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Protocol for a randomised phase 3 trial evaluating the role of Finasteride in Active Surveillance for men with low and intermediate-risk prostate cancer: The FINESSE Study

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Abstract

Background

Prostate cancer (PCa) is the commonest male malignancy in the western world. Many men (40%) are diagnosed with localised low or intermediate-risk PCa, which is suitable for Active Surveillance (AS). AS affords careful monitoring to identify changes in otherwise non life-threatening cancers. Whilst AS reduces overtreatment (and quality of life impact), long term compliance can be poor, with many men undergoing radical treatment after starting AS.

Methods and analysis

FINESSE is a prospective, open label, two-arm, phase 3 trial, in which men with low or intermediate PCa are randomised (1:1) to receive AS with or without finasteride (5mg once a day for 2 years). Randomisation is stratified by age and PCa risk. AS includes regular Prostate Specific Antigen (PSA) testing, Magnetic Resonance Imaging (MRI) scans and the offer of repeat biopsy (at 3 years, or if imaging suggests progression). Additional MRI scans and/or biopsies will be performed for biochemical or clinical indications. We aim to recruit 550 men (aged 50 to 75-years) from up to 8 sites. Active outpatient follow up will be for 3-5 years (depending upon date recruited), followed by passive registry-based follow up for up to 10 years. Primary outcome is adherence to AS. Secondary outcomes include rates and type of disease progression, treatments received (for PCa and benign prostatic enlargement), overall and PCa-specific mortality, an understanding of patients/professionals views of this approach, and health-related quality of life. An external panel of experts blinded to allocation, will review all AS cessation and progression events. Trial pathologist's and radiologist's, blinded to allocation, will review representative cases. Analysis is Intention to Treat.

Ethics and dissemination

The study received Health Research Authority and South-Central Oxford Research Ethics Committee (14/12/2021: 21/SC/0349) and CTA/MHRA (29/12/2021: 21304/0274/001-0001) approvals. Results will be made available to providers and researchers via publicly accessible scientific journals.

Trial registration: ISRCTN16867955

Article summary

Strengths and limitations

- Prostate cancer is a common disease and an important public health problem.
- Active surveillance is an established method of managing men with prostate cancer.
- Finasteride is widely available, has a known safety profile, is well tolerated and is used in a similar patient population for benign prostate enlargement.
- This study will determine AS outcomes in a large cohort of intermediate-risk cancers.
- There remains some scepticism about the role of pharmacological PSA manipulation for AS patients.
- Pre-biopsy MRI may reduce the pool of eligible men and hamper recruitment.

Introduction

Prostate cancer (PCa) is the commonest male malignancy in the western world [1]. Prostate Specific Antigen (PSA) screening of asymptomatic men has been used to reduce mortality from the disease. However, most men diagnosed through this route have clinically localised disease and may not benefit from treatment as their cancers are indolent, with a long natural history, or metastatic at diagnosis [2]. There has yet to be a universally accepted screening program for PCa and most men are diagnosed through 'case-finding' using PSA testing for lower urinary tract symptoms or known risk factors (e.g. family history). The detection and radical treatment of PCa 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. Radical treatment is reserved for men whose tumours progress biochemically, clinically, or radiologically.

In men with low-risk PCa undergoing AS, the risk of disease-specific mortality is small (e.g., 0.3% at 8 years and lower than that from competing diseases [5]). AS is popular amongst men with localised PCa [6, 7] and recommended by NICE guidelines in the United Kingdom [https://www.nice.org.uk/guidance/ng131]. However, there are concerns regarding the accuracy of PCa risk stratification and the reliability of monitoring tools [8-10]. Clinicians and patients fear that deferring radical treatment could reduce the chance of cure and lead to higher morbidity [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 the Toronto trial 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. Therefore, many men with rising PSA values may not have disease progression and may not need radical treatment. For 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], highlighting the potential for overtreatment.

Various approaches have been tried to improve compliance with AS, including pharmacological interventions. The REDEEM study group randomised 302 men with low-risk PCa 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). The ENACT study group randomised 227 men with low or intermediate-risk PCa to AS with or without 160mg daily Enzalutamide [17]. The addition of Enzalutamide reduced progression (pathological or therapeutic) by 46% at 12 months, although no difference was present at 2 years, there were side effects with this agent and its cost poses financial challenges to healthcare providers (especially if for long term AS regimens).

Contemporary AS cohorts include many men with intermediate-risk PCa, as MRI may have changed the spectrum of PCa's diagnosed. Many men with small, low risk PCas are often no longer diagnosed either because they do not have a biopsy or there is less random prostate sampling [18, 19, 20]. Within the PRECISION trial, 38% of men with mpMRI guided biopsy (versus 24% in ultrasound Scan (USS) guided-biopsies) had Gleason 3+4 PCa [18]. Van der Leest et al. found mpMRI guided biopsy reduced the rate of insignificant PCa diagnosis from 25% to 14% [19]. Therefore, the focus to improve the care of men with PCa is shifting to using AS in men with intermediate-risk PCa [21-26]. This population is common and includes more men with lethal cancer than in the low-risk cohorts [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 PCa management [Question #1: What is the most suitable surveillance protocol? https://www.nice.org.uk/guidance/ng131]. Given the positive signals from the REDEEM and ENACT trials, this study aims to test if the drug Finasteride can increase men's adherence to AS and reduce radical treatment rates, using a more contemporary cohort.

Methods and analysis

Design

FINESSE is a randomised, prospective, non-blinded, open-label, parallel group, phase 3 trial. Men will be randomised 1:1 to receive Active Surveillance plus finasteride (5 mg) for 2 years or Active Surveillance alone.

Randomisation and population

Randomisation is through a web-based tool bespoke to the King's Clinical Trials Unit (KCTU). Once participants have completed a signed consent form their data will be stored on the system. The randomisation process is at the individual level using the method of permuted block randomisation with block sizes stratified by PCa risk (low vs. intermediate), and participant age (<65 vs. >65 yrs).

Blinding

This is an open label study. Both participants and clinicians will be aware of the study arm to which they are randomised. Whilst test results e.g. MRI scans and PSA values can make it obvious that a participant is taking finasteride, the following will be blinded (not informed) to treatment allocation:

1) Lead Trial Radiologist responsible for reviewing MRI scans.
2) Lead Trial Pathologist responsible for reviewing histopathology.
3) Independent PCa Progression Review Panel (PCPP), made up of three urologists.

Study setting

The FINESSE trial is recruiting in secondary care sites. The trial is funded by Yorkshire Cancer Research, a charity whose remit is to fund research which will save lives in Yorkshire, and so initial sites have been established within the Yorkshire region. Non-Yorkshire centres will be included to expedite recruitment. Eligible patients are identified by secondary care clinicians (urologist) in outpatient clinics and multi-disciplinary team meetings (MDTs). Research nurses will support the screening, consent and follow-up processes.

