men with stable prostate cancer, once they have completed their 3 to 5 yrs. study follow-up. In men with fluctuating or concerning parameters, surveillance by their referring urologist will be recommended.

Prostate biopsy

If a routine or a 'for cause' prostate biopsy is carried out after the diagnostic biopsy, further repeat prostate biopsies should be conducted in line with routine care.

A 'Tissue Sample Collection' eCRF should be completed and a minimum of two anonymised formalin Heamatoxylin and Eosin representative stained slides, sent to Leeds Teaching Hospital NHS Trust for central review by the Lead Trial Pathologist, for all 'for cause prostate biopsies, regardless of study timepoint. Corresponding anonymised pathology report forms will also be requested.

bpMRI/mpMRI Scan

If a routine or a 'for cause' bpMRI/mpMRI scan is carried out after the diagnostic bpMRI/mpMRI but prior to the 12-month scan, then a further bpMRI/mpMRI scan at the 12-month timepoint is not mandatory. Similarly, if a routine or a 'for cause' bpMRI/mpMRI scan is carried out after the bpMRI/mpMRI at 12 months but prior to the previously recommended 36-month scan, then a further bpMRI/mpMRI scan at the 36-month timepoint may be unnecessary. Repeat bpMRI/mpMRI scans should be conducted in line with routine care.

A Radiological Assessment eCRF should be completed and a copy of the bpMRI/mpMRI scan transferred via an Image Exchange Portal to STHNFT for central review by the Lead Radiologist, for all 'for cause'

bpMRI/mpMRI scans, regardless of study timepoint. The corresponding report may be sent via NHS-to-NHS email.

Full details of the pathology and bpMRI/mpMRI scans, including reporting protocols will be documented respectively in the FINESSE Study Pathology and Radiology Manuals.

6.6 Qualitative assessments

Following completion of the study, participants who have previously provided consent to be approached will be invited to participate in a 60-minute telephone interview with a trained researcher. We will aim to ensure good representation of men from both the treatment and control groups who have and have not adhered to

a) active surveillance, and

b) finasteride.

We will also purposively sample men of African descent for these interviews to ensure their views are represented.

Interviews will ask questions that give insight into the experience and acceptability of finasteride (intervention group only), including attitudes towards side-effects and different treatment pathways. Men from both the intervention and control groups will be asked about the decision-making process for the treatment(s) they have chosen.

We will also approach healthcare professionals involved in the care of men with prostate cancer (urologists, urological surgeons, nurses etc) at participating and non-participating sites to identify individuals willing to take part in a 60-minute telephone interview with a trained researcher. Interviews will also ask questions that give insight into the experience of the FINESSE trial (for participating sites only), and to identify any potential problems with implementing finasteride within clinical care, if the trial data supported it. We would like to speak with non-participating centres as healthcare professionals as those sites may be less likely to hold a favourable opinion towards the use of finasteride.

Pilot interviews will be carried out to assess comprehension, relevance, and appropriateness of the interview schedule.

We aim to interview 20 men and 10 healthcare professionals (5 from participating sites and 5 from non-participating sites) initially and make an assessment as to whether any new themes are continuing to emerge from the data (i.e., data saturation). Further interviews will be undertaken if we deem further themes are likely to be reported in subsequent interviews. Interview data will be transcribed verbatim, then thematic analysis will be used to extract emerging themes.

Participants will be informed that they will not be identified in any future reports, and that we will use a pseudonym when using any quotes. Participants can request that their quotes from the interviews not be used publicly (e.g., in any subsequent reports or publications).

6.7 Withdrawal criteria

6.7.1 Early withdrawal

Participants may withdraw from the trial at any time at their own request or they may be withdrawn at any time at the discretion of the investigator if it is considered to be in their best interests. Participants can withdraw without giving a reason, but if a reason is given this should be documented in the relevant eCRF and medical notes.

It is possible for a participant to withdraw from treatment only but continue to be followed up in clinic or by telephone, and this should be encouraged. In this case the IMP Reconciliation and Drug Dispensing and Pill Count Logs/eCRFs must be updated. In addition, all further follow-up forms will continue to be completed until the end of the follow-up period.

If participants wish to withdraw from both follow-up and the study IMP, a 'Withdrawal from Study' eCRF will be completed and they will not have any further trial visits. However, unless explicitly requested in writing, by the participant, they will continue to be followed up long-term via national registries.

The main analyses will be by intention to treat, therefore, data and samples collected up to the time of withdrawal of consent will be included in the study analyses, as stated in the consent form.

Participants may be withdrawn from trial medication, and/or the study in the event of:

- Unacceptable toxicity/intolerable side effects
- Inter-current illness
- Occurrence of any other malignancy
- Participant withdrawing consent
- Participant unable to comply with the study schedule
- Participant chooses to come off active surveillance and undergo active therapy
- Identification of higher risk disease unsuitable for surveillance following 'For Cause' repeat prostate biopsy precipitated by an increasing PSA
- Development of a condition not compatible with the study, or the addition of a new incompatible medication or other product.
- Disease progression

Data concerning toxicity will be collected on the 'Adverse Event' eCRF and via participant self-reporting.

Participants will be considered to be lost to follow-up if there has been no contact for ≥12 months from the last scheduled clinic visit. These participants will be included in the intention to treat and safety analyses.

Participants who change their mind about leaving the trial, may be permitted to re-join, providing:

1) They wish to re-join ≤3months after leaving the trial
2) The site has obtained written CI approval.

6.7.2 Treatment discontinuation due to cancer progression

Any participant whose cancer has progressed as defined in the objectives table may continue on the study, providing they;

- are still deemed suitable for continued surveillance by their treating clinician
- do not undergo radical therapy and
- are authorised to do so by the PI at that centre.

The reason for continuing on Active surveillance should be documented in their medical notes.

The decision to proceed with radical therapy will be at the clinician's and participant's discretion. Participants undergoing radical therapy will discontinue study medication but will be followed up in the long-term via NCRAS and HES registry data. Consent for this aspect of follow-up will have already been given at the time of registration. The CPTU should be informed in writing, if the participant later wishes to withdraw consent for long-term follow-up, but this should be discussed with the participant and exploration of all avenues to allow for retention is encouraged.

Where a radical prostatectomy is carried out, every effort will be made to obtain pathological data and/or tissue, together with any related bpMRI/mpMRI scans/reports

Participants who stop trial follow-up early will not be replaced.

6.7.3 CIRCUMSTANCES UNDER WHICH THE TRIAL MAY STOP PREMATURELY:

The IDMC will usually advise the TSC and TMG if they believe the trial should be terminated early. This may be for one or more of the following reasons:

- Serious Adverse Reactions or safety concerns.
- Inability to recruit or enrol an adequate number of participants.
- Protocol found to be unpracticable or unworkable
- Loss of Investigator interest
- Problems arise in the medicine's stability or manufacture
- New toxological findings affect the benefit to risk ratio
- Failure of the investigator(s) and or staff to follow good clinical practice or adhere to the protocol

6.7.4 PARTICIPANT TRANSFERS

If a participant moves from the area, every effort should be made for them to be seen at another participating trial centre, and this should be discussed with the FINESSE CCO at the earliest opportunity. Where used the participant's original pCRFs should be provided to the new centre, together with relevant source data. Copies of the original pCRFs should be kept by the original site. Their PIN will remain the same. The participant will be required to sign a new Consent Form. Once this has been done, the new centre will take over responsibility for the participant within the trial; until this has been done, responsibility for the participant lies with the original centre.

6.8 Storage and analysis of clinical samples and imaging data.

We have no plans to collect blood or store any blood or pathology samples, or any MRI scans outside of those collected as part of routine care. We will request 100% of the bpMRI/mpMRI scans for central review by the Trial radiologist.

As previously described in section 6.5, Trial Assessments, the Trial Pathologist will review representative samples of the first 10% of diagnostic Gleason 3+4 tumours

The trial pathologist will not record their review findings against the PIN. They will be recorded at site level only.

The pathology samples will be returned to the sites once the review is complete, and in accordance with site's pathology release conditions. Therefore, sites must ensure all slides and corresponding reports are labelled in such a way they cannot be linked back to a participant by the Lead Trial Pathologist, but that they can be re-identified by the local pathologist once the slides are returned to them.

Full details can be found in the FINESSE Study Pathology Manual.

6.9 End of trial

The end of trial definition for the FINESSE Study will be when the following has occurred:

- Last Participant Last Visit (LPLV), i.e., when the final 'Active Surveillance Adherence' eCRF has been completed and submitted. Safety reporting stops at this stage, and the CTIMP ends.
- All data collected has been monitored, cleaned, and is ready for final analysis.

The 'End of Trial Declaration' will be submitted to the MHRA and REC at this stage.

Trial types such as this benefit from long term assessment of outcomes, benefits and harms and therefore we aim to collect passive follow up data for up to five years after the EoT. Since long-term follow-up beyond EoT is an aim of this research but not a study listed endpoint for this protocol, this will be covered under a separate ethically approved protocol post EoT . Consent to do this will be sought during this current protocol to minimise the need for re-consent and thus additional participant burden at the EoT.

7 TRIAL TREATMENTS (refer to the FINESSE Pharmacy Manual for comprehensive IMP management details)

7.1 Name and description of investigational medicinal product(s)

- **Trial IMP:** Finasteride 5mg film-coated tablets. There are no placebos.
- **Composition:** 5mg finasteride will be used in the FINESSE trial.
- **Dosage regimen over 24 months:** 1 x 5mg daily
- **Route of administration:** Oral
- **Formulation:** Exact formulation dependent on brand. Excipient with known effect: lactose monohydrate (97.5mg)
- **Packaging:** Finasteride 5 mg tablets are available in PVC/PE/PVDC/Aluminium blister and white opaque HDPE bottle closed with polypropylene closure.
- **Pack sizes:**
  - **Blister packs:** 10, 14, 15, 20, 28, 30, 45, 50, 60, 90, 98, 100 and 120 film-coated tablets.
  - **HDPE bottle packs:** 30, 50, 60, 90, 98, 100 and 500 film-coated tablets
- **Shelf Life:**
  - **Blister Pack:** 4 years
  - **HDPE bottle** Pack: 3 years

Not all pack sizes may be marketed, which means that whilst they are approved in the UK, they are not necessarily used or available.

7.2 Regulatory status of the drug

Finasteride 5mg has a marketing authorisation in the UK. It is indicated for the treatment and control of benign prostatic hyperplasia (BPH).

7.3 Product Characteristics

The SMPC with current regulatory approval for the study, together with version and date numbers of the current version, will be detailed in the FINESSE Pharmacy manual. Copies will be kept in the pharmacovigilance sections of FINESSE TMF, the locally held ISFs, and on the library facility of the FINESSE REDCap application.

The SmPC will be reviewed periodically by the FINESSE CCO to ensure that it is up to date, and accurately reflects the knowledge currently available about the product. This review will be at least annual, and the process will be detailed in a trial specific SOP.

The FINESSE CCO will also be responsible for:

- Updating the sites if on review it is decided that an alternative version of the SmPC, will be adopted
- Managing the change in a timely fashion
- Submitting a substantial amendment covering the change, to the competent authority prior to implementation.

Each site will be required to file a copy of the FINESSE pharmacy manual in their ISF and PSF.

7.4 Drug storage and supply

Please refer to the FINESSE Pharmacy Manual for full details.

This is an open label study. FINESSE IMP will be sourced directly from standard NHS stock at trial site hospital pharmacies, hub Trial Sites in the case of sites operating a Hub and Spoke model). Note however that the pharmacy purchasing policy may mean that the manufacturer of non-branded (generic) drugs in stock may vary from time to time. Any brand/manufacturer of the IMP with a marketing authorisation in the UK can be used. Initial and subsequent supplies need to be per usual local procedures. Sites will be responsible for ensuring adequate supply and storage of all IMPs.

Ring Fencing of supplies: If the decision is made at a specific hospital site to order supplies for use within the trial that are to be 'ring-fenced', full details of the procedure for ordering, receipt and storage must be noted in the Pharmacy File and cumulative accountability logs maintained. Full details can be found in the FINESSE Pharmacy Manual.

7.4.1 Accountability/Receipt /Storage and Handling of IMP

The Investigator, or a delegated individual (e.g., pharmacist), must ensure that the study drug is stored and dispensed in accordance with hospital standard operating procedures and applicable regulatory

requirements. Full instructions regarding how to take the IMP must be documented in the participants' notes.

Template drug dispensing and accountability logs will be provided to the sites in a Pharmacy Site File and a system will be established to ensure that:

- Investigational products are dispensed only to study participants, and in accordance with the protocol

- Participants return any unused investigational product and empty containers to the research nurse who will reconcile these, before returning to pharmacy.

- A Dispensing Log is accurately maintained. This will include the initials and PIN of the participant, the date of dispensing, the quantity dispensed, the brand of finasteride, the batch number and the expiry date of the IMP dispensed to each participant. Any unused investigational product will be returned to pharmacy and recorded on the log. Any discrepancies must also be accounted for on the Dispensing Log. This record is in addition to any drug accountability information recorded on the IMP Reconciliation Log eCRF.

- On completion of each participant's treatment, the Dispensing Log will be returned to the coordinating centre or collected at a monitoring visit, and a copy retained in the FINESSE pharmacy file.

- The participants return unused tablets at every visit to the trial site, (Hub Trial Sites in the case of sites operating a Hub and Spoke model), for an accountability check before a new prescription is issued. Details of the remaining quantities of drugs will be collected by a member of the research team at regular intervals so that these are verified against the Drug Dispensing and Pill Count Log eCRF.