Recruitment

We aim to recruit 550 men over 24 months. The trial management group (TMG) will monitor this in real time and recommend action if recruitment is behind projections (such as opening

additional sites, extending recruitment duration or adjusting eligibility (e.g. removing biopsy restrictions, increasing the time since diagnosis)). PPI representatives and behavioural scientists will be involved from the outset to ensure the research questions and study design are relevant to the needs of PCa patients, to inform the patient facing literature, and to facilitate effective recruitment. Patients may self-refer by contacting their local FINESSE investigator. Informed consent will be obtained by recruiting physicians (supplemtary files 1-2).

Eligibility criteria

1). Male subjects aged 50 to 75 years, with an estimated life expectancy of 10 years or more, who have opted for AS as their preferred PCa management option.

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.

5). A histological diagnosis of Gleason grade group ≤ 2 (i.e. Gleason grade 3+3=6 or 3+4=7) PCa within the last 6 months.

6). Radiological stage ≤T2b cN0 cM0 as defined by mpMRI imaging within the last 6 months (from the date of the mpMRI scan to the date of the patient's randomisation). A copy of the mpMRI scan, and report confirming eligibility will be required.

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

8). PSA Density ≤0.2ng/ml/ml. The result must be within 3 months of the date of the patient's randomisation

9). Biopsy criteria (via either trans-rectal or trans-perineal routes) within the last 6 months of the patient's randomisation date):

- If targeted biopsy then the maximum cancer core length is ≤10mm
- If targeted and systematic sampling biopsy then the maximum cancer core length should be ≤10mm, and ≤2 or ≤15% of non-targeted cores involved with cancer.

- If non-targeted biopsy (i.e. USS template or sampling irrespective of lesions) then maximum cancer core length is ≤10mm AND ≤3 or ≤20% of total number of cores involved with cancer.

Ineligibility criteria

1). Previously received treatment for PCa (including radiotherapy, hormone therapy, brachytherapy or surgery). Of note, men who have received treatment for benign prostate enlargement are eligible.

2). Current or recent (≤12 months) 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 dutasteride.

6). Known allergy to any excipients of finasteride.

7). Any malignancy (other than non-melanoma skin cancer and/or PCa) 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.

12). High-risk disease.

Usual care: Active surveillance

Men randomised to usual care will receive AS (see figure 1). Patients will not receive a placebo, as PSA and MRI changes make masking impossible, 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, know they are independent of the treatment, participants unaware they are taking finasteride may opt for radical treatment earlier, and placebo controlled trials are expensive. Concerns regarding PSA

changes or digital rectal examination (DRE) changes will lead to MRI scans outside the schedule. Changes in MRI and PSA will lead to either a re-biopsy (to detail histological grade) or radical treatment. Radical treatment without radiological or pathological evidence of progression is discouraged, but not prohibited.

Finasteride plus Active surveillance

Men randomised to the intervention group will receive finasteride (oral 5 mg) to be taken once a day for 2 years, in addition to AS (as above). Participants will be prescribed finasteride on a 3-monthly basis and this will be dispensed from their recruiting hospital pharmacy. Compliance will be measured using pill counts and patient questionnaires.

Study aims

1. To understand whether the addition of finasteride to AS increases adherence in men with low/intermediate-risk PCa.
2. To understand the tolerability and compliance with finasteride within an AS regimen.
3. To understand whether the addition of finasteride to AS reduces disease progression in these men.

Objectives and outcomes

The primary and secondary objectives, with matching outcomes, are detailed in tables 1-2. We will also detail health related quality of life, over time, using validated Patient Reported Outcome tools, including decision regret and conflict findings (table 3).

Sample size

We estimate finasteride will reduce AS cessation rates by 50% (from 20% to 10%) after an average of 4 years follow-up. 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. We assume that 50% of control participants will progress (or be treated) during follow-up and that the hazard ratio is 0.65. The exact number needed is 271 per arm. We believe we will need to screen 1,500 men to obtain 550 eligible, consenting recruits.

Statistical methods

Participant population

The main endpoint analysis of progression from AS will be performed on all participants who have been randomised on an intention-to-treat (ITT) basis. 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 Schemper's weighted model. The analysis of QOL questionnaires will be performed on the set of men who complete the questionnaires. Tolerability of Finasteride analysis will be performed on all participants randomised to Finasteride.

Procedure(s) to account for missing or spurious data

We anticipate the dropout level will 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.

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.

Other statistical considerations

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

Prostate cancer progression panel (PCPP)

Some of the progression events in PCa or reasons for cessation of AS can be open to investigator bias. Given that this trial is open label, to minimise bias and inform broader clinician agreement regarding progression, an independent panel of urologists will review each case of progression or AS cessation. Members of this panel were selected based on recognition of their expertise in managing PCa and knowledge of AS. The panel will agree to the presence (or absence) of progression and classification (e.g. radiological, pathological, biochemical). It was considered optimal to have a panel that is independent of the NHS.

Data collection, monitoring and harms

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 electronic data capture system (EDC, referred to as simply the EDC within the protocol): a web-based EDC system designed, using the InferMed Macro 4 system for collection screening log information, trial eCRFs and generating prescriptions.

3). REDCAP: used to collect patient identifiable data, participant surveys, PROMs, and registry data.

Several methods will be implemented to maximise data completeness. The Finesse EDC has in-built validation checks to alert for missing or unusual data. There will also be manual reviews where data monitoring queries can be raised. There will be league tables for posting metrics on completeness of data from each site. Lastly, there will be automated phone Short Text Messages (SMS) and email reminders to participants to optimise Quality of Life questionnaires completion.

A formal risk assessment has been undertaken for the trial to identify and propose mitigation strategies for the main 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 DM/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. The PI will be met at each visit, where possible.

Ethics and dissemination

Approval, protocol amendments, consent

The Chief Investigator has ensured that the protocol and participant-facing documentation received HRA approval and favourable opinion from a relevant Research Ethics Committee. Full Sponsor approval will be sought before the trial is submitted for ethical and regulatory approval. Sheffield Teaching Hospitals NHS Foundation Trust will act as sponsor for this Trial. The sponors have no role in the collection, interpretation or dissemination of the trial findings.

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 Patient Information Sheet (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 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.

Confidentiality and 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. 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.

Amendments to protocol since recruitment started

Several amendments to the protocol have been completed since the initial protocol and the trial opened to recruitment. Please see these detailed in appendix 1.

Trial Status:

The trial opened to recruitment in August 2022 with the first participant randomised at St. James's University Hospital, Leeds on the 23rd September. The study is in the active recruitment phase.

Acknowledgements:

The trial is led by Professor James Catto, sponsored by Sheffield Teaching Hospitals NHS Foundation Trust (STH21032) and coordinated by the Cancer Research UK & Queen Mary University of London Cancer Prevention Trials Unit (CPTU). The authors would like to thank members of the Trial Steering Committee (Professor Caroline Moore (Chair), Dr. Tristian Barrett, Ms. Phyllis Goodman, Professor Rakesh Heer, Mr Ray Monk, Professor Matthew Sydes and Mr Jeff Willmott), members of the Independent Data Monitoring Committee (Professor Emma Hall (Chair), Professor Chris Parker, Dr Peter Albersten and Dr Sam Merriel) and members of the Prostate Cancer Progression Panel (Professor Declan Murphy, Professor Piet Ost and Dr Roderick C.N. van den Bergh).