7.4.2 IMP Stability

Site pharmacies will be responsible for dispensing in line with their local dispensing procedures and excursion management normal practices. There are no special storage conditions for finasteride. Storage in line with normal clinical processes will be appropriate.

7.4.3 Return/Recall or Destruction of IMP

The LCO is responsible for ensuring the returned pill count information is recorded on the IMP Reconciliation Log eCRF. As part of their standard procedures, pharmacy staff will count and record returned medication on the participants' dispensing logs.

IMP reconciliation by both the LCO and pharmacy is not mandatory, and sites are permitted to follow local pill count practices. However, we recommend the following:

- Site staff should confirm all returns in the source data (i.e. the participant's notes) e.g. number of bottles returned, whether empty or not.
- Returns should then be transferred to pharmacy, and pharmacy staff should perform full pill counts and document accordingly in the trial accountability logs.

LCOs must visit or request copies of the logs from pharmacy in order to enter the pill count data into the relevant eCRF. CCO trial monitors will check for any discrepancies between the initial notes, eCRFs and the pharmacy records.
There are no trial specific destruction arrangements for this study as the IMP will be sourced locally and the destruction will therefore be in accordance with local policy. No specific trial related certificate of destruction will be provided for this study, however local pharmacists should keep full records of the destruction and may use their own internal forms for recording the drug destruction before filing in the FINESSE PSF.

Where local practice allows for the LCOs to carry out pill counts themselves, they should be aware of the safety risk* associated with manipulating Finasteride and use appropriate PPE.
**Women should not handle crushed or broken tablets of finasteride when they are or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus. However, Finasteride tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.*

Should sites wish to use their own drug dispensing and accountability logs, they will require prior permission from the FINESSE CCO.

Local pharmacies are responsible for managing product recalls as per local procedures and informing the FINESSE CCO accordingly. Information provided should contain a brief outline of which batch is affected and what action should be taken.

If the recall is at participant level, the site should check the participant dispensing logs, and if necessary, contact every participant who has received the affected product since the date of first distribution. The site will also provide replacement medication for these subjects.

Once the medication has been quarantined the site should notify the CCO by scanning and emailing all related local documentation regarding IMP recall and actions taken, as per local policy to the FINESSE CCO, (see Pharmacy Manual).

7.4.4 a) Unused Medication (Expired and/or Never Dispensed)

Once the product has had FINESSE clinical trial labels added, the IMP may not be used for any purpose other than that outlined in the protocol. As stated above, local destruction policies apply.

7.4.4 b) Participant Returns

The participants should be clearly instructed to return their empty, partially used or never opened study medication at the appropriate visit – three monthly, including their final study visit if they withdraw from the trial prematurely. This is important for measuring compliance and in order to keep full drug reconciliation records. It will also help to identify possible dispensing errors.

7.4.4 c) Withdrawals

When a subject withdraws early from the study (from one or more treatments), they should return their remaining study medication to the site where a pill count will be performed and recorded in the participant's dispensing log held in the pharmacy file. The returned medication will then be destroyed as per local policy relating to waste medication.

7.5 Preparation and labelling of Investigational Medicinal Product

The Medicines for Human Use (Clinical Trials) Regulations 2004 specifies that clinical trial drugs be labelled in a way that allows for their proper use and identification of the product, the trial and the trial participant. It must be possible to identify and trace any IMP supplied to a trial participant for which purpose it is necessary to maintain a record of the manufacturer/supplier and batch number. This is an important safety measure in the event of a drug recall that may be issued at any stage during the course of the trial.

If the supplies are to be 'ring-fenced' they can either be labelled at the point of ring-fencing or at the point of dispensing, according to local preference. If the supplies are to be used off the shelf, they should be labelled at the point of dispensing.

Since finasteride has a marketing authorisation in the UK and is not being repackaged or manufactured for use in the trial, reduced labelling can be used.

A MHRA approved template label will be provided to the sites at the outset of the trial. The template label includes the following:

- The words 'For Clinical Trials Use Only'
- Trial Patient Identification Number (PIN).
- Participant initials
- Trial reference code (e.g., EudraCT No) to allow identification of the trial site, contact details of CCO and Sponsor.
- Directions for use as per standard NHS dispensing.
- Date of issue
- Name/address of hospital/primary care supplier
- The words 'Keep out of the reach and sight of children'.

IMP labels will need to be printed locally, as per local policy, since the Finesse CCO will not be providing label supplies for this trial. Local pharmacy staff will create their own label ensuring it includes all the information provided on the MHRA approved template. There may be any additions or changes in size / layout to this wording, but NO omissions. There is no need to seek further approval from the FINESSE CCO. The trial label can be combined with the local dispensing label as needed. This should be affixed to the original pack of the marketed product without obscuring the existing labelling information.

Space provided for trial label on commercial stock would be used to adhere the label so as not to over-label information about storage conditions.

7.6 Dosage schedules

The Investigator Site File (ISF) Delegation Log will specify the names of all staff (usually a physician) authorised to prescribe the IMP for this study, and study specific prescription and dispensing forms that

have been agreed with the pharmacy will be used. It is possible for a suitably qualified Advanced Nurse Practitioner to prescribe. Evidence of training should be filed in the ISF and a copy sent to CCO for filing within the TMF.

Pharmacies will be provided with a copy of the current Delegation Log to ensure that they are aware of the assigned prescribing healthcare professionals for the study at that site.

Trial medication will be dispensed to the participants according to their randomisation and will consist of a 3-month supply plus 2 weeks overage, except in the rare occasion when a medical decision may be made by the local PI to provide a shorter supply e.g., due to safety reason. The quantity of IMP dispensed on each occasion must be sufficient to allow a two-week delay with the participant's next appointment.

Pharmacies will dispense the relevant number of original packs to cover this, which may vary from site to site depending on the pack size being used locally.

The film-coated tablets, each containing 5mg finasteride, should be swallowed whole and should not be divided or crushed. They should be taken either on an empty stomach or with a meal. If a participant misses a dose, he should take one dose as soon as he remembers. If it is almost time for the next dose, he should skip the missed dose. He should not double the dose. If a participant vomits a dose, he should continue to take the next dose at the usual time. Participants who vomit after taking the study medication will be advised not to take any further study medication that day. Subsequently, if they continue to vomit after taking their medication, they should stop the medication and contact their local centre. Participants who are unable to tolerate the medication will be withdrawn from the study.

7.7 Dosage variations

Should a participant become concerned that a symptom is potentially related to a study medication, it would be preferable to consider a dose reduction e.g., an alternate daily dose, or offer a 'treatment holiday', rather than stop treatment completely. Dose reductions can be up to 30 days in the case of suspected toxicity. Longer 'treatment holidays' must be discussed with the FINESSE CCO.

'Treatment holidays' can also be used in other special circumstances, at the discretion of the PI, but any dose interruptions of greater than two weeks, for reasons other than toxicity must be discussed with the FINESSE CCO. All variations in dose regime/daily dose, must be documented on the IMP Reconciliation Log eCRF.

Full treatment may be restarted after an appropriate interval, if symptoms have resolved, or a decision may then be made about withdrawal, if symptoms persist. A participant can choose to withdraw from the treatment only and continue to be followed up in clinic. Please see section 6.7. Any variation in dose regime should always be documented on the relevant Case Report Form. Where it is not local pharmacy policy to supply relabelled IMP, site staff are responsible for communicating the dose reduction/treatment holiday and treatment resumption details to the participant verbally, in person or via telephone. This must be followed up in writing.

Participants who discontinue the IMP for any reason will not be considered to have left the study and will be followed up for primary and secondary outcome measures. These participants will be included in the intention to treat and safety analyses.

7.8 Known drug reactions and interaction with other therapies

No drug interactions of clinical importance have been identified. Finasteride is metabolized primarily via, but does not appear to affect significantly, the cytochrome P450 3A4 system. Although the risk for finasteride to affect the pharmacokinetics of other drugs is estimated to be small, it is probable that inhibitors and inducers of cytochrome P450 3A4 will affect the plasma concentration of finasteride. For this reason, the 'Concomitant medications' eCRF will ask explicit questions about the use any inhibitors and inducers of P450 3A4. See appendix 7 for a list.

Some herbal remedies, e.g., St. John's Wort and Saw Palmetto may also inhibit finasteride's activity. Therefore, the 'Concomitant Medications' eCRF will also ask explicitly about the use of any herbal remedies.

7.9 Concomitant medication

Finasteride is contraindicated in the following:

- Hypersensitivity to any component of this product. Please see appendix 5 for a list of excipients.

7.10 Trial restrictions

- Pregnancy – please see section appendix 1 and section 8.3.2.4.

7.11 Assessment of compliance with treatment

Adherence will be assessed three monthly. Participants will be requested to bring their remaining study medication to their 3, 6, 9, 12, 15, 18, 21 & 24 month visits for reconciliation. The number of tablets taken will be calculated by the site research staff by subtracting the number of tablets returned from the number of tablets dispensed. In addition, participants will be asked to complete a dose adherence scale questionnaire to measure the extent of, and reasons for, nonadherence, at the 3, 6, 9, 12, 15, 18, 21 & 24 month timepoints.

7.12 IMP Management for the Hub & Spoke Sites

Prior to randomisation, men will be given the choice of transferring their active surveillance care to the main hospital or not. Men who do not transfer their must be willing to travel to their nearest hub to collect and return their IMP. During the active follow-up phase, all men will be given regular consultations with a hub staff investigator. This will be to ensure clinical oversight of their IMP by a trial trained clinician and/or a delegated trial team member for men randomised to take finasteride, and for the purpose of collecting adverse event data in both standard care and active treatment arms. These appointments will be three monthly during the treatment phase, and reduced thereafter. They may be conducted remotely.

As stated above, collection will be on a three-monthly basis during the two-year treatment phase only. Participants travelling to Sheffield may claim travel expenses of up to £25 per visit.

All IMP reconciliation must take place at the hub sites, with staff adhering to the requirements detailed in sections 7.4.1 and 7.4.4b) above.

Where hub sites have the capacity for staff to run spoke based clinics, collection of the IMP on behalf of the participant by a hub research nurse, and is permitted, providing an IMP chain of custody form is completed. There are no special carriage conditions for Finasteride.

8 PHARMACOVIGILANCE

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in the following sections.

8.1 Medicinal Products

An IMP is defined as the tested investigational medicinal product and the comparators used in the study. (EU guidance ENTR/CT 3, April 2006 revision). In FINESSE, finasteride is the IMP and there are no comparators.

8.2 Definitions

The definitions of the Guideline for good clinical practice E6(R2)EMA/CHMP/ICH/135/19, based on principles of ICH GCP apply to the trial protocol. These definitions are given in figure 2.

Figure 2: Definitions	
Term	**Definition**
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in section 4.8 of the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening* • requires inpatient hospitalisation** or prolongation of existing hospitalisation**

Figure 2: Definitions	
Term	**Definition**
	• results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if, in the opinion of the investigator, they jeopardise the participant or require an intervention to prevent one of the above consequences.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPC suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

* The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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 is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for pre-existing conditions, (including elective procedures) that have not worsened, do not constitute an SAE.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

8.3 (S)AEs Management

8.3.1 CLARIFICATIONS AND EXCEPTIONS

ADVERSE EVENTS ALSO INCLUDE:

- An exacerbation of a previous illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected after trial drug administration, (even though it may have been present prior to the start of the trial)

- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment.
- Clinically significant abnormal laboratory values, e.g., new onset renal failure (eGFR <60).

EXEMPT SERIOUS ADVERSE EVENTS:

The following events in the context of this trial, do not require expedited reporting as SAEs.

- Progression of prostate cancer, since this is an expected outcome for participants in this study, but it will be recorded on the appropriate CRF.
- Death due to prostate cancer. This should be recorded on the appropriate eCRF.
- Medical or surgical procedures: the condition that leads to the procedure is the potential SAE.
- Pre-existing disease or condition present, that was diagnosed before the participant commenced trial treatment, and which does not worsen. All pre-existing conditions should have already been recorded when the participant's medical history was taken at the beginning of the trial,
- Hospitalisation, which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition, e.g., pre-planned hip replacement operation which does not lead to further complications.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious as given above and not resulting in hospital admission.
- Overdose of the IMP, unless it results in an AE which meets SAE criteria as a direct consequence.
- Non clinically significant abnormal laboratory values, e.g., new onset renal failure (eGFR <60).

8.3.2 Recording and reporting of AEs, SAEs, SARs AND SUSARs 8.3.2.1 Notification and reporting of Adverse Events or Reactions

All AEs occurring from the time of written informed consent trial until the LPLV, must be recorded in the participants' medical notes and on the Adverse Event Log eCRF within the FINESSE MACRO EDC. If the AE is not defined as serious, the participant is followed up by the local research team. (See Appendix 8 for Flowchart for Safety Reporting)

8.3.2.1 Notification and reporting of Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs).

All SAEs and SARs occurring from the time of written informed consent until the LPLV, must be reported to the CPTU, acting on behalf of the sponsor. Reporting must be within 24 hours of the PI or research team becoming aware of the event (this delegation is documented in the 'Conditions of Sponsorship Agreement'). They should also be recorded in the subjects' medical notes. The reporting process is as follows:

- Complete an AE eCRF **WITHIN** the FINESSE MACRO EDC (MACRO Log In (kcl.ac.uk)), reporting the AE as meeting SAE criteria.
- Print, date and sign a copy of this AE eCRF. NB: It must be signed by the PI or delegate.

- If the EDC cannot be accessed, an AE pCRF should be completed.
- Once identified as a SAE on the AE Log eCRF within the FINESSE MACRO EDC, a SAE Report CRF must be completed and signed by the PI or delegate.
- Scan and email , the signed and dated AE ECRF printout AND the signed and dated SAE Report CRF to the following address - finesse@kcl.ac.uk

Nominated co-investigators will be authorised to sign the SAE forms in the absence of the CI at the coordinating site or nominated Sub-investigators in the absence of the PI at the participating sites.

NB: the SAE Report forms are held OUTSIDE of the MACRO EDC system. Word and PDF versions of the SAE Report form will be available within the study REDCap library, and paper copies can be found in the ISF. Sites must ensure they are always using the current version of the SAE Report Form.

The report should be as complete as possible, and include the following information:

- Event duration (start and end dates, if applicable)
- Action taken
- Outcome
- Seriousness criteria
- Severity, (mild, moderate, severe, life threatening).
- Causality (i.e., relatedness to trial drug / investigation), in the opinion of the investigator
- Whether the event would be considered expected.

The CI (or delegate) will conduct an immediate review of all SAEs and confirm expectedness and relatedness. He/she has the right to upgrade if judged to be necessary, but only once discussed with the PI. A record of this discussion should be made in the participant's medical notes, and within the notes section of the SAE Report CRF.

Requests for any missing information will be made to the site by the CPTU.

The original and any subsequent follow up of Serious Adverse Event CRFs will be filed in the FINESSE TMF. The local sites should keep all signed copies of SAE reports within their ISF.

Whilst the IMPs in this study are expected to be well tolerated, the contents of Section 4.8 'Undesirable Effects' in the SmPC for finasteride, with current regulatory approval for the trial, (See the FINESSE Pharmacy Manual), will act as the RSI for the trial. This SmPC must be used to assess SAE reports to identify SUSARs.

Line listings of SAEs that are not upgraded to SUSAR status will reported on a 6 monthly basis, by the CPTU, to the Sponsor, as documented in the 'Delegated Duties Log'.

8.3.2.2 The Hub and Spoke Model:

Whilst the on-going clinical responsibility for the care of each participant remains with the spoke site, the Principal Investigator at each hub will ensure trial oversight for the safety of participants identified via the spoke.

Hub staff will be responsible for reviewing AEs at the scheduled follow-up appointments, and reporting adverse events and serious adverse events, to the CPTU, on behalf of the Sponsor, as outlined in the protocol.

As with non-spoke participants, Hub staff will be expected to use all sources of adverse event data available to them. These include, but are not limited to reporting by patients at their follow-up consultations, from internal hospital databases including clinical patient records, hospital discharge summaries, and test results.

The spoke shall permit Hub staff access to the records of trial participants, to the extent considered necessary by the PI for their safety. The method may vary depending on what is pragmatically feasible between the Hub and Spoke, and this will be agreed before any participants are referred from spoke to hub sites.

In between trial follow-up appointments spoke staff must report all Serious Adverse Events to the Principal Investigator, as soon as they become aware. The PI or delegate must inform the spoke site of the name and contact details of the individual(s) who will be available as a point of contact to enable adverse and serious adverse event reporting. The Hub site PI or delegate is responsible for reporting the serious adverse event to the CPTU on behalf of the Sponsor, and for assessing causality. The reporting requirements, event exemptions and timelines, as documented in sections 8.3.1 and 8.3.2 must be observed.

Spoke sites will be provided with a 'Hub and Spoke' Manual, containing simple instructions and associated forms for tasks and reporting information back to the PI. The sub-investigator should also report any significant protocol deviations that may impact on participants' safety. Records of these interactions should be kept on file. However, the PI remains responsible for the conduct of the research study at a spoke site, and evidence that effective oversight was provided is required. The PI is expected to be proactive and maintain regular contact with the spoke sites for which they are responsible.

8.3.2.3 Notification of deaths

All deaths which do not constitute SARs or SUSARs will be reported to the Sponsor as part of the 6 monthly SAE line listings, irrespective of whether the death is related to disease progression, the IMP, or an unrelated event.

All deaths which constitute or are a result of SARS or SUSARs will be reported to the Sponsor within 24hours of the CPTU becoming aware of the event. In addition to a SAE Report CRF, a Death eCRF must also be completed by the site.

8.3.2.4 Pregnancy reporting

- All pregnancies (i.e., the participant's partner falls pregnant), within the trial, where the participant is randomised to take finasteride, should be reported to the CI and the Sponsor as a 'notable event' using the SAE Reporting Form available within the trial REDCap library within 24 hours of notification.
- Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE and should be reported as such.
- A pregnant partner of a male trial participant taking finasteride, will be followed up as per standard clinical care, i.e., by the gynaecology/midwifery/paediatric team caring for the pregnant partner. Participants and/or their partners are advised to notify the team the male partner is/has been taking finasteride.

- A child born to the partner of a male trial participant taking finasteride, will be followed up as per standard clinical care, i.e., by the gynaecology/midwifery/paediatric team caring for the neonate/infant. Participants and/or their partners are advised to notify the team the male partner is/has been taking finasteride.

8.3.2.5 Overdose

- Overdoses could be identified on the IMP reconciliation and the participant completed Dose Non-adherence Scale. However, the SmPC for finasteride states participants have received single doses of finasteride up to 400mg and multiple doses up to 80mg/day for three months without adverse effects.
- Overdose of the IMP should only be reported as an SAE if it results in an AE meeting an SAE criterion, which is a direct consequence of the overdose. It should be fully reported on an AE eCRF.
- Participants who take an overdose of the IMP on one occasion will be retained, in the Finasteride arm. Participants who take an overdose of the IMP on more than one occasion will be withdrawn from the trial. Both will be analysed as Intention to Treat.
- The SmPC currently approved for use in the trial, as detailed in the FINESSE Pharmacy Manual should be referred to when treating an overdose.

8.3.2.6 The type and duration of the follow-up of participants after adverse events.

Participants must be followed up until clinical recovery is complete and / or laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and follow-up if necessary.

Adverse events and reactions must be recorded and reported until the LPLV. All SARs will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred until resolved.

8.4 Regulatory Obligations

8.4.1 Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The sponsor will inform the MHRA, the REC and Marketing Authorisation Holder of SUSARs within the required expedited reporting timescales.

For SUSARs, the PI or co-investigator(s) will need to complete additional SUSAR related questions within the SAE Report CRF.

These questions constitute the SUSAR report CRF, which must be signed by the PI or delegate, scanned and emailed as detailed in section 8.3.2., within 24 hours of becoming aware of the event.

The CPTU will inform the CI (or delegate), and sponsor immediately so that they can review the information jointly and report to the MHRA within the allocated timelines.

The sponsor has a legal obligation to report SUSARs to the MHRA within 7 days (for fatal or life threatening SUSARs), or 15 days for all other SUSARs. The CPTU will notify the REC of any SUSARs within the same timeframes.

All participating sites will be informed of SUSARs that occur during the trial by the CPTU, as and when they occur. If warranted, an investigator alert may be issued, to inform all investigators involved in any study using the same drugs that this serious adverse event has been reported.

The original and any subsequent follow up of SUSAR CRFs must be filed in the FINESSE TMF. The local sites should keep all signed copies of SAE reports within their ISF.

Completed and signed forms must also be emailed to the sponsor. A copy of the form(s), together with the email confirmation of receipt, from the Sponsor, must be kept within the TMF. The local sites should keep all SUSAR CRFs within their ISF.

8.4.2 Investigator Assessment

Seriousness: When an AE occurs, the investigator responsible for the care of the participant must first assess whether the event is serious using the definition given in figure 2. If the event is serious, and not related to an event exempted from reporting, then an SAE Report form must be completed and the CPTU notified within 24 hours.

Severity or grading of Adverse Events: The severity of all AEs and/or ARs (serious and non-serious) in this trial, should be graded using:

1) The Common Terminology Criteria for Adverse Events (CTCAE V5.0) CTCAE_v5_quick_reference_8.5x11.pdf OR

2) The following definitions where the event is not covered by the CTCAE;
    a. Mild - event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache).
    b. Moderate – event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication).
    c. Severe and undesirable Adverse Event – Event results in significant symptoms that prevents normal daily activities; may require hospitalisation or invasive intervention (e.g., anaemia resulting in blood transfusion)
    d. Potentially life threatening

Causality: The investigator must assess the causality of all serious events in relation to the trial therapy, using the definitions in figure 3. There are five categories; unrelated, unlikely to be related, possibly, probably, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as a SAE. If the causality is assessed as possibly, probably, or definitely related, then the event is classified as a SAR. If an event warrants stopping, or modifying the dose of finasteride, regardless of whether it is considered to be related to trial treatment, please refer to section 8.7.

Figure 3: Assigning Type of AE Through Causality

RELATIONSHIP	DESCRIPTION	AE TYPE
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely	There is little evidence to suggest that there is a causal relationship, (for example the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event, (e.g., the participant's clinical condition, other concomitant treatment).	Unrelated SAE
Possible	There is some evidence to suggest a causal relationship, (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the participant's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

Expectedness: An unexpected adverse reaction is one not previously reported in the SmPC currently approved for use as the RSI in the trial, or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in figure 2.

If the AR is both unexpected and serious then this SAR becomes a SUSAR. If there is at least a possible involvement of the trial treatment, the local Investigator should make an initial assessment of the expectedness of the event. The Sponsor will have the final responsibility for the determination of expectedness (for reporting purposes), and this decision will be made on the basis of the above definition and the information provided by the Investigator.

As specified previously, the contents of Section 4.8 'Undesirable Effects' in the SmPC for finasteride, will act as the RSI for the trial.

Additional Information:

- Action taken with the IMP, i.e., dose reduction, temporary halt, alternate days, withdrawal, or none.
- Outcome: i.e., resolved, resolved with sequelae, ongoing or fatal.

8.4.3 Urgent Safety Measures

The CI may take urgent safety measures (USM) to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004. The measures should be taken immediately. In this instance, the authorisation of the Licensing Authority Approval prior to implementing these

safety measures is not required. However, the CI will make every effort to discuss the USM with the Sponsor and if possible, the MHRA via telephone prior to implementation.

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, give written notice to the MHRA and the relevant REC of the measures taken in the form of a substantial amendment, and the circumstances giving rise to those measures. A copy of the correspondence with regards to this matter will be sent to the sponsor.

The PI may also take USMs. In this instance they must report the measures taken to the CI immediately where possible, or within 24hrs of the measures being taken at the latest. Notification must be in writing.

Please refer to the following website for details on clinical trials safety reporting: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

8.4.4 Development safety update reports

The CI will provide (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or as necessary, to the Competent Authority (MHRA in the UK), the Research Ethics Committee and the sponsor.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

8.5 Responsibilities

8.5.1 Principal Investigator (PI)/delegate:

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.
2. Using medical judgement in assigning seriousness and causality and providing an opinion on whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.
3. Checking the self-completed participant questionnaires within REDCap for ALL potential events and recording and reporting any which are identified following the guidelines in section 8.3.
4. Ensuring that all SAEs are recorded and reported to the CPTU within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with CPTU if a record of receipt is not received within 2 working days of initial reporting.
5. Ensuring that AEs and ARs are recorded and reported to the CPTU in line with the requirements of the protocol.
6. Providing spoke sites with the name and contact details of the individual(s) who will be available as a point of contact to enable adverse and serious adverse event reporting.

7. Providing trial oversight for participants identified via the spoke, and proactively maintaining regular contact with the spoke Sites for which they are responsible.

8.5.2: Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of participants participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning whether an event/reaction was anticipated or expected in line with the Reference Safety Information.
3. Immediate review of all SAEs, SARS and SUSARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
4. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
5. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

8.5.3 Spoke Sites

1. Assume on-going clinical responsibility for the care of each participant with trial oversight by the hub Principal Investigator.
2. Permitting hub staff access to the records of trial participants, to the extent considered necessary by the PI for their safety.
3. Reporting all Serious Adverse Events to the Principal Investigator or delegate, in between scheduled trial follow-up appointments with the hub research staff.
4. Reporting any significant protocol deviations to the Principal Investigator or delegate, that may impact on participants,

8.5.4: Sponsor: (NB where relevant these can be delegated to CI and/or CPTU)

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol.
2. Reporting safety information to the CI, delegate, or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial IDMC and/or TSC according to the Trial Monitoring Plan.
4. Cumulative review of 6 monthly line listings of SAEs sent by the CPTU.
5. Notification of any upgrades of SAEs to the CI and CPTU.
6. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
7. Notifying Investigators of SUSARs that occur within the trial.
8. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.

9. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

8.5.5: Trial Steering Committee (TSC):

In accordance with the Trial TSC Charter, periodically reviewing safety data and liaising with the IDMC regarding safety issues.

8.5.6: Independent Data Monitoring Committee (IDMC):

In accordance with the Trial IDMC Charter, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis, and providing recommendations regarding safety, based on their review, to the TSC.

9 STATISTICS AND DATA ANALYSIS

A Statistical Analysis Plan is to be produced separately, therefore only the most relevant information has been condensed here.

9.1 Sample size calculation

We estimate finasteride will reduce active surveillance cessation rates by 50% (from 20% to 10%) after an average of 4 years follow-up. This would be a hazard ratio of 0.47.

Under that scenario the sample size of 550 men (275 perm arm) is based on a time to event analysis with 90% power to reject H0: Hazard Ratio ≠ 1 i.e. the detection of a significant difference in AS cessation rates between arms by use of a two-sided log-rank test with alpha=0.05.