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Authors contributions:

MGC - construction, critical review of the protocol and writing of the manuscript

BN - statistics and critical review of the manuscript

RK – protocol and study document development, trial management and critical review of the manuscript

SS - behavioural science and critical review of the manuscript

RH – development of radiological manual and critical review of the manuscript

SK – development of radiological manual and critical review of the manuscript

BS – development of the pathological manual and critical review of the manuscript

WC - critical review of the manuscript

RC - critical review of the manuscript

RB - critical review of the manuscript

AL - critical review of the manuscript

SL - critical review of the manuscript from the PPI view point

PS - concept, funding, trial design, statistics and writing of the manuscript

JWFC - concept, funding, trial design, protocol development and writing of the manuscript

Competing interests statement:

MGC has received speaker fees from Ipsen and Pfizer. JWFC has received reimbursement for consultancy from Astra Zeneca, BMS, Ipsen, Janssen and Roche, speaker fees from BMS, Ipsen, MSD, Nucleix and Roche, honoraria for membership of advisory boards from Astra Zeneca, Ferring, Roche and Janssen, and research funding from Roche. PS is a paid member of the Scientific Advisory Board of GRAIL and the medical advisory board of NSV. The remaining authors declare no potential conflicts of interest.

Participant Consent for Publication:

Not required. No identifiable personal data will be used in publications.

Data Availability:

All information related to participants will be kept confidential and managed in accordance with UK General Data Protection Regulation (GDPR), Data Protection Act (2018), NHS Caldicott Principles, UK Policy Framework for Health and Social Care Research (2017), and the conditions of Research Ethics Committee Approval. Upon reasonable requests to the study team, only deidentified participant data will be available after publication of the study outcomes. Use and projects need approval by the Trial Steering Committee. Data will be shared via secure NHS email or a secure data sharing platform. Robust data sharing agreements will be put in place with all collaborating organisations as necessary to ensure the confidentiality and appropriate data handling. No identifiable personal data will be shared with organisations or individuals outside of these collaborating organisations.

Ethics and regulatory approvals:

The study received the following approvals: Health Research Authority and South-Central Oxford Research Ethics Committee (14/12/2021: 21/SC/0349) and CTA/MHRA (29/12/2021: 21304/0274/001-0001). The trial is registered as ISRCTN16867955.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

References:

1. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. *Eur Urol 2020;77(1):38-52.*

2. Martin RM, Turner EL, Young GJ, et al. Prostate-Specific Antigen Screening and 15-Year Prostate Cancer Mortality: A Secondary Analysis of the CAP Randomized Clinical Trial. *JAMA* 2024;331(17):1460–1470.

3. Loeb S, Bjurlin MA, Nicholson J et al. Overdiagnosis and overtreatment of PCa. *Eur Urol 2014;65(6):1046-1055.*

4. Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, Jain S, Yamamoto T, Mamedov A, Loblaw A. Long-term follow-up of a large active surveillance cohort of patients with PCa. *J Clin Oncol 2015;33(3):272-277.*

5. Yamamoto T, Musunuru HB, Vesprini D, Zhang L, Ghanem G, Loblaw A, Klotz L: Metastatic PCa in Men Initially Treated with Active Surveillance. *J Urol 2016;195(5):1409-1414.*

6. Cooperberg MR, Carroll PR. Trends in Management for Patients With Localized PCa, 1990-2013. *JAMA 2015;314(1):80-82.*

7. Loeb S, Folkvaljon Y, Curnyn C, Robinson D, Bratt O, Stattin P: Uptake of Active Surveillance for Very-Low-Risk PCa in Sweden. *JAMA Oncol 2017;3(10):1393-1398.*

8. Tosoian JJ, Trock BJ, Landis P, Feng Z, Epstein JI, Partin AW, Walsh PC, Carter HB: Active surveillance program for PCa: an update of the Johns Hopkins experience. *J Clin Oncol 2011;29(16):2185-2190.*

9. van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T, van Leeuwen PJ, Roobol MJ, Schröder FH, Hugosson J: Is delayed radical prostatectomy in men with low-risk screen- detected PCa associated with a higher risk of unfavorable outcomes? *Cancer 2010;116(5):1281-1290.*

10. Simpkin AJ, Tilling K, Martin RM, Lane JA, Hamdy FC, Holmberg L, Neal DE, Metcalfe C, Donovan JL: Systematic Review and Meta-analysis of Factors Determining Change to Radical Treatment in Active Surveillance for Localized PCa. *Eur Urol 2015;67(6):993-1005.*

11. Johansson E, Steineck G, Holmberg L, Johansson JE, Nyberg T, Ruutu M, Bill-Axelson A. Long- term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian PCa Group-4 randomised trial. *Lancet Oncol 2011;12(9):891-899.*

12. Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, Martin RM, Young GJ, Walsh EI, Bryant RJ, Bollina P *et al*. Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med 2023;388(17):1547-1558.*

13. Bokhorst LP, Valdagni R, Rannikko A, Kakehi Y, Pickles T, Bangma CH, Roobol MJ: A Decade of Active Surveillance in the PRIAS Study: An Update and Evaluation of the Criteria Used to Recommend a Switch to Active Treatment. *Eur Urol 2016;70(6):954-960.*

14. Godtman RA, Holmberg E, Khatami A, Pihl CG, Stranne J, Hugosson J: Long-term Results of Active Surveillance in the Göteborg Randomized, Population-based PCa Screening Trial. *Eur Urol 2016;70(5):760-766.*

15. Hong SK, Sternberg IA, Keren Paz GE, Kim PH, Touijer KA, Scardino PT, Eastham JA: Definitive pathology at radical prostatectomy is commonly favorable in men following initial active surveillance. *Eur Urol* 2014;66(2):214-219.

16. Fleshner NE, Lucia MS, Egerdie B, Aaron L, Eure G, Nandy I, Black L, Rittmaster RS: Dutasteride in localised PCa management: the REDEEM randomised, double-blind, placebo- controlled trial. *Lancet 2012;379(9821):1103-1111.*

17. Shore ND, Renzulli J, Fleshner NE, et al. Enzalutamide Monotherapy vs Active Surveillance in Patients With Low-risk or Intermediate-risk Localized Prostate Cancer: The ENACT Randomized Clinical Trial. *JAMA Oncol* 2022;8(8):1128–1136.

18. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, Briganti A, Budäus L, Hellawell G, Hindley RG *et al*: MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med 2018;378(19):1767-1777.*

19. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, Zamecnik P, Bakker D, Setiasti AY, Veltman J *et al*: Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve

Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. *Eur Urol 2019;75(4):570-578.*

20. Kasivisvanathan V, Stabile A, Neves JB, Giganti F, Valerio M, Shanmugabavan Y, Clement KD, Sarkar D, Philippou Y, Thurtle D *et al*: Magnetic Resonance Imaging-targeted Biopsy Versus Systematic Biopsy in the Detection of PCa: A Systematic Review and Meta-analysis. *Eur Urol 2019;76(3):284-303.*

21. Cooperberg MR, Cowan JE, Hilton JF, Reese AC, Zaid HB, Porten SP, Shinohara K, Meng MV, Greene KL, Carroll PR: Outcomes of active surveillance for men with intermediate-risk PCa. *J Clin Oncol 2011;29(2):228-234.*

22. Ahmed HU, Arya M, Freeman A, Emberton M: Do low-grade and low-volume PCas bear the hallmarks of malignancy? *Lancet Oncol 2012;13(11):e509-517.*

23. Overland MR, Washington SL, 3rd, Carroll PR, Cooperberg MR, Herlemann A: Active surveillance for intermediate-risk PCa: yes, but for whom? *Curr Opin Urol 2019;29(6):605-611.*

24. Kim SP, Shah ND, Meropol NJ, Tilburt JC, Nguyen PL, Yu JB, Abouassaly R, Kim A, Gross CP: Recommendations of Active Surveillance for Intermediate-risk PCa: Results from a National Survey of Radiation Oncologists and Urologists. *Eur Urol Oncol 2019;2(2):189-195.*

25. Tosoian JJ, Carter HB: Patients with Intermediate-risk PCa May be Good Candidates for Active Surveillance: Con. *J Urol* 2017;198(5):997-999.

26. Nyame YA, Almassi N, Haywood SC, Greene DJ, Ganesan V, Dai C, Zabell J, Reichard C, Arora H, Zampini A *et al*: Intermediate-Term Outcomes for Men with Very Low/Low and Intermediate/High Risk PCa Managed by Active Surveillance. *J Urol 2017;198(3):591-599.*

27. Francis JJ, Johnston M, Robertson C, Glidewell L, Entwistle V, Eccles MP, Grimshaw JM. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. *Psychol Health 2010;25(10):1229-1245*

28. C. Englman, D. Maffei, C. Allen, A. Kirkham, P. Albertsen, V. Kasivisvanathan, *et al*. PRECISE Version 2: Updated Recommendations for Reporting Prostate Magnetic

Resonance Imaging in Patients on Active Surveillance for Prostate Cancer. *Eur Urol 2024;86(3):240-255*

Figure legends

Figure 1. Recruitment and participant flow within the FINESSE study. Follow up within Active Surveillance includes PSA testing, MRI Scans and the offer of a repeat biopsy (times in months (m) shown).

Tables

Table 1. Primary objectives and outcomes within the Finesse trial.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
Primary Objective: To compare adherence with AS in men with low or intermediate PCa 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. - Rate of other treatment for PCa. - Rate of participant death from PCa. - Rate of men discontinuing AS for any other reason.	- 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. - Later analysis will use passive follow up (up to 10 years after trial closure).	- Rates in each arm will be measured by patient self-reporting. - Participants who are lost to follow up, or who die of a cause unrelated to PCa will be taken as censored.

Table 2. Secondary objectives and outcomes within the Finesse trial.

1. To compare between Finasteride with AS and AS alone, the rates of cessation of AS due to: i. ADT and/or chemotherapy initiation ii. Radical Prostatectomy iii. Radical Radiotherapy initiation. iv. Other treatment including watchful waiting V. Death from prostate cancer **Outcome Measures** Time until cessation of AS due to initiation of: i. ADT and/or chemotherapy ii. Radical Prostatectomy or iii. Radical Radiotherapy **Timepoint(s) of evaluation of this outcome measure (if applicable):** All occurrences of cessation of AS events due to i) ADT initiation, chemotherapy, ii) Radical Prostatectomy iii) Radical Radiotherapy, iV) Other treatment including watchful waiting, and v) death from prostate cancer during participant follow-up, 4 years on average, will be included in the analysis. The listed reasons for AS cessation will be treated as competing events. Cumulative incidence plots will be presented with a curve for overall AS cessation and for cessation for the individual post AS treatment. **Additional Information:**
2. To measure prostate cancer progression. **Outcome Measures** Progression is defined as either: - Increase in MRI stage from T2a to ≥T2c, T2b to ≥T2c, or T2x to ≥T3b [28] - Increase in grade from Gleason 3+3 to ≥3+4 or 3+4 to ≥4+3 - RARP histology revealing 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. - Death from prostate cancer. - Clinical DRE deterioration* - Extra-prostatic disease (note *DRE results alone will not be considered a definitive endpoint). **Timepoint(s) of evaluation of this outcome measure (if applicable):** **Additional Information:**
3. To measure PCa mortality. **Outcome Measures** Participant death from PCa. **Timepoint(s) of evaluation of this outcome measure (if applicable):** All deaths from PCa occurring during the 3-5 years follow-up of the study will be analysed.
4. To study the changes in MRI appearances of the prostate over time in men with/without finasteride. **Outcome Measures** bpMRI/mpMRI scan results at baseline (the diagnostic MRI), 12 and 36 months. (Please note, a 36-month MRI scan is strongly recommended). **Timepoint(s) of evaluation of this outcome measure (if applicable):** Baseline, 12 and 36 months. **Additional Information:** We will record: - Prostate volume from (height, width, length). - PCa stage: Using the Prostate Imaging Reporting and Data System (version 2) and Tumour, Nodes, Metastasis staging.

- PCa size: Taken as the maximum diameter on an axial slice from the MRI acquisitions. The pMRI/mpMRI images will be quality controlled centrally by the Lead radiologist. 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 AS for this disease. **Outcome Measures** Semi-structured one-to-one interviews led by a trained interviewer, with selected individuals during the follow- up phase. **Timepoint(s) of evaluation of this outcome measure (if applicable):** Months 48 to 60 **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 similar). **Outcome Measures** Patient self-reporting. **Timepoint(s) of evaluation of this outcome measure (if applicable):** All symptoms during the follow up of between 3 and 5 years until trial end. **Additional Information:** Determined from new prescriptions for 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 similar).
7. Overall (all cause) mortality. **Outcome Measures** Death eCRF completed by sites. **Timepoint(s) of evaluation of this outcome measure (if applicable):** All deaths during the follow up of between 3 and 5 years until trial end. **Additional Information:** Cause of death will be decided by note review (and CRF completion) and death certificates.

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Table 3: Schedule of events for quality-of-life measures (collected through eCRFs (electronic Case Report Forms)) during the FINESSE trial.

	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]

Footnote:

[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 1: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1). (Non-substantial)	2.0	03.03.2022	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.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
2). (Substantial)	3.0	18.05.2022	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.