The exact number needed is 268 per arm.

We believe we will need to screen 1500 men to obtain 550 eligible, consenting recruits.

9.2 Planned recruitment rate

We will recruit 550 men with recently diagnosed low or intermediate risk prostate cancer from Yorkshire's urological centres, and some sites outside of the region, including Oxford. In 2016, there were 3,642 men diagnosed with prostate cancer in Yorkshire [Yorkshire Cancer Research data]. The 2018 National Prostatectomy Cancer Audit reported 60% of new diagnosis had localised (stage T1 or T2) cancer. In the ProtecT RCT (using PSA screening), most men with localised disease were low or intermediate risk (T1-T2 and Gleason 3+3 (77%)/3+4 (15%)) thus indicating 2,185 such men in Yorkshire. Thus, we estimate 90% of 2,185 are suitable for this improved pathway (i.e., 1,966 men in Yorkshire per annum).

In the Oxford area, there are approximately 50 prostate cancer diagnoses per month, (600 per year), of which we would expect 25% to be low risk, 50% intermediate risk and 25% high risk or advanced.

If roughly half of the men diagnosed with low to intermediate risk are suitable for the study, it would suggest around 19 men per month could potentially be randomised [35].

We believe therefore that it is achievable to recruit 550 over 24 months from Yorkshire major cancer centres and additional sites outside of the region, including Oxford.

9.3 Statistical analysis plan

9.3.1 Summary of baseline data and flow of participants

We will compare, without significance tests, the finasteride and AS groups at baseline for the following measures: Gleason index (counts with percentages by randomisation group), baseline PSA (mean, SD, median, IQR, min and max by group), ECOG (counts with percentages by group) and baseline EQ-5D-5L value (counts with percentages for categories in each dimension and mean, SD, median, IQR, min and max for overall scores all by group).

A CONSORT diagram will be contained in the Statistical Analysis Plan.

9.3.2 Primary outcome analysis

We will compare rates of non-adherence to active surveillance between Finasteride with AS and AS alone by use of the log rank test, with survival outcomes of time until cessation of active surveillance due to radical prostatectomy, radiotherapy, androgen deprivation treatment prior to radiotherapy or other treatment for prostate cancer or death from prostate cancer. Participants who are lost to follow up, or who die of a cause unrelated to prostate cancer will be taken as censored.

All randomised participants will be analysed for the primary endpoint in an ITT approach, according to originally randomised treatment arm, with Finasteride cessation unrelated to an end of active surveillance (e.g., due to side effects) ignored in the sense of a treatment policy approach to the treatment withdrawal intercurrent event.

Median time to cessation of AS in each arm will also be presented by Kaplan-Meir survival curves and by medians (if cessation rates sufficiently high to allow median estimation).

9.3.3 Secondary outcome analyses

- The EQ-5D QOL questionnaire has five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three qualifying levels of response roughly corresponding to 'no problems', 'some difficulties/problems', and 'extreme difficulties'. The results of the EQ-5D-5L questionnaire completed at 3, 6, 12, 18, 24, 36, 48 & 60 months will be summarised by counts of each level for the five dimensions and compared between Finasteride and AS alone by the Cochran-Armitage trend test. The total EQ5D score will be summarised for each arm by mean, SD, median, quartiles and minimum, maximum, and compared by the Mann-Whitney U test.
- The tolerability of Finasteride treatment will be summarised in the Finasteride arm by the count of adverse events and a summary of tablet returned count (median and minimum, maximum).
- Separate secondary analyses will compare Finasteride and AS by log rank test the time until
    - Cessation of AS due to initiation of ADT and/or chemotherapy OR
    - Cessation of AS due to Radical Prostatectomy, OR
    - Cessation of AS due to Radical Radiotherapy.

In each case, in the event of loss to follow up the censoring time will be taken as the last visit where participants were known to have not started ADT/chemotherapy, RP or RR respectively. Participants who experience one of the events e.g., the initiation of ADT will not be followed up for occurrence of the others i.e., RP and RR and will be censored at that event time for analysis of the other individual outcomes.

All occurrences of cessation from AS events due to i) ADT initiation or chemotherapy ii) Radical Prostatectomy or iii) Radical Radiotherapy during participant follow-up will be treated as competing risks in the separate secondary analyses.

Cumulative incidence plots will be presented with a curve for overall AS cessation and separate curves for cessation for the individual post AS treatments.

9.3.4 Per-protocol Analysis

The primary endpoint will be analysed a second time using the per protocol approach. The per protocol population will mirror the ITT population but exclude any participants with a defined protocol deviation or who have insufficient adherence to the trial medication defined as having missed ≥ 6 consecutive months of treatment or half the time to progression, if progression is within the first year of randomisation.

9.4 Subgroup analyses

In addition to the overall comparisons of primary and secondary outcomes we shall also perform comparisons between Finasteride and AS alone for low risk and intermediate risk men separately.

9.5 Adjusted analysis

We will also compare rates of non-adherence to active surveillance between Finasteride with AS and AS alone by use of a Cox proportional hazards model adjusting for stratification factors low vs. intermediate and participant age (<65 vs. ≥65 yrs) and baseline Gleason, PSA and ECOG status.

9.6 Interim analysis and criteria for the premature termination of the trial

There is no intention to perform an interim analysis to stop on grounds of efficacy. Although there are no safety concerns related to Finasteride the IDMC will review safety data produced by the trial statistician and have the power to recommend termination on that basis.

9.7 Participant population

The main endpoint analysis of progression from AS will be performed on all participants who have been randomised on an ITT basis.

The analysis of QOL questionnaires will be performed on the set of men who complete the questionnaire.

Tolerability of Finasteride analysis will be performed on all participants randomised to Finasteride.

9.8 Procedure(s) to account for missing or spurious data

We anticipate the dropout level to be low. For the main endpoint of progression from AS participants who withdraw from the trial or who are lost to follow-up will be censored at the last attended visit or the time of notification of withdrawal.

The analysis of QOL questionnaires will be performed on the set of men who complete the questionnaire.

9.9 Other statistical considerations.

For the log-rank and Cox proportional hazards assessment of time to AS progression the assumption of proportional hazards between the AS and control arms will be conducted by plotting log cumulative hazards plots.

Kaplan-Meier plots will be produced to both aid the comparison of time to AS between treatment arms and to assess violation of the non-proportional hazards assumption. A formal assessment of proportional hazards will be performed by cumulative martingale residual plots with p-value assessment of the Brownian bridge property present when proportional hazards is approximately satisfied.

In the event of the occurrence of a significant degree of non-proportional hazards then we will compare groups using a time-dependent model.

Any deviations from the statistical analysis plan will require justification to the IDMC and approval by the TSC.

10 DATA MANAGEMENT (Full details can be found in the FINESSE Data Management Plan)

10.1 Data collection tools and source document identification

Data Collection Tools. Please refer to xii at the beginning of the protocol.

Three systems will be used to collect data for the FINESSE trial.

1) The randomisation system: used to randomise participants and allocate a PIN.
2) The FINESSE EDC, (also referred to as simply the EDC within the protocol): a web-based EDC system designed, using the InferMed Macro 4 system for the collection of trial eCRFs.
3) REDCap: used to collect patient identifiable data, participant surveys, and PROMs data. A library of study documents will also be available within REDCap. NB: It is here that site staff will access blank SAE Report CRFS.

NB: 1) and 2) will be used by site staff and FINESSE CCO personnel only. 3) will be used by site staff, FINESSE CCO personnel AND FINESSE participants. Please see below for full details.

Source Documents

ICH E6 1.52, defines source documents as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists,

pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)."

It is the responsibility of the PI or site staff delegate to maintain adequate and accurate study documents used to record observations and other trial related data for each participant enrolled onto the study. All source documents should be original or certified copies. A certified copy in a clinical trial is a paper or electronic copy of the original document, e.g., a laboratory report, that has been verified (I.e., dated signature by the PI or trained clinical delegate) or has been generated through a validated process to produce an exact copy having all the same information, including data that describe the context, content, and structure, as the original. Confirmation of clinical review must take place before being entered into the relevant eCRF.

Where data has been collected from the participant (e.g., weight, well-being questions) and entered directly into the trial EDC, this can be considered source data, but it should also be documented in the participant's notes.

Where paper CRFs (pCRFs) are used, they should be kept in the ISF and will be reviewed alongside the corresponding source data during site monitoring.

If any CRF is transmitted to the sponsor, it is necessary for the trial site to retain a copy to ensure that the PI has an independent account from the sponsor as to what has occurred during the trial at his/her site. Additional information can be found in ICH E6, section 6.4.

Sites may also design their own care plans/worksheets depending on their preference, but this must be discussed and pre-agreed with the FINESSE CCO at site initiation visits. Where used, such worksheets must be filed with the participant's hospital notes.

At the start of the study, the site will be asked to complete a source document location sheet which should be signed off by the PI and filed in the ISF. Thereafter, data collection processes will be reviewed and verified at scheduled monitoring visits to ensure validity, accuracy, and consistency.

Where data has been entered directly by the participant into REDCap (e.g., questionnaires) this will be considered source data. Note: Paper formats of the questionnaires may be used if requested by the participant. Local site staff will be responsible for receiving, entering, and securely storing these, i.e., individuals with no monitoring or oversight roles. All paper questionnaires completed, must be available for SDV.

An inclusive but not exhaustive list of source data for the trial is as follows:

- eCRFs completed in the FINESSE EDC where data has been collected from the participant and entered directly into the EDC.
- Questionnaires completed by participants in REDCap
- Paper versions of the questionnaires where they have been completed by participants and subsequently entered into REDCap by site staff on behalf of the participants.
- PID entered into REDCap where this data has been collected from the participant and entered directly into the EDC by site staff.
- Original laboratory results – e.g., PSA level results, pathology reports
- Original MRI scans and corresponding reports.
- Certified copies (e.g. Printed, signed and dated photocopies) of handwritten notes.

- Certified copies (e.g., signed and dated) of completed study specific worksheets.

The source data for each site will be identified via a Source Data Agreement, completed before trial initiation.

Spoke sites will be provided with study specific work/prompt sheets for their use, where required. Once source data is provided to Hubs, this will be used for EDC data entry. Source data will subsequently be reviewed and verified via monitoring as usual.

Spokes sites will be expected to ensure any other potential source data relevant to the trial is documented and provided via printed (or photocopied i.e., if handwritten notes) certified copies. Full details and template study specific work/prompt sheets will be provided in the FINESSE Hub and Spoke Manual.

(See appendices 5a, b and c) for CRF summary of data capture)

Case report forms

Two systems will be used specifically to collect trial data:

1) The FINESSE EDC, (developed using InferMed Macro 4)
2) REDCap

NB: Spoke site staff will not be required to perform data entry for the FINESSE Study, and therefore will not be granted access to the FINESSE EDC or REDCap. All reference to site or local staff includes hub staff only, where applicable.

The FINESSE EDC

A web-based EDC system will be designed, using the InferMed Macro 4 system. The FINESSE EDC will be created in collaboration with the trial TC, statistician and the CI and maintained by KCTU for the duration of the project. It will be hosted on a dedicated server within KCL.

MACRO will serve as the main eCRF repository for the study where site staff will be expected to enter data related to:

- Eligibility
- Randomisation
- Demographics
- AEs/SAEs
- Concomitant medications
- Study procedures (bpMRI/mpMRIs, biopsies, and PSA results)
- Follow-up data including treatment compliance/pill counts.

The CI or delegate (TM/TC) will request usernames and passwords on behalf of site staff, from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (TM/TC) from the KCTU team and a request for access to be revoked must be made when staff members leave the project. Study site

staff experiencing issues with system access or functionality should contact the CI or delegate (TM/TC in the first instance).

Participant initials and date of birth will be entered on the EDC. NHS number, email addresses, participant names and addresses, and full postcodes will not be entered into the EDC. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial. Source data will be entered by site staff, typically within 5-7 days of data collection, (excluding SAEs), by authorised staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the EDC system. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

The PI has overall responsibility for ensuring the accuracy, completeness, and timeliness of the data entered into the eCRF at their site. Data reported on the eCRF should be consistent with the source documents.

The CI team (TM or TC) will undertake appropriate reviews of the entered data, (in consultation with the statistician) for the purpose of data cleaning and will request amendments as required. No data will be amended independently of the study site responsible for entering the data.

At the end of the trial, the site PI will review all the data for each participant and provide electronic sign-off to verify that all the data are complete and correct. At this point, all data can be formally locked for analysis.

Upon request, KCTU will provide a copy of the final exported dataset to the Trial Statistician in .csv format

Paper-based backup case report forms will be available in case of system failure or for additional convenience. Where pCRFs are used, participants will be identified by their initials and trial number only. When completing the pCRFs, data should be written in black ink with a ball-point pen. If the Investigator or delegate makes an error, the entry should be crossed through with a single line to ensure that the original entry can still be read. The correct entry should then be clearly written and initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid (example, Tippex) is not permitted. It remains the responsibility of the local site to transfer the data collected on paper to the EDC system. Completed pCRFs should be kept in the ISF and will be reviewed as part of source data verification during site monitoring.

REDCap

A second web-based EDC system will be designed using REDCap (a secure web application for building and managing online surveys and databases).

The REDCap database will be used by;

- Site staff to:
  - Enter PID. PID collected will include the participant email address, NHS number, mobile phone number, date of birth and home address. This is so that triggered questionnaires for completion, SMS reminders and study IMP in the event of untoward circumstances, e.g., a pandemic lockdown, can be sent to the participants. Questionnaires and eCRFs will be distributed via email containing a unique URL link, and can be completed on a smartphone, tablet or computer.