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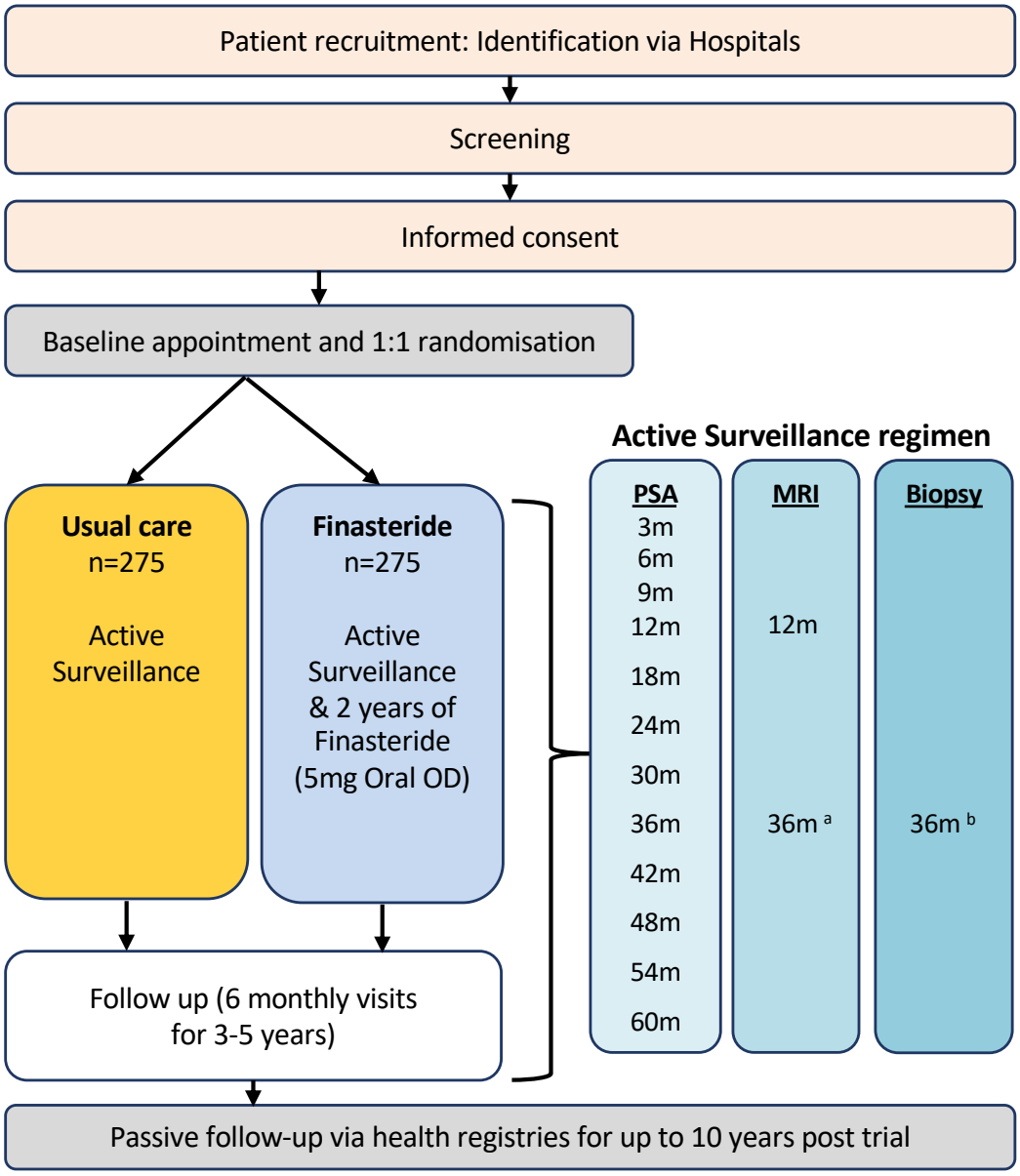
Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
3). (Substantial)	4.0	19.06.2023	Roseann Kealy	The following significant changes have been made to the protocol: • Eligibility criteria updated to increase the time since PCa diagnosis from 6 months to 2 years 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 PCa', 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.
4). (Non-substantial)	4.0	27.09.2023	Roseann Kealy	The following changes have been made to the protocol to address three sections where updates to the timelines were missed within the recently approved substantial amendment: • The trial summary table states, "Men aged 50 to 75 years diagnosed with low/intermediate-risk localised prostate cancer in the 6 months preceding their date of randomisation". This has been corrected to, "Men aged 50 to 75 years diagnosed with low/intermediate-risk localised prostate cancer in the 24 months preceding their date of randomisation". • Section 5.1 states, “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”. This has been corrected to read, Eligible men aged 50 – 75 years with low or intermediate-risk prostate cancer diagnosed within the last 24 months will be invited to join the trial”. • Section 6.1b states “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." This has been corrected to read, "Prior active surveillance populations: Recruiting hospitals can assess their databases to identify potentially eligible patients already managed by active surveillance, diagnosed within the last 24 months."
Substantial	5.0	Ongoing	Harriet Strachan & Roseann Kealy	• Change of institution of the Cancer Prevention Trials Unit from King's College London to Queen Mary University of London. • Change of institution for Peter Sasieni (Co-Lead Applicant & Trial Statistician), Bernard North (Independent Trial Statistician) and Roseann Kealy (FINESSE Study Trial Manager) from King's College London to Queen Mary University of London. • Update to indemnity section to add Queen Mary University of London. • Clarification: ○ That the secure restricted access server Data Safe Haven maintained by a contracted GDPR compliant third-party storage provider that stores patient identifiable data for the study will now be retained by King's College London and Queen Mary University of London. ○ Of the IMP destruction policy. ○ Of the requirements for a valid PSA density result. ○ Of the 'outcome measures' for the secondary objective 'To compare between Finasteride with AS and AS alone, the rates of cessation of AS due to initiation of ....' • Removal of the limit on number of cores and maximum cancer core length, from inclusion criterion 10, to increase the pool of potentially eligible men.



Footnote
a. Strongly recommended
b. Offered as a routine to all men. Also strongly recommended for changing MRI appearances and/or where indicated by the MRI scan

Figure 1. Recruitment and participant flow within the FINESSE study. Follow up within Active Surveillance includes PSA testing, MRI Scans and the offer of a re-biopsy (times in months (m) shown).

[Please print on local headed paper and add contact details of the local research team & Trust Logo]

Short Title: FINESSE – A research study to improve treatment for men with early prostate cancer

Scientific Title: 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.

You are being invited to take part in the FINESSE study. This is a clinical trial for men diagnosed with prostate cancer. To help you decide whether to take part you need to understand why the research is being carried out and what it would involve.

For the purposes of this information sheet, the term 'we' refers to the Cancer Prevention Trials Unit at Queen Mary University of London (QMUL), who are responsible for co-ordinating and running this study on behalf of the Sponsor and the Chief Investigator. Please see section 21.

If this information sheet and consent form contain words you do not understand, please ask the study doctor or nurse to explain anything unclear. Please take time to read the information carefully. You will be able to take a copy of this sheet home so you can read it again. If you want to, you can discuss it with family or friends before deciding. If you choose not to take part, your healthcare will not be affected.

You should not sign the consent form until you have read this information sheet carefully, asked any questions you might have, and received satisfactory answers.

Part 1

1. What is the purpose of this study?

This trial will try to find out if a drug called finasteride can support men to continue with active surveillance after they have been diagnosed with localised prostate cancer. If this works, it will increase the number of men who avoid or delay the need for further treatment, and the side-effects accompanying this.