  - Enter paper PROMS questionnaires and surveys on behalf of participants, where used.
  - Review PROMs questionnaires entered by participants for potential AEs & SAEs requiring reporting.
  - Access study documents within the library section. Participants will not have permissions to view this. All patient facing documents will be available on the trial website.
- The study participants to input participant surveys and Patient Reported Outcome Measures (PROMs).
- CPTU staff to:
  - Send automated questionnaires, appointment reminders and prompts to complete outstanding questionnaires, to the participants.
- The Lead Trial Pathologist and Lead Trial Radiologist to enter the findings from their central reviews of the pathology samples and bpMRI/mpMRI scans respectively. These will be recorded at site level only. If a site is perceived as an outlier in reporting variability, the Trial Pathologist must in the first instance alert the TMG.

The REDCap trial database will be created in collaboration with the CPTU Senior Clinical Trials Application Developer, Trial TC, and the CI, maintained by CPTU for the duration of the project and kept in a Data Safe Haven (DSH). The DSH will be maintained by AIMES, (AIMES https://www.aimes.uk/) a contracted GDPR compliant third-party storage provider based within the UK..

The DSH is a controlled and secured service environment for undertaking research using sensitive data (personal, sensitive-personal, or confidential). The service provides robust controls and safeguards to enable the secure transfer of sensitive data into a highly secure environment where it can be stored, manipulated, and analysed by approved members of a research team. Only designated members of the FINESSE trial team will have access to the study database and the DSH.

Data transferred/saved in the DSH a, will be cleaned/queried/checked for missing data. The final dataset will be exported and analysed in STATA or R.

Data held within the REDCap database will be exported as .csv files and will be imported into a statistical programme (e.g., STATA) for final data cleaning and analysis.

Direct access to the eCRFs will be maintained by the trial team. Since PID is being collected on REDCap, two-factor authentication will be enabled before staff can access the database, and the PID will be kept separate from all clinical data. Staff access to data may also be restricted to only that essential to their role (e.g., a delegated data entry assistant may not require access to PID, and so would be blocked from accessing this data)

If a participant does not have an email address, or access to a computer, tablet, or smartphone, they will be able to request paper questionnaires. As stated previously, where completed, paper questionnaires will be entered by local site staff, into REDCap, on behalf of the participants.

10.2 Data Completeness

Several methods will be used to ensure the data is as complete as is possible. These include:

a) **FINESSE EDC validation checks**

The FINESSE EDC has in-built validation checks which identify and alert the user to missing, unusual and invalid data, allowing study sites to validate their data in real-time. Reference should be made to the FINESSE user requirement specifications and CRF specifications documents. When validation checks are performed the user will be prompted to check if the values entered meet the individual field's validation rules.

Validation checks are performed to verify:

- the accuracy of data types (numeric, date and text etc.)
- ranges for numeric and date fields
- future date errors
- mandatory fields (marked with an asterisk on the eCRF) have been completed
- branching questions are correctly completed
- results that have been inputted are correct

b) **Manual Reviews and Queries**

The TC will also carry out manual reviews of the study data to:

- Check aspects of the dataset that cannot be checked via the automatic validations (e.g., complex reconciliation of data across two or more eCRF pages) or to perform checks for data which require medical interpretation (Medical Review). Medical review will be undertaken by a medically qualified individual delegated this responsibility.
- Ensure existing checks coded within the EDC are adequate i.e., if there are a high number of checks, the CRFs may have to be locked manually (as the CRF cannot be validated), too few checks and an increased level of manual data cleaning will be required.
- Ensure risk group and pathology review quotas are observed, (see sections and respectively).

In addition, regular queries will be run to identify inconsistencies and blank fields. For further central monitoring details, please refer to the monitoring plan.

The TC will review data queries on an ongoing basis. Data queries will be raised and transferred to local sites within the FINESSE EDC. Persistent failure by sites to complete queries within a month will result in the PI and LCO of the site being alerted. Persistent non-compliance may indicate the need for some sort of remediation, including additional training, triggered monitoring visits, or even site closure.

If, for any reason, a site is unable to resolve a query, the matter will be discussed by the FINESSE research team and an appropriate decision will be made as necessary.

The TC will raise queries on completed eCRFs in the FINESSE EDC by flagging missing or inconsistently/incorrectly answered questions and forwarding them to the relevant site personnel. Each user will be able to view their site's queries upon logging in to the EDC. The user will be responsible for answering the raised queries and amending the answers in the eCRF and

pCRF where applicable. The TC will check that this process has been completed satisfactorily and then close the query.

Authorised users will be able to view the outstanding queries flagged each time they log into the FINESSE EDC. An email with all outstanding queries will also be generated and sent approximately every 8 weeks to each site.

If the resolution proposed by the person entering data at the site is incomplete, either because the eCRF was not amended or the answer provided contradicts existing data, the query will remain open in the FINESSE EDC and will be included in the query reports sent to sites. The TC will have the facility within the EDC, to generate reports identifying a list of participants with raised queries, and/or missing data.

Missing and unobtainable data will be coded to ensure that repeat queries are not raised unnecessarily. The codes used can be found in the FINESSE Data Management Plan and will be identical for both the FINESSE EDC and REDCap.

c) Website League Tables

We will consider posting missed visits and missing data metrics within the FINESSE study EDC system, to create a climate to encourage other investigators to collect more complete data.

d) Automated SMS text message/Email reminders to participants

Participants will be sent both appointment reminders and prompts to complete the PROMs questionnaires. This is explained in the PIS and consent is collected at the trial outset. It is envisaged this will help participants stay on track with the clinical trial protocol by improving adherence, compliance, and retention.

e) Continued Data Collection after Dropout

The trial procedures allow for an informed withdrawal of consent so that participants recognise the importance of continued follow-up for data collection if they discontinue study treatment. This is covered in the PIS.

10.3 Data handling and record keeping

All data transferred between stakeholders will be covered by appropriate data sharing, data processing agreements or in the case of data transferred from trial sites to KCL, the site agreement. Trial data will be stored securely and made available for audit according to CPTU and KCTU SOPs. Please refer to section 10.1 for details regarding the Data Safe Haven for REDCap (

Further information on data handling and record keeping can be found in the FINESSE Study Data Management plan.

10.4 Access to Data

The Investigator(s)/site(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data and documents.

Spoke sites shall permit hub site staff access to the records of participants to the extent considered necessary by the Principal Investigator for the conduct and oversight of the study, and safety of participants. In theory all monitoring should be conducted at the hub site, but the spoke site shall also permit the Sponsor's appointed representatives, access to all relevant Clinical Data for monitoring, source data verification and adverse event reporting or investigation if required. Full details will be documented in a 'Hub and Spoke Agreement' signed by representatives for both parties.

Study participants will be informed of this during the informed consent discussion. The process will include participants being asked to consent to provide access to their medical notes and or to any online registries that contain information related to their diagnosis. Access to data will be limited to the minimum number of individuals necessary for quality control, audit, and analysis.

10.5 Archiving

Archiving will be authorised by the Sponsor following confirmation that all the trial-related documents are complete, the data have been analysed and the end of study notification has been submitted and acknowledged by the regulatory authority. KCL CPTU TC 04 Archiving SOP will be observed with the exception of the archiving duration where the Sponsor's requirement of 15 years takes precedence. CPTU will coordinate the archiving of all study records, including databases, eCRF, and the TMF.

Whilst it is each sites' responsibility to archive their ISF and participants' study records locally, the CPTU will work with the PIs to ensure secure archiving of all relevant trial information. Throughout the retention period, sites must ensure that the study documents are kept in secure conditions and made available for regulatory or sponsor audits. Destruction of essential documents will require authorisation from the Sponsor.

11 MONITORING, AUDIT and INSPECTION

A formal risk assessment has been undertaken for the trial to identify the main risks and to propose mitigation strategies for these risks to ensure safe and successful delivery of the trial. A list of these risks is explained in greater detail in the FINESSE Risk Assessment Log.

The risk assessment has defined the FINESSE study as MODERATE risk and as such, monitoring of the trial will be conducted using a risk-based approach following the monitoring plan developed by the trial team.

A combination of onsite, remote and central monitoring will be undertaken, to an agreed frequency and schedule. The interval for monitoring visits may be longer or shorter, dependant on subject enrolment rates, quality issues, trial site compliance, other trial site issues or any event(s) that affect the overall conduct of the study.

The trial TC/Monitor will arrange a date and time with the appropriate person and site staff to ensure documents are available for the visit. Sites will be given at least 2 weeks' notice of any monitoring visit. Ideally, the PI will be met at each visit, where possible.

The following areas may be reviewed as part of trial monitoring:

- Consent and eligibility checks prior to randomisation
- Rates of recruitment, withdrawals, and losses to follow up by site
- Adherence to trial procedures
- Study specific site training and delegation logs to ensure all personnel working on the trial have adequate training and trial functions have been correctly delegated to authorised individuals.
- Completeness, accuracy, and timeliness of data collection and of data entry into the validated eCRF
- Any treatment modification, adverse events, concomitant medications, and inter-current illness is reported in accordance with the protocol in the eCRFs
- Maintenance of essential documents kept in the ISF
- Source Data Verification
- Pharmacy checks (drug dispensing, management, and accountability logs)

Full details on monitoring, audit and inspection are documented in the FINESSE Study Monitoring Plan.

In order to manage and oversee the study, a TMG, a TSC and IDMC have been put together. Members of these Committees, their responsibilities, and frequency of their meetings are explained in the General Section of this protocol.

The trial may be audited by the sponsor and/or CPTU.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Health Research Authority (HRA) and Research Ethics Committee (REC) approvals

The CI will ensure that the protocol and supporting participant-facing documentation receive HRA approval, including being presented to a relevant Research Ethics Committee for favourable opinion. Following ethical review, research will only take place once appropriate HRA approvals are in place. The trial team will prepare the Annual Progress and Annual Safety Reports on behalf of the CI within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. They will also on behalf of the CI:

- notify the REC of the end of the trial
- if the trial is ended prematurely, will notify the REC, including the reasons for the premature termination
- within one year after the end of the trial, will submit a final report with the results, including any publications/abstracts, to the REC

12.2 Confidentiality Advisory Group (CAG) approval

Participants will give consent at the start of the study for the collection and storage of their PID in an encrypted database for the purposes of patient reported outcomes data collection, long-term follow-up via NHS registries, and to notify their GPs of their participation in the study. Therefore, CAG approval will not be sought.

Participants have the right to revoke their consent for their identifiable data to be stored by the FINESSE trial coordinating centre at any time.

12.3 Other approvals

Full Sponsor approval will be sought before the trial is submitted for ethical and regulatory approval. STHNFT will act as sponsor for this Trial.

The protocol will be submitted by those delegated to do so to the relevant Research and Development (R&D) department of each participating centre. A copy of the local Confirmation of Capacity and Capability and of the PIS and Consent Form, on local headed paper should be forwarded to the CPTU before participants are entered. An agreement will be in place between each centre and the CPTU, and each between each hub and spoke where applicable, setting out respective roles and responsibilities.

Approval for release of HES data and access to data processed by the National Cancer Registration and Analysis Service (NCRAS) will be obtained from the Public Health England Office for Data Release (PHE ODR) or replacement body at the time of application.

The Trial Master File will hold all approvals and relevant communications with the aforementioned bodies and be maintained by the CPTU.

12.4 Peer review

The protocol has received independent, expert, and proportionate reviews including review by the TSC Chair or delegate, and an independent clinician.

12.5 Public and Patient Involvement

We recruited eight PPI representatives with lived experience of prostate cancer. Our PPI representatives are aged between 63 and 71 years old, and of varying ethnicities and prostate cancer experience. Two of the members have joined the TSC and TMG, respectively.

At the study planning stage, the PPI representatives informed the design of the study to ensure that the research questions and study design are relevant to the needs of patients with prostate cancer. PPI contributors at this early stage of the research cycle emphasised the importance of knowing their PSA test results and potential anxiety that taking a drug which could 'mask' true PSA levels might cause among patients. Therefore, patients considering taking part in this study would need to understand clearly why taking the drug might be beneficial for more accurate assessment of prostate cancer progression.

PPI representatives also suggested replacing some of the words and phrases commonly used by clinicians with those more acceptable to patients, within the trial documents e.g., 'castration-resistant prostate cancer' with 'hormone-resistant prostate cancer').

Based on PPI input a draft Participant Information Sheet (PIS) and Participant Information Leaflet were prepared. PPI representatives were subsequently asked to read and comment on both to ensure readability, that it contains sufficient detail for potential participants to make an informed decision about taking part, without being overly complex or long, and that the research being proposed is ethically sound and addresses issues deemed important from a public perspective.

PPI members commented on the importance of highlighting the random treatment allocation in this study, by explicitly stating men will not be able to select their preferred study arm or be able to change their allocated study arm, once randomised. Many men use complementary medicines for their prostate cancer so the members advocated that including information on the products they would and

would not be able to use whilst on the study, would be important to help men make an informed decision about participating. They also suggested additional information regarding prostate cancer treatment options should be provided in the Participation Information Sheet, since men who have been recently diagnosed, often have limited knowledge of this.

All feedback provided by the PPI members was presented to and discussed by the Trial Management Group. Where deemed appropriate, the PIS and PIL were amended in accordance with the suggestions. The revised versions of the PIS and PIL were sent to two PPI members for further review. Subsequent suggested amendments were considered and added where appropriate, before the documents were finalised.