One of the popular treatment options for low or intermediate risk prostate cancer is active surveillance. Active surveillance means, rather than treating you with surgery or radiotherapy, your doctor will monitor you for signs that your cancer is changing. That way you would only need further treatment if you and

your doctor agree you do. Active surveillance is used because some prostate cancers never progress beyond the stage they are at when they are found, and so do not need further treatment.

Once active surveillance begins, you'll have regular tests to check on the cancer. One of the tests is a prostate specific antigen (PSA) test. This test measures the amount of PSA in your blood. PSA is produced by normal cells in the prostate and also by prostate cancer cells. A raised PSA level may suggest a problem in your prostate, but not necessarily cancer. PSA tests can be unreliable and can suggest prostate cancer is present when no cancer exists. They can also incorrectly indicate that a man does not have prostate cancer when they in fact do. PSA levels in men with prostate cancer can vary and can go up even when cancer is not progressing. Most men with low or intermediate risk prostate cancer do not require further treatment, but higher PSA levels may make men worry and this is a common reason why men decide to have further treatment.

We aim to improve what is offered for men like you so that you feel more confident in safely staying on active surveillance, using a drug called finasteride. Finasteride is used to improve symptoms of enlarged prostates, but also reduces PSA levels. We think that reducing PSA levels with finasteride might help your clinician to assess your prostate cancer more accurately by stopping it from rising due to factors that are not related to your prostate cancer (such as inflammation or normal enlargement associated with ageing). The decision regarding the need for further treatment will be more focused on the results of a prostate biopsy and prostate MRI, rather than fluctuating PSA levels. However, PSA levels will still be considered by your doctor because if your cancer is progressing, they can still rise, even if you are taking finasteride.

This is a randomised controlled trial, which means if you take part, you will be allocated to one of two study arms chosen at random. You and your medical team cannot choose which group you are put into. Half of the men will be placed into the active surveillance AND finasteride group (intervention arm) and half into active surveillance ONLY (control arm). We will recruit 550 men and allocate them to these groups. You and your doctor will both know which group you are in. This is what we call an 'open label' study. The study will run for five years, but if you are randomised to the intervention arm you will only take finasteride tablets for two of those years. Please note, if you are randomised to the control arm but are then prescribed finasteride for another medical reason by your treating clinician or GP, you will have to be withdrawn from the study.

2. What does taking part in this study involve?

Men who choose active surveillance for further treatment are seen regularly in a hospital clinic. Most of the time, the clinic and research appointments will be at the same time. However, participants will be required to attend up to three additional appointments as part of the trial, including a consent and randomisation visit at the start and two additional visits during the second year of the study. You can claim up to £25 per visit for your travel expenses to attend these extra visits. Please note, if current pandemic

policies change during the study, your study appointments may happen by telephone or video call, and your study drug if you are randomised to the finasteride arm may be posted to you.

Consent and randomisation visit – consent and random allocation to the study group can take place on the same day for men who have had a PSA test done in the last 3 months.

First year of the study – Local staff have been asked to ensure as far as possible, that research appointments coincide with regular active surveillance appointments, so that no extra study appointments are required during this period. Men allocated to the treatment arm will also take one tablet of finasteride (5mg) every day during this year.

Second year of the study - during the second year of active surveillance, men are usually seen every 6 months in their regular active surveillance Clinic. Finesse study visits will continue to be scheduled every 3 months so participants will be asked to attend **two extra visits, one at month 15** and the other **at month 21,** during this period. Men in the treatment arm will continue to take one tablet of finasteride (5mg) every day during this year. The treatment will be stopped after two years.

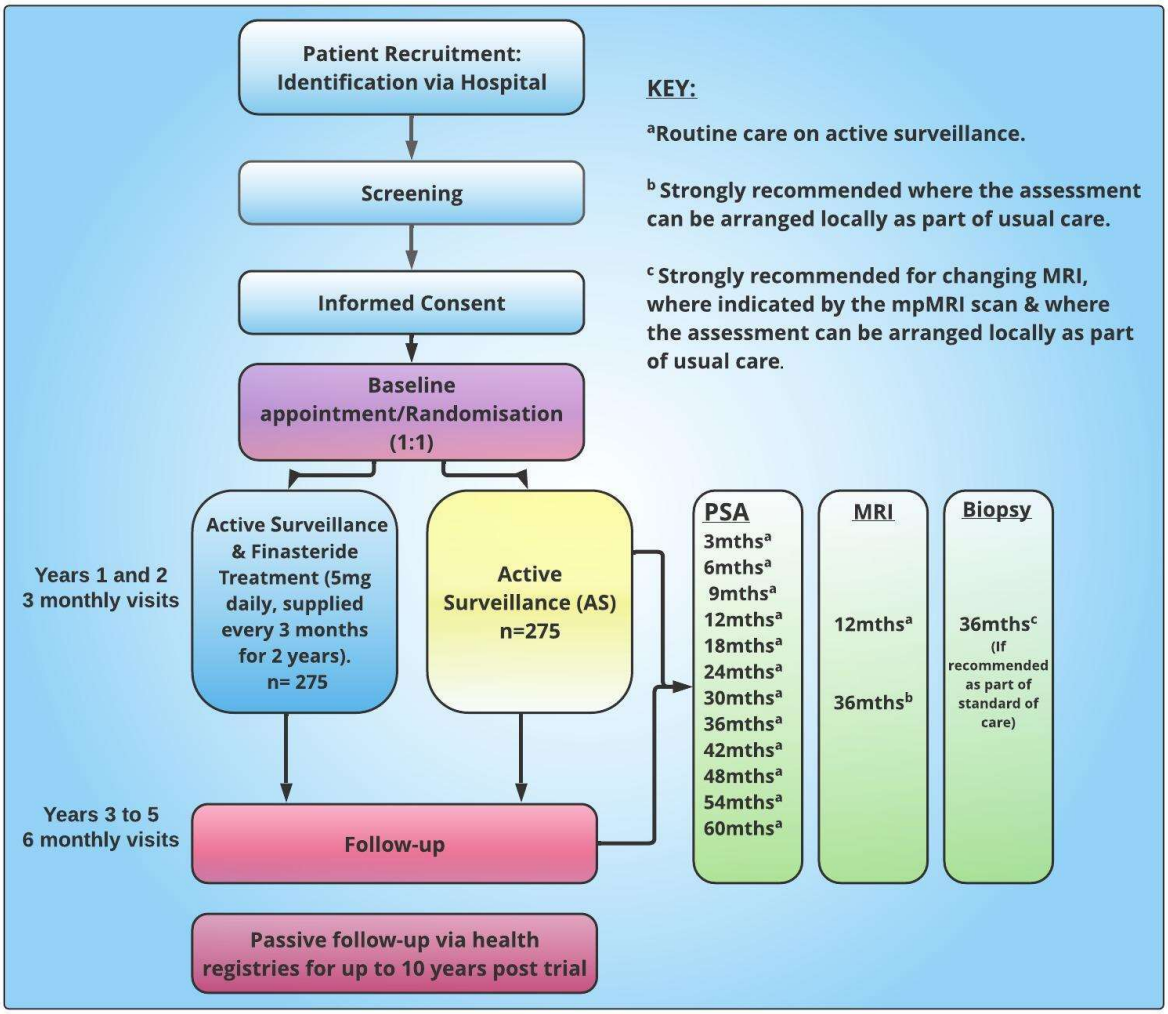
Third, fourth and fifth year of the study - men will continue to attend routine active surveillance appointments every 6 months and all study appointments will take place at the same time. Men allocated to the treatment arm will no longer take finasteride tablets during this period.