PPI members were consulted in the choice of self-completed patient questionnaires measuring cancer-related quality of life and cancer treatment decision-making. They commented on their relevance, appropriateness, length, and on possible methods to encourage study participants to complete all study questionnaires in timely manner.

PPI members were also involved in the design of the study flyer, poster and invitation letter for use in participating hospital clinics to aid recruitment.

Since study launch, PPI members have also been consulted for each protocol amendment. For example, the information additional to the PIS for spoke sites was subjected to PPI review. We will involve patients in the later stages of the project to help interpret findings and promote dissemination of study results. We have budgeted for the costs of attendance at meetings, including travel, subsistence, and reimbursement for time spent.

12.6 Regulatory Compliance

This is a Clinical Trial of an IMP as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK and the trial will not commence until one is obtained from the competent authority/MHRA, in addition to favourable REC opinion. Furthermore, the protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials)

The progress of the trial and safety issues including safety reports, expedited reporting and SUSARS will be submitted to the competent authority in accordance with the MHRA's requirements, in a timely manner.

The Trial Master File will hold all approvals and relevant communications with the MHRA, and be maintained by the CPTU.

12.7 Protocol compliance

All unintentional protocol deviations will be adequately documented on the relevant forms, reported on the trial deviation log and notified to CPTU. Deviations from the protocol which are found to frequently recur will require immediate action and could potentially be classified as a serious breach. The CI will retain oversight of the trial deviation log.

12.8 Notification of Serious Breaches to GCP and/or the protocol

The sponsor of the Clinical Trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial; or
- The protocol relating to the trial, as amended from time to time in accordance with regulations 22-25, within 7 days of becoming aware of that breach

For the purposes of this regulation a 'serious breach' is a breach which is likely to effect to a significant degree:

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

The CI is responsible for reporting any serious breaches to the sponsor (STHNFT) within one working day. The sponsor will notify and report to the MHRA within 7 working days of becoming aware of the serious breach.

12.9 Data protection and patient confidentiality

Information with regards to study participants should be kept confidential and managed in accordance with the Data Protection Act 2018, NHS Caldicott Guardian, UK GDPR, the Research Governance Framework for Health and Social Care and Research Ethics Committee Approval. The Investigator and site study team and spoke site staff must adhere to these parameters to ensure that the patient's identity is protected at every stage of their participation within the study.

The Investigator has a responsibility to ensure that patient anonymity is protected and maintained from any unauthorised parties throughout the study. However, in keeping in line with GCP, applicable regulatory requirements for conducting clinical trials and as specified in the study monitoring plan, parts of the patient's medical records and the data collected for the trial will be looked at by authorised staff from the individual hospital trusts where the trial is based. The data may also be looked at by representatives of the trial team for monitoring and regulatory authorities to ensure that the trial is being carried out correctly, as stated on the consent form.

Upon enrolment into the study, each participant will be allocated a unique PIN as determined by the computer-generated randomisation system. Throughout the duration of the study, this number (along with the participants initials) will be used to identify the participant on study related databases, the eCRF, any study document and sample labels. However, the PI is still responsible for keeping sufficient information to link records e.g., CRFs, hospital records and samples of all participating patients at their site.

Linkage of trial data to other sources of electronic health data will be used to improve the reliability of long-term follow-up data collected on this study. Participants will be asked to give informed consent for information about their health status to be obtained from any health or social care provider (i.e. NCRAS and HES data via NHS Digital or Public Health England) who holds information about them in the UK. To enable this, direct identifiers/Personal Identifiable Data (PID) such as the patient's name, DoB and NHS number and/or hospital number will be collected to ensure the study data is updated with accurate data held by others. The collection of PID will also allow for annual follow-ups to be conducted by authorised study personnel.

Health data collected from any health or social care provider will be securely transferred to the trial team in a CSV format and uploaded onto the REDCap database. Restricted access to this data will be given to authorised and trained personnel working on the study, and the PID will be stored on a secure, restricted access server DSH maintained by AIMES, a contracted GDPR compliant third-party storage provider based within the UK.. The data will be stored for a period of 15 years following completion of the study.

Note: Although we are collecting consent, the legal basis for processing this data will be under UK GDPR Articles 6(e) and 9(g): Public interest and the data will be used for the purposes stated above only. Study participants may revoke their authorisation for the use of their personal information at any time.

The CI and Co-Lead Applicant at KCL will be the joint custodians of the data collected, and with the exception of the participant's mobile number, used to send participants text message reminders, no patient identifiable details will be accessed by any third parties outside the UK. Access to this data, (mobile number only), will be in accordance with UK GDPR, and personal-identifiable data will never be stored outside of the UK.

Should patient information need to be sent to a third party within the UK (including correspondence/communication to central laboratories and the sponsor), the PI and the study team should adhere to data protection requirements and where possible, should only use the unique study number and participants initials when corresponding. Exceptions will include the sending of patient identifiable information to trial registries, e.g., NCRAS, for long-term follow-up purposes, and scans/slides for central review.

Upon completion of the trial, all information generated in the trial will be kept strictly confidential and only anonymised data will be used in future publications relating to this study, as detailed in the PIS and Consent Form.

12.10 Financial and other competing interests

At present there are no financial or other competing interests for the CI, PIs at each site and committee members for the overall trial management. However, at the time of writing, not all sites/personnel have been identified. In the event that competing interests are identified in the future, disclosure will reflect:

- ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
- commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- any non-commercial potential conflicts e.g., professional collaborations that may impact on academic promotion.

This information will be held in the TMF, and will be reported to the REC as appropriate.

12.11 Indemnity

The overall sponsor of the trial is the STHNFT and the trial is coordinated by the CPTU.

NHS indemnity will provide cover for negligent harm relating to STHNFT' role as trial sponsor. As employers of the authors, King's College and the UoS provide indemnity to cover negligence only liabilities arising from the design of the research. Participants may be able to claim compensation if they can prove that STHNFT, KCL and/or the UoS has been negligent.

However, as this clinical trial is being carried out in hospital, the hospital continues to have a duty of care to the participant of the clinical trial. STHNFT, KCL and UoS do not accept liability for any breach

in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise. In the case of NHS sites, NHS indemnity will provide cover for negligent harm occurring from the conduct of the trial at NHS sites.

Participants who sustain injury as a result of negligence and wish to make a claim for compensation should do so in writing in the first instance to the CI via the CPTU. This will then be passed to the relevant insurer. Hospitals participating in the FINESSE Study must provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary should be provided upon request.

No arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises have been made by the Sponsor.

12.12 Hub and Spoke Indemnity Arrangements

Both the Hub and spoke sites acknowledge that former has entered into a mNCA with the Sponsor that includes liability and indemnity provisions whereby the Sponsor shall indemnify the Hub Site and its agents, against any reasonable claims, proceedings and related costs, expenses, losses, damages and demands to the extent they arise or result from the negligent acts or omissions of, or the wilful misconduct of the Sponsor, and/or contracted third party, in its performance of the mNCA or in connection with the Study. The spoke site is a contracted agent of the Hub Site. Full details of the indemnity responsibilities for each party can be found in the Non-commercial Hub and Spoke Service Level Agreement.

12.13 Amendments

Trial amendments will be prepared by the CPTU trial team according to local SOPs, and Sponsor, REC, HRA and MHRA requirements for submission. Protocol changes will be approved by STHNFT and CPTU prior to submission, and potentially by the TSC depending on the nature of the amendment as detailed in the TSC Charter.

It will be the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to regulatory bodies. The CPTU Trial team will be responsible for cascading amendments to participating sites, communicating substantive changes to all other stakeholders e.g., trial registries, the funder), and updating the Trial specific protocol and study documents version logs.

12.14 Post trial care

Men in the Finasteride arm may be allowed to continue the treatment after 2 years, in agreement with their GP. We will discourage men in the AS only arm (non-finasteride) opting for either finasteride or dutasteride until the trial outcomes are analysed. If the trial shows a benefit from finasteride, then after reporting we will recommend men discuss the possibility of further treatment with their GP.

All men will return to their routine active surveillance appointments once they have completed the trial. If participants have given permission, they will be contacted directly with the ongoing progress and the aggregate results of the trial. Results will also be available to participants and the public on the FINESSE Study website and through their clinician.

12.15 Access to the final trial dataset

12.14.1 MACRO

The KCTU will have controlled access to the full dataset. The final data extract and codebook will be provided by KCTU to Trial Statistician, as per the FINESSE SAP for analysis.

12.15.2 REDCap

The Trial Statistician will ask the Senior Database Developer (DD) to extract and send the agreed dataset to them. The extraction will be provided in an encrypted form (with passwords sent separately). The receiving party will confirm receipt of the files and return a signed copy of the report.
A copy of any protocol deviation logs should be provided to the statistician by the TC when the export is sent. The data analysis method is covered in the SAP.

Neither the CI, nor site investigators will have access to the full dataset. However, should they require access post analysis, a formal request describing their plans should be submitted to and approved by the CI and TSC.

The wider data-sharing and dissemination plans will be agreed with the funder. Results/reports for the study will be written up and reported to the applicable regulatory authorities within the required timeframes, and to the sponsor, funder and scientific publications, as agreed in the wider data sharing policy.

Further details on the final data set and data transfer timelines are detailed in the data management plan.

13 DISSEMINATION POLICY

13.1 Dissemination policy

This is an investigator-led study sponsored by STHNFT. The data arising from this trial will be co-owned by STHNFT, UoS and KCL. A final study report will be completed and posted on the EudraCT website within 12 months of the end of trial. In addition, the data gathered from the study will be collated and analysed by researchers at KCL. Summary reports of the main trial findings will be written and shared with the study sites, the funder YCR, the Sponsor and Cancer Research UK. Findings will be published at the aggregate, not individual level, in peer reviewed scientific journals, online, and presented at national and/or international conferences.

Individual groups and clinicians must not publish data concerning their participants, which are directly relevant to questions posed by the study until the TMG has published its report, or unless approved by the TMG and Sponsor first. The TMG will form the basis of the Writing Committee and will advise on the nature of all publications.

If at any point it is felt to be justified and appropriate to release specific data prior to publication, this would require discussion and agreement from the IDMC, who would be asked to provide guidance regarding the data to be released and how widely they should be disseminated.

If participants have given permission, they will be contacted directly with the ongoing progress and the aggregate results of the trial. Results will also be available to participants and the public on the FINESSE Study website and through their clinician.

The data collected will not be used to licence/register any pharmaceuticals, and the trial will be registered on the ISRCTN registry.

13.2 Authorship eligibility guidelines and any intended use of professional writers

The final study report and related publications will be authored in line with the arrangements set out in the Collaborative Agreement and any subsequent variations or amendments. All publications will be approved by the CI. Authorship will follow the criteria established by the International Committee of Medical Journal Editors.

Authorship of the final manuscript(s), interim publications, or abstracts will be decided by the TMG. Authors are likely to include relevant members of the TMG and collaborators, CPTU Head of Operations as well as high-recruiting Investigators. All participating centres and corresponding PIs/co-PIs will be acknowledged in all relevant publications, along with members of the IDMC and TSC.

In the event that there are a number of resulting publications, authorship may vary for each.

14. PANDEMIC FUTURE PROOFING

Given the potential for a pandemic or similar event to influence the study viability, we have endeavoured to future proof the trial so that it may continue successfully, should circumstances change, by adding the following to the trial design and study procedures:

- A willingness to conduct SIVs remotely if required, using presentations, videos, and short quizzes to consolidate understanding and electronic training logs. We will consider offering regular training drop-in slots, which staff could join depending on their availability. Sites might benefit from queries other sites ask.
- Facilitation of e-consent and video/telephone assessments.
- We will secure consent to communicate with participants via text and email to keep them informed and to encourage compliance.
- Where participants cannot or are reluctant to attend appointments we will;
    - Use telephone or video consultations
    - Consider asking GPs to check PSA levels
    - Deliver the IMP to the participant's address, and/or consider dispensing 2 trial visits worth of IMP at a time if the budget is restrictive. We will prepare for this in advance by securing the participants' consent to store their nominated delivery address. In terms of pharmacovigilance there may also be a need to develop alternative processes**.**
- Treatment breaks and +/-6 month windows around imaging and prostate biopsies have been built into the protocol.

- Provision has been made to collect data via NCRAS, including during the active phase of the trial which will potentially compensate for any study data unreported by sites.
- Development of a trial website - in addition to promoting the trial it will be used to communicate with both trial staff and participants, and as a repository for patient facing documents.
- Provision of a central repository for trial documents for sites within REDCap .
- Should it be necessary to pause the trial, we will administer refresher training. We will maintain contact with the sites during the break to keep them informed and to maintain their enthusiasm for the study. In addition, local staff may offer valuable perspectives of what is happening on the ground.

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16. APPENDICIES

Appendix 1-Trial Risk Assessment Summary

Risks associated with trial interventions

☒ A ≡ Comparable to the risk of standard medical care

☐ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification:

We believe a grading of Type A is justified on the basis of MHRA risk adaptation guidance since there is extensive clinical experience with the product, and no reason to suspect a different safety profile in our trial population, despite concerns of an increased incidence of higher grade prostate cancer amongst men in trials using finasteride compared with placebo.

A very recent meta-analysis provides reassurance that the increased incidence of higher-grade prostate cancer in initial studies does not translate to an adverse impact on the quantity (or even quality) of life. Specifically, Knijnik et al [[31], showed a reduction in prostate cancer diagnosis, with no increase in higher-grade disease, overall- or cancer-specific mortality. This meta-analysis included the seminal studies (e.g., PCPT, CombaT, REDUCE) which had previously generated some of the uncertainty. Furthermore, this meta-analysis supersedes that published by Wilt et al. in 2008 [42] which had been unable to draw conclusions on cancer-specific survival.

Additional analyses also suggest that the increase in the prevalence of high-grade prostate cancer observed in the finasteride group may be explained by a detection bias due to the effect of finasteride on prostate volume.

The adverse reactions reported during clinical trials and/or post-marketing use are listed in the table below.

Frequency of adverse reactions is determined as follows:

Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), not known (cannot be estimated from the available data).

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports.

IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
Finasteride	Reproductive system and breast disorders	PSA levels decrease in patients treated with finasteride. In most patients, a rapid decrease in PSA is seen within the first months	Common	It is well known [43] that 5-alpha reductase inhibitors reduce serum PSA levels by approximately half. This is incorporated

		of therapy, after which time PSA levels stabilize to a new baseline. The post-treatment baseline approximates half of the pre-treatment value.		into the management of men worldwide receiving finasteride during standard practice, including the follow up of men with known prostate cancer who are taking finasteride for benign prostate hyperplasia (BPH)/benign symptoms. As such, we do not believe that patients in the treatment arm (open-label finasteride) will have their 'true' PSA value masked in any way different to standard and common practice. Additionally, PSA-levels are only one of several forms of surveillance that will be used. We believe the use of MRI, digital rectal examinations (DRE) and where indicated, further biopsies are more reliable than PSA. Our study participants will be receiving these in a stringent and safe manner. PSA fluctuates in active surveillance and would not be used alone. For these reasons we are confident that the effect of finasteride on PSA will not lead to missed disease.
		Impotence	Common	• Potential participants will be informed of all the possible risks associated with taking
		Ejaculation disorder.	Uncommon	
		Breast tenderness Breast enlargement	Uncommon	
		Testicular pain	Unknown	

		Erectile dysfunction that continued after discontinuation of treatment	Unknown	finasteride, and they will also be documented in the Patient Information Sheet (PIS) • Information on the IMP will be discussed at the SIV where sites will also be provided with an IB in their ISF. • AEs and SAEs will be closely monitored and reviewed on an ongoing basis.
		Hematospermia; male infertility and/or poor seminal quality	Unknown	
	Immune system disorders	Hypersensitivity reactions including swelling of the lips tongue, throat and face	Unknown:	
	Psychiatric disorders	Decreased libido	Common:	
		Depression, decreased libido that continued after discontinuation of treatment, Anxiety	Not known:	
	Cardiac disorders	Palpitation	Unknown:	
	Hepatobiliary disorders	Increased hepatic enzymes	Unknown:	
	Skin and subcutaneous tissue disorders	Rash	Uncommon:	
		Pruritus, urticaria	Unknown:	
	Investigations	Decreased volume of ejaculate	Common	

Other processes to mitigate risks to participant safety

An IDMC comprised of at least one independent statistician, and one independent clinician, has been established. In accordance with the Trial Terms of Reference, the IDMC, will periodically review the overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis. The committee will advise the TSC, and the discontinuation of any research arm, temporary cessation or early closure of the trial as deemed necessary will be at the discretion of the IDMC and TSC.

Although not prescribed for women generally, or within the FINESSE trial, finasteride is contraindicated for use in women when they are or may potentially be pregnant. Due to this type II 5α-reductase-inhibitor's ability to inhibit conversion of testosterone to dihydrotestosterone, finasteride may cause abnormalities of the external genitalia of a male foetus when administered to a pregnant woman. For this reason, men trying for a baby or with a pregnant partner are excluded from the trial.

Women should not handle crushed or broken tablets of finasteride when they are or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus. Finasteride tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. In addition, small amounts of finasteride have been recovered from the semen in subjects receiving finasteride 5 mg/day. It is not known whether a male foetus may be adversely affected if his mother is exposed to the semen of a patient being treated with finasteride.

Therefore, the FINESSE PIS advises participants taking finasteride to use a condom when having sex with a female partner and to inform their female partner not touch any crushed or broken finasteride tablets if there is any chance, she could be pregnant.

Appropriate counselling will be given to participants by the site clinical team. Confirmation of this discussion should be documented in the participants' records which will be reviewed at monitoring visits.

Sites are expected to report all pregnancies within the trial where the participant is randomised to take finasteride, to the CI and the Sponsor using the relevant Pregnancy Reporting Form, within 24 hours of notification.

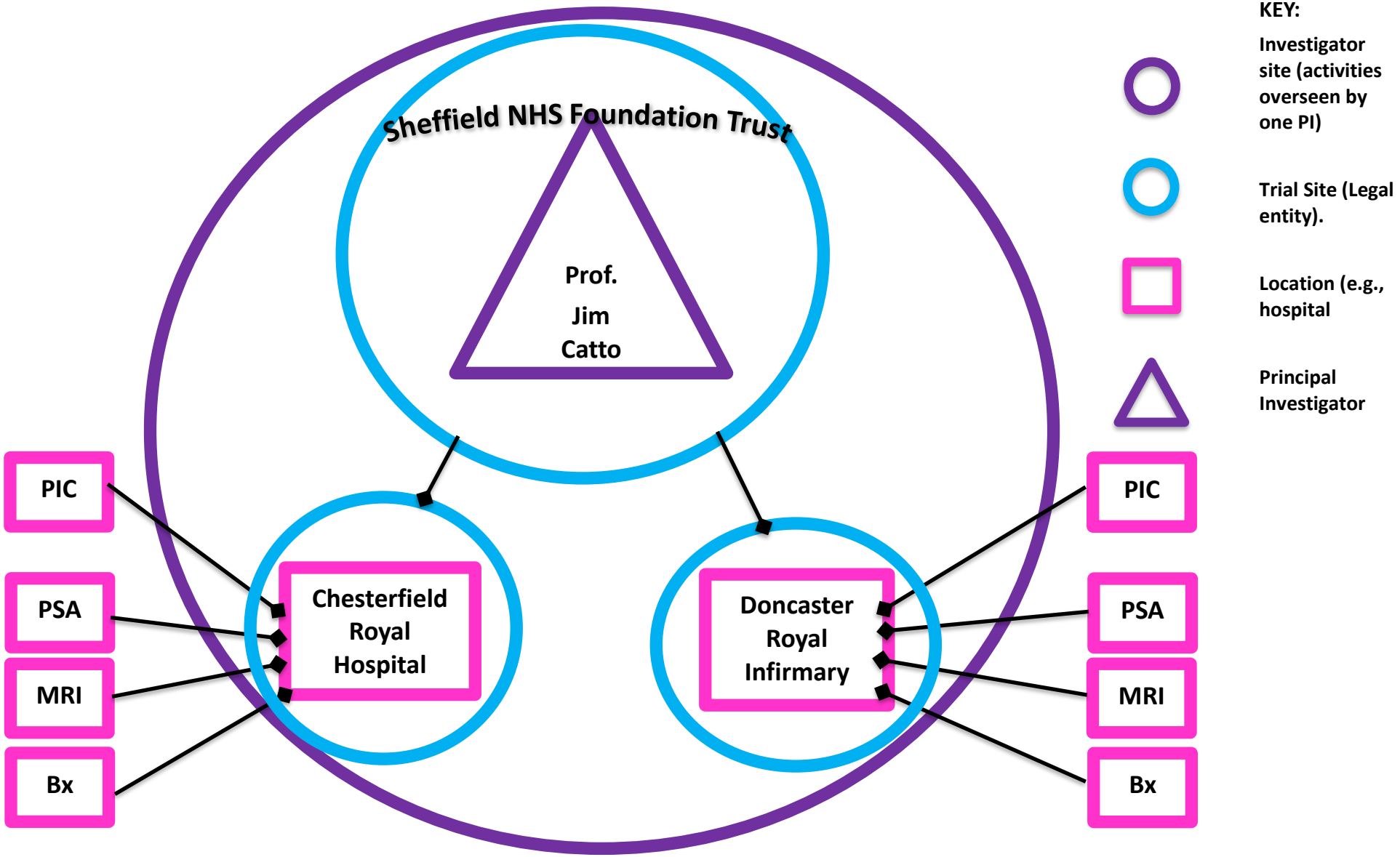
In line with the type A grading, the following processes have been simplified based on the risk adapted approach:

- The SmPC will replace the Investigator's Brochure
- The IMP will be stored in accordance with normal clinical practice
- IMP recalls will be managed according to local pharmacy policy.
- Reduced IMP labelling will be used, with labels being applied at site, and dispensing logs will require less detail.

Appendix 2: List of Planned Participating Centres and Potential PICS/Spokes

NHS Cancer Centre	Potential Participant Identification Centre (PIC)/Spokes
Bradford Teaching Hospitals NHS Foundation Trust Bradford Royal Infirmary Smith Lane Bradford BD9 6DA	• Airedale General Hospital • Calderdale and Huddersfield NHS Foundation Trust
Leeds Teaching Hospitals NHS Trust St James's University Hospital, Beckett Street, Leeds, LS9 7TF.	• York and Scarborough Teaching Hospitals NHS Foundation Trust
Oxford University Hospitals NHS Foundation Trust Churchill Hospital Old Road Headington Oxford OX3 7LE United Kingdom	• Buckinghamshire Healthcare NHS Trust • Milton Keynes University Hospital
Sheffield Teaching Hospitals NHS Foundation Trust Royal Hallamshire Hospital Glossop Road Sheffield S10 2JF	• Chesterfield Royal Hospital • Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust • Rotherham General Hospital • Barnsley Hospital NHS Foundation Trust
Mid Yorkshire Teaching NHS Trust Aberford Road Wakefield WF1 4DG	

Appendix 3: Example Hub and Spoke Model



Appendix 4: Schedule of Assessments Table:

FINESSE Schedule of Assessments Table			TREATMENT PHASE (Years 1-2)										FOLLOW UP PHASE (Years 3-5)					
			Timepoint in months (visit can be +/- 2 weeks).															
	Screening	Baseline	Randomisation	3	6	9	12	15	18	21	24	30	36	42	48	54	60	Early Withdrawal[b]
PIS & PIL given[d]	x																	
Screening log updated[d]	x																	
ICF signed		x																
Registration		x																
Eligibility (Inclusion & Exclusion Assessment)		x																
Medical History		x																
Demographics		x																
Height & Weight		x					x				x		x		x		x	x
ECOG/Performance status		x					x				x		x		x		x	x
Physical Examination (Inc. DRE)[a]		x					x				x		x		x		x	X
Randomisation			x															
Drug dispensing*			x	x	x	x	x	x	x	x								
Drug accountability*				x	x	x	x	x	x	x	x							x
Adverse Event(s) review		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

FINESSE Schedule of Assessments Table

			TREATMENT PHASE (Years 1-2)										FOLLOW UP PHASE (Years 3-5)					
			Timepoint in months (visit can be +/- 2 weeks).															
	Screening	Baseline	Randomisation	3	6	9	12	15	18	21	24	30	36	42	48	54	60	Early Withdrawal [b]
Serious Adverse Event (s) review		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medication(s) review		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Procedure(s) review		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PSA Test[a]		x		x	x	x	x		x		x	x	x	x	x	x	x	
MRI Scan[a c]		x					x						x					
Biopsy <not mandatory at 36M>[a c]		x											x					

Key:

* Treatment arm only, (active surveillance PLUS finasteride)

[a] In line with standard practice for active surveillance. The baseline PSA test must have been in the last 3 months and the MRI scan and prostate biopsy must have been within the last 12 months of the date of randomisation. The result from the DRE, if taken as local/standard practice for active surveillance, should be entered. However, this is not a mandatory assessment at any time point.

[b] Where a participant stops treatment before the 24mth time point and fails to attend their 'End of Study' appointment, the LCO is responsible for checking their AE status at least 30 days after the date the participant states they have stopped their IMP dose.

The participant will not be required to attend clinic for this 30 day post treatment cessation pharmacovigilance check. It may be conducted via the telephone.

[c] Where a radical prostatectomy is carried out, every effort will be made to obtain pathological data and/or tissue, together with any related bpMRI/mpMRI scans/reports

[d] In cases where the 'Hub & Spoke' model is in use, these activities will be conducted by the spoke site.

Appendix 5: List of finasteride excipients

Core:	Cellulose, microcrystalline
	Sodium starch glycolate (Type A)
	Starch pregelatinised (maize)
	Docusate sodium
	Magnesium stearate
Film-coating:	Hydroxypropyl cellulose
	Hypromellose
	Titanium dioxide
	Talc
	Indigo carmine aluminium lake (E132)
	Iron oxide yellow (E172)

Appendix 6a: ECRFs Completed by Site Staff on MACRO, Summary Table

Form name	Baseline	Randomisation	Ongoing	Month 3	Month 6	Month 9	Month 12	Month 15[a]	Month 18	Month 21[a]	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60	End of Study	Early Withdrawal[b]
1. Registration Form	X																		
2. Eligibility	X																		
3. Prostate Cancer Details	X																		
4. Medical History	X																		
5. Demographics	X																		
6. Randomisation Form		X																	
7. Status Form				X	X	X	X	X	X	X	X	X	X	X	X	X	X		
8. Prostate Cancer Progression				X	X	X	X	X	X	X	X	X	X	X	X	X	X		
9. Active Surveillance Adherence			X																
10. Height and Weight (Height only required at baseline)	X						X				X		X		X		X		X
11. Adapted ECOG/Performance Status	X						X				X		X		X		X		X
12. Physical Examination (DRE[c])	X						X				X		X		X		X		X
13. Drug Dispensing and Pill Count Log*			X																
14. IMP Reconciliation Log*			X																
15. Adverse Events Log			X																
16. Concomitant Medications Log			X																
17. Concomitant Procedures Log			X																
18. PSA Test	X			X	X	X	X		X		X	X	X	X	X	X	X		
19. Radiological Assessment (MRI)	X						X						X						
20. Tissue Sample Collection Form (Biopsy)	X												X						
21. Withdrawal from Study Form			X																X
22. Participant Death			X																
23. PI Sign Off																		X	

FINESSE Study

Key

* Active surveillance and finasteride treatment arm only

a. These appointments may be virtual, although participants on the active surveillance and finasteride treatment arm will be expected to return their remaining IMP for pill counts.

b. Where a participant stops treatment before the 24mth time point and fails to attend their final appointment, the LCO is responsible for checking their AE status at least 30 days after the date the participant states they have stopped their IMP dose. The participant will not be required to attend clinic for this 30 day post treatment cessation pharmacovigilance check. It may be conducted via the telephone.

c. The result from the DRE, if taken as local/standard practice for active surveillance, should be entered. However, this is not a mandatory assessment at any time point.