All men in the trial will be asked to complete questionnaires approximately every three months, which should take between 20 and 30 minutes in total to complete. This is to check how you are getting on, as we want to keep track of how your health and treatment may affect your quality of life.

These questionnaires will be emailed to you in between your visits. For this reason, we will collect your personal contact details, with your permission.

Some men will be invited to take part in a telephone interview at the end of the trial. Questions in this interview will relate to their experiences of taking part in the trial. The interview is optional.

Flow Diagram of Order of Events:



3. Why have I been invited?

You are being invited to take part in this study because your doctor believes your type of prostate cancer and treatment makes you suitable.

You **are potentially able** to take part in this trial if you:	You are **not able** to take part in this trial if you: • have previously received treatment for prostate cancer

• have been diagnosed with prostate cancer in the last 24 months • have not received previous treatment for prostate cancer • have opted for active surveillance for prostate cancer • are fit and suitable for radical treatment • are aged 50-75 years old at diagnosis	• are currently taking or have been taking finasteride or dutasteride in the last 12 months • you are planning to father a child • you have been told you have a terminal illness

There are some additional eligibility criteria related to your diagnosis and other medical conditions you may have. A research nurse will ask you questions in person at the clinic, or over the phone, and look at your medical records, to check that you are suitable.

If you are interested in the trial, but unsure whether you can take part, please contact your research nurse (contact details on the front page).

4. I am transgender or a non-binary person, can I still take part?

Yes. Whilst the terms 'men' and 'male' are used throughout the study documents, 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. Do I have to take part if I am suitable?

No. It is completely up to you whether you take part or not. If you do not wish to take part, your healthcare will not be affected in any way. If you do decide to take part, you will be asked to read and sign a consent form. Even if you consent to taking part in this trial, you can change your mind and leave the study at any time, without giving a reason.

6. What is the medicine being tested?

The medicine being tested is finasteride. Finasteride will be in tablet form, 5mg in a single tablet, taken once a day. Ideally this will be around the same time every day, with water. The tablet will be coated to avoid irritating the stomach lining. All men in the treatment arm will be asked to take finasteride for 2 years.

Finasteride is also known by the brand names Proscar and Propecia. It is a type of medicine called a 5-alpha reductase inhibitor which works by stopping testosterone (a sex hormone) turning into another hormone called dihydrotestosterone (DHT), which can cause your prostate to grow bigger. Finasteride

stops DHT being produced which helps shrink your prostate. It is therefore used to treat men with an enlarged prostate (benign prostate enlargement). It can help ease symptoms such as frequent and urgent urination, difficulty completely emptying the bladder or starting urination. Some studies have suggested that it **MAY** shrink the prostate tumour, but this is not the main objective of the FINESSE study.

In this study, finasteride is being used 'off label' which means the medicine is being used in a way that is different to that described in the licence.

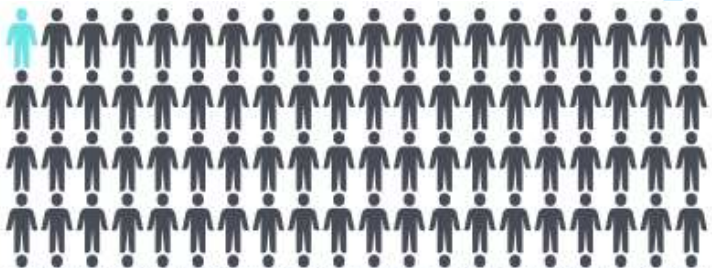
7. Are there any alternative treatment to the study?

For men who have already made the decision to join an active surveillance programme, your alternative to this study is not to take part. There are alternatives to active surveillance which your doctor will have discussed with you, including surgery. However, if you are unsure what those alternatives are, or you would like to discuss them again, please ask your doctor, who will talk you through them in detail.

8. What are the possible side effects of taking part?

Like all medicines, finasteride can cause side effects, but not everyone will get them. Finasteride is well tolerated and does not normally cause serious side effects.

Common Side Effects (happen in more than 1 in 100 people):

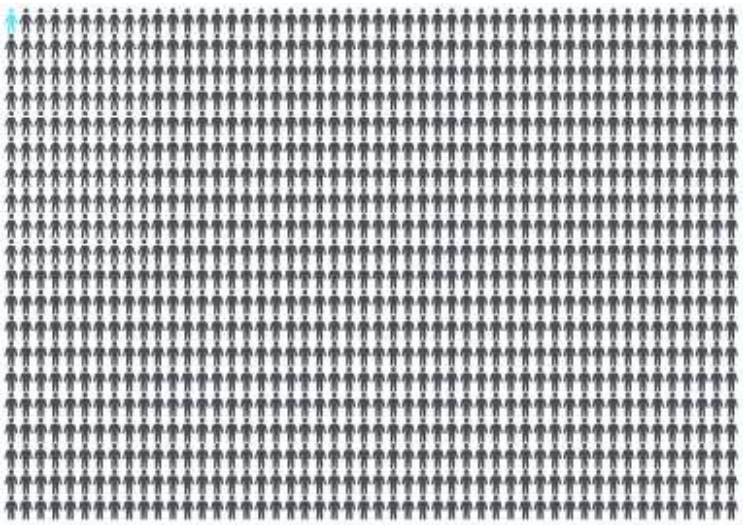


These usually improve after a while, but they should be discussed with a doctor if they bother you or do not go away:

- less interest in having sex (decreased libido/sex drive)
- trouble getting or keeping an erection.
- problems with ejaculating, such as little or no semen

- increase in breast size and tenderness.
- skin rash

Serious side effects:



Serious side effects are rare and happen in less than 1 in 1,000 people. Some people may notice these side effects after taking finasteride for a few months. These should always be reported to a doctor.

- Lumps, pain or swelling in your chest area or discharge from your nipples
- Unusually low mood (depression) or thoughts of harming yourself
- Allergic reaction- in rare cases, finasteride may cause a serious allergic reaction (anaphylaxis), in which case immediate action such as calling 999 or going to A&E, would be required

A full list of side effects will be provided inside the medicine packet.

Special note on pregnancy:

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:

1) Men trying for a baby or with a pregnant partner will not be allowed to take part in the trial.
2) Participants taking finasteride will be advised to:
   a. Use a condom when having sex. 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's any chance they could be pregnant. Finasteride can get into your bloodstream through your skin if you handle **broken** tablets. This is why the tablets come with a protective coating.

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.

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

If you have already chosen to have active surveillance a disadvantage is that some of your appointments might take a little longer than normal. You will need to remember to take a tablet every day, unless advised otherwise. Completing the online questionnaires may also take some time.