Appendix 6b: ECRFs Completed by Site Staff on REDCap, Summary Table

In addition, site staff will be required to enter PID on behalf of each participant on REDCap, as follows:

Completed by Site Staff on FINESSE web-based EDC, (REDCap)			**TREATMENT PHASE (Years 1-2)**								**FOLLOW UP PHASE (Years 3-5)**						
			Timepoint in months (visit can be +/- 2 weeks).														
		Randomisation/ Baseline	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**Early Withdrawal**
	Personal details (e.g., name, address, NHS number).	x		x		x		x		x	x	x	x	x	x	x	x

Appendix 6c: Summary table of eCRFs completed by participants on FINESSE web-based EDC, (REDCap)

Completed by participants on FINESSE web-based EDC, (REDCap)			TREATMENT PHASE (Years 1-2)								FOLLOW UP PHASE *(Years 3-5)*						
			Timepoint in months (visit can be +/- 2 weeks).														
		Randomisation/ Baseline	3	6	9	12	15	18	21	24	30	36	42	48	54	60	Early Withdrawal
Quality of Life Measures	EQ-5D-5L	x	x	x		x		x		x		x		x		x	x [a, b]
	EORTC QLQ C30	x	x	x		x		x		x		x		x		x	x [a, b]
	EPIC	x	x	x		x		x		x		x		x		x	x [a, b]
	EORTC QLQ FA12	x	x	x		x		x		x		x		x		x	x [a, b]
	Memorial Anxiety Scale Prostate Cancer	x	x	x		x		x		x		x		x		x	x [a, b]
	Depression Anxiety Stress Scales (DASS) 21	x	x	x		x		x		x		x		x		x	x [a, b]
Decision Making Measures	Decisional Conflict Scale	x				x				x		x		x		x	x [a, b]
	Subjective Decision Quality	x				x				x		x		x		x	x [a, b]
	Decisional Regret	x				x				x		x		x		x	x [a, b]
	Decisional Involvement	x				x				x		x		x		x	x [a, b]
Adherence	Voils DOSE-Non adherence measure		x	x	x	x	x	x	x	x							x [c]

KEY for appendix 6c:

a Where a participant stops treatment and/or trial participation early, due to radical treatment, they will continue to receive these questionnaires for completion, for the remainder of their intended period of follow-up, providing they consent to do so. The exception for this group is the 'Decisional Conflict Scale' which will not be assessed again, and the decisional involvement scale which will only be administered once more, post radical therapy.

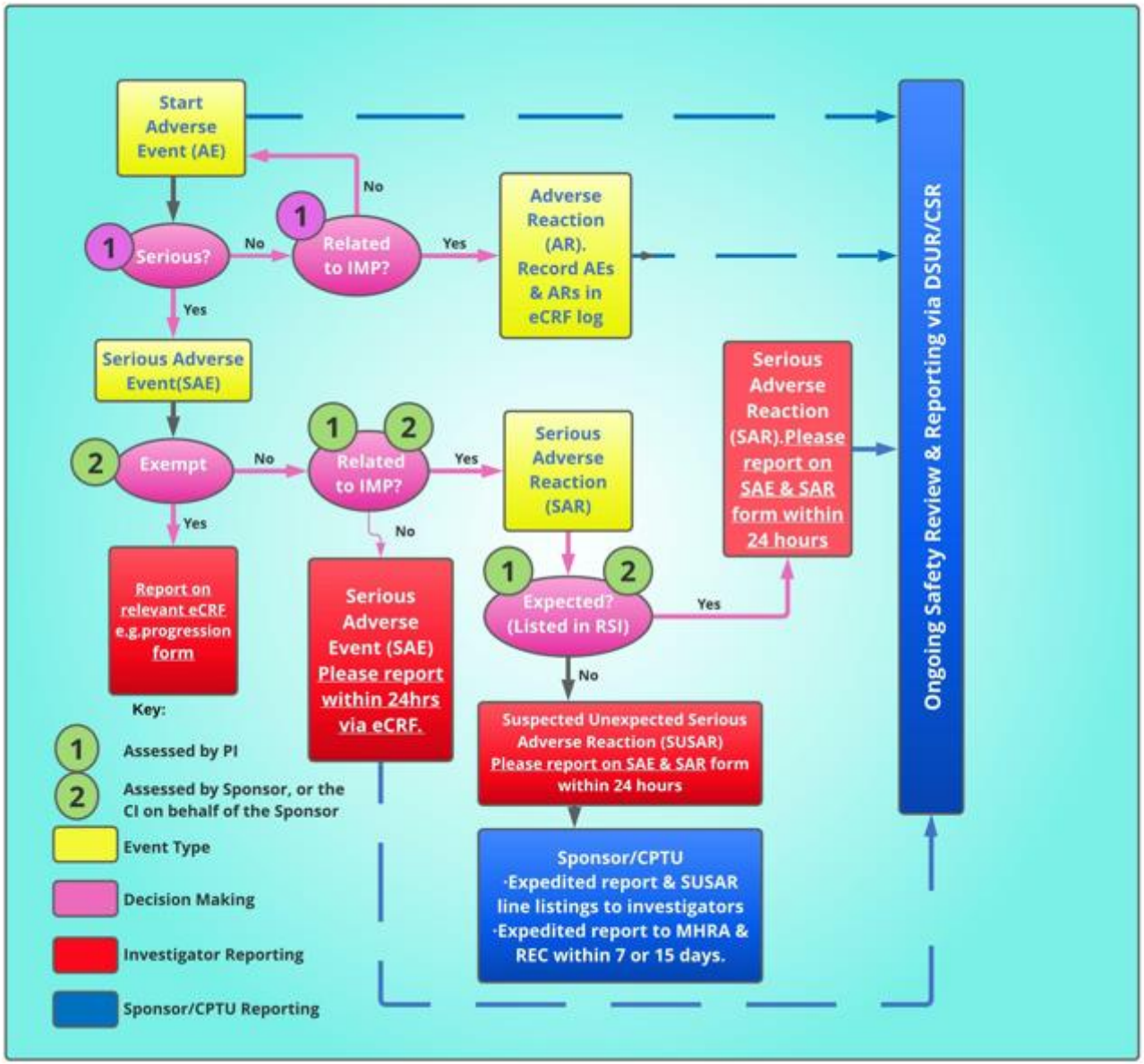
b Where a participant stops treatment and/or trial participation early, for any reason other than radical treatment, they will continue to receive these questionnaires for completion, for the remainder of their intended period of follow-up, providing they consent to do so.

c If the participant is still on treatment at the point of early withdrawal, one final Voils DOSE-Nonadherence measure – Extent Scale will be sent for completion

Appendix 7: List of P450 3A Inducers and Inhibitors

ACTION	DRUG NAME
Cytochrome P450 Inducers: CYP450 inducers reduce the concentration of drugs metabolised by the CYP450 system.	Carbemazepines
	Rifampicin
	Alcohol
	Phenytoin
	Griseofulvin
	Phenobarbitone
	Sulphonylureas
Cytochrome P450 Inhibitors: CYP450 inhibitors increase the concentration of drugs metabolised by the CYP450 system.	Sodium valproate
	Isoniazid
	Cimetidine
	Ketoconazole
	Fluconazole
	Alcohol and Grapefruit juice
	Chloramphenicol
	Erythromycin
	Sulfonamides
	Ciprofloxacin
	Omeprazole
	Metronidazole

Appendix 8: Safety Reporting Flowchart



Appendix 9: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1 (Non-substantial)	2.0	03/Mar/2022	Roseann Kealy	Administrative changes to the protocol to reflect a shift of responsibility to the study team for some of the functionality originally assigned to the MACRO Electronic Data Capture (EDC) system. The build of the latter is being outsourced and the vendor in question was unable to support all the features we had anticipated. Changes include: • Centrally monitoring the number of participants allocated to the low and intermediate risk groups to ensure set quotas are observed. Previously this was being managed by the application. • Sites to keep local screening logs outside of the EDC. • Some electronic case report form names have been changed to align with the vendor's nomenclature system. • Removal of the provision of a back-up randomisation system. The treatment is not urgent, and we have been informed outages are very rare. • If e-consent is required, e.g., in the event of a pandemic, this will now be in REDCap, not MACRO. • Prescriptions will no longer be printed by the application. • SAE reporting and data collection for the MRI & Pathology Central Reviews are now being conducted outside of MACRO. • The data flow diagram (xii) and appendices 5a & 5b summarising the eCRFS completed by site staff on MACRO and REDCap respectively, have been updated to reflect the above. • Removal of the self-referral process for patients contacting the FINESSE CCO directly.
2 (Substantial)	3.0	18th May 2022	Roseann Kealy	The following administrative changes have been made to the protocol: • Amendment of the term 'transgender women' to 'transgender persons'.

				• References for the qualitative assessment tools being used in the trial have been added to section 15 of the protocol. • The IMP destruction policy has been clarified. • Units added to PSA density • All text stating no data will be transferred outside of the UK has been amended, since TWILIO, the third party we are using to send SMS reminders to participants on our behalf, has servers based in the US and Europe. No REDCap data is ever stored on the Twilio servers. REDCap requires disabling Twilio's Request Inspector. The Request Inspector is a tool provided by Twilio that lists all requests made between Twilio and an external application. When configuring Twilio for a REDCap project, REDCap checks that the Request Inspector is disabled before enabling Twilio for the project. • Details regarding the issuing of the Participant Identification Number (PIN) have been clarified, in particular which system generates it - EDC MACRO, not the Randomisation System. • Further detail regarding the transfer of patient identifiable information. • Revision of the pathology review process. It will be the responsibility of the FINESSE CCO to monitor pathology reporting discrepancies at site. Should the Lead Pathologist record a higher rate of disagreement than expected, this will be discussed with the TMG, who may consider increasing the proportion of biopsies to be centrally reviewed.
3 (Substantial)	4.0	19th June 2023	Roseann Kealy	The following significant changes have been made to the protocol: • Eligibility criteria updated to increase the time since prostate cancer diagnosis from 6 months to 2 years and participants' last MRI scan from 6 months to 12 months. • Inclusion and explanation of the 'Hub and Spoke Model' (HSM), in the protocol and PIS, to augment the use of district general hospitals (DGHs) as PICs, with the potential to conduct standard of care procedures (SoC), and those within usual care competence (WUCC), for the FINESSE trial. DGHs will act as 'spoke' trial sites to the 'hub' investigator site. It will also

				allow for reduced patient burden (i.e., complete transfer to the hub) incorporating patient choice. The HSM will be used in accordance with the HRA Integrated Research Guidelines. • The addition of Pinderfields Hospital, Mid Yorkshire Hospitals NHS Trust as a site. • Clarification that it is also the sites' responsibility to check the completed patient quality of life questionnaires in the FINESSE Study database for adverse events and serious adverse events. • Minor changes to the wording of the primary and some secondary objectives to make them clearer. • The addition of an outcome measure 'Rates of participant death from prostate cancer', to the primary objective. • Separation of the quality-of-life objectives from the secondary objectives and recategorised as explanatory objectives, to reflect their role more accurately. These explanatory objectives provide further context to the primary and secondary objectives relating to adherence. • Anonymisation of the central pathology and radiology review process. • Correction to the location of the Data Safe Haven (DSH). • Clarification that MRI reports only, not scans, may be sent from NHS-to-NHS email instead of via IEP. • Change of Principal investigator at Oxford. Mr Richard Bryant will be replacing Mr Alastair Lamb. • Clarification of the sample size calculation wording. • Removal of the maximum threshold value of 33% of low-risk participants across all sites. The recruitment rate is lower than anticipated, and we do not wish to restrict it further. The following non-significant changes have also been made to the protocol: • Typo of age eligibility criteria on page 39 corrected to <65 years.

				• Clarification that participants will be asked to return their unused medication every 3 months including the 18 months timepoint which was erroneously missed form the following list: 3, 6, 9, 12-, 15-, 21- & 24-month time points. • Clarification that for radiological stage, MX will be treated as M0, and NX as N0 in this study. • Updates to the contact details of Data Monitoring Committee member, Dr Sam Merriel, who has changed institutions. • Clarification that bpMRI scans will be accepted instead of mpMRI scans when determining radiological disease stage, to accommodate sites not conducting multi parametric scans. Finally, the following two additional new documents are also being submitted: • A new patient information sheet addendum to be used with the PIS at hub and spoke sites explaining the Hub and Spoke model. • A new version of the ICF to cover the hub and spoke model.