10. What are possible benefits of taking part?

- You may avoid or delay more intensive treatment for prostate cancer, which may have benefits for your quality of life.
- The growth of your prostate cancer **MAY** be slowed down (with the drug), although further research is needed to see if this is definitely true, and this is not the main objective of the FINESSE study.
- You may help improve the care of men with prostate cancer who opt for active surveillance and help us better manage the disease e.g., by promoting the use of other technologies in active surveillance such as MRI scans.
- If you have benign disease in addition to prostate cancer, you may see improvements in this.
- You will have more regular follow-ups than is standard practice.

11. What happens at the end of the trial?

The study will run for five years (two years to cover the treatment period, and three years of follow-up). Men taking finasteride will be asked to stop taking the drug after two years. The trial is not funded to offer

finasteride treatment after two years. Because the drug is being used 'off-label' in this study, you will need to consult your urologist if you wish to continue taking finasteride after your two years' trial treatment.

Men whose prostate cancers have remained unchanged at that point will continue to be followed up as part of the normal active surveillance programme. In addition, during years 3, 4 and 5 of the study, you will continue to complete study questionnaires every 12 months.

If at any stage your cancer shows signs of change and you need further treatment, your doctor will advise you to stop the study treatment. You can still complete the study questionnaires.

With your permission, once you have finished your trial appointments, the research team will continue to collect information from your doctor or from central NHS records for up to ten years to track your health, including whether you have received further treatment for prostate cancer. This is sometimes called 'Passive follow-up' because it takes place without requiring any involvement from study participants. If you do not want this to happen, you can say you want to stop any more information being collected.

At the end of the trial, your data will be stored securely and used to answer our research questions. The findings from the trial may be reported at meetings, conferences, and published in journals in a way that no-one can work out who took part in the study. More information on the storage and use of your data can be found on in section 23. Data handling and confidentiality.

12. What if something goes wrong?

You should contact your doctor or nurse if you have a question or a problem while taking part in the research. Their contact details can be found in section 13 of this information sheet. If you are seen by a doctor outside the study, you should remind them you are taking part in FINESSE. In case of emergency, you should act in the same way you would if you were not on the study. It is unlikely that you will need emergency hospital treatment as a result of this trial. However, you should always inform any doctor treating you that you are taking finasteride 5mg.

The overall sponsor of the trial is the Sheffield Teaching Hospitals NHS Foundations Trust (STHNHSFT), and the trial is coordinated by the Cancer Prevention Trials Unit at Queen Mary University of London

NHS indemnity will provide cover for negligent harm relating to STHNHSFT's role as trial sponsor. As employers of the authors, QMUL and the University of Sheffield (UoS) provide indemnity to cover negligence only liabilities arising from the design of the research. You may be able to claim compensation if you can prove that STH NHS, QMUL, and/or the University of Sheffield has been negligent.

However, as this clinical trial is being carried out in hospital, the hospital continues to have a duty of care to you. STHNHSFT, QMUL, & 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.

If you sustain injury as a result of negligence and wish to make a claim for compensation, you should do so in writing in the first instance to the Chief Investigator via the CPTU. Address details can be found on the trial website. 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.

13. Will my taking part in the study be confidential?

Yes. All the information about your participation in the study will be kept confidential. Further details about this can be found in Part 2.

14. Who should I call if I have questions, queries and/or complaints?

- You can ask more questions about the study at any time, and you can contact the following people for more information: 'local PI name' and 'research study nurse' – the study doctor and research nurse

  Telephone: [Sites to enter local number]
- You can also visit the FINESSE study website at: www.finessetrial.org
- For independent advice on taking part in a clinical trial please contact 'local' Health Patient Advice and Liaisons Service (PALS) on Sites to enter local PALS number] or email: [Sites to enter local PALS email]

  The PALS service is available [Sites to add local PALS opening hours]
- If you want to complain about how researchers have handled your information, you should contact the research team. If you are not happy after that, you can contact the Data Protection Officer. The KCL Data Protection Officer provides oversight of KCL activities involving the processing of personal data, and can be contacted at info-compliance@kcl.ac.uk

- The QMUL Data Protection Officer provides oversight of QMUL activities involving the processing of personal data and can be contact via data-protection@qmul.ac.uk

  If you are not happy with their response or believe they are processing your data in a way that is not right or lawful, you can complain to the Information Commissioner's Office (ICO) (www.ico.org.uk or 0303 123 1113).

This completes part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering taking part, please continue to read the additional information in Part 2 before making any decision.

Part 2

15. What should I do if I want to take part?

If you have received this leaflet from one of the urological clinics at participating NHS centres please contact the research nurse working on the trial (see section 13).

If you have found this Patient Information Sheet on the FINESSE website, or elsewhere on the Internet, please register your interest by emailing finesse@kcl.ac.uk

If you are interested in taking part, the next steps include the research nurse:

- Checking that you are suitable (if they have not already done so), by asking you a series of questions about your health
- Booking a consent and randomisation visit. During this visit you will be asked to complete a consent form indicating that you understand what the trial involves and that you agree to take part. Once all of these have been completed, you will then be randomised to one of two groups.

Please only agree to take part in this study if you are willing to accept allocation to either group. Participation in both groups is important to help us find out whether finasteride can reduce the number of men who receive radical treatment for prostate cancer.

16. What if new information becomes available?

Sometimes, during a research study, new or important information about the medicine(s) being studied becomes available. If this were to happen, the trial staff would let you know and discuss it with you. Depending on what the information is, you may wish to withdraw from the study, or your doctor may advise you to withdraw. If you withdraw you would continue to be seen in the normal active surveillance clinics. If you decided to continue in the study, you may be asked to sign an updated consent form.

A special group of experts, known as a Data Monitoring Committee, who are independent from the trial staff and doctors, has been set up to oversee the study on a regular basis to make sure any issues are looked into properly and that the men taking part are informed about any relevant new information. The information sheet and other study documents will also be updated with any new details.

17. What will happen if I don't want to carry on in the study?

You are completely free to leave the study any time you wish and for any reason. The standard of care you receive will not be affected. However, the more men we have on the study, the more data we collect, and the better our chances of answering our research questions accurately. Your participation is important to us and valued. Therefore, we would encourage you to talk to us before making your final decision, to see if we can address any problems that you may be having and improve your trial experience.

If you change your mind about taking part in the study, you can withdraw at one of three levels:

1. It is possible for you to stop the study medication (finasteride), and remain in the study, under follow-up clinic, or by telephone. In this case, you will be asked to continue completing the study questionnaires. During follow-up, and for up to ten years after the trial has finished, the research team will continue to collect some information from central NHS records to track your health, in particular if you had received further treatment for prostate cancer during that period. This type of follow-up is often called 'passive follow-up' because trial participants are not actively involved or inconvenienced.
2. You can decide to stop the study medication (finasteride) AND stop completing the study questionnaires. During follow-up, and for up to ten years after the trial has finished, the research team will access central NHS records to check if you had received further treatment for prostate cancer during that period, (passive follow-up).
3. Alternatively, you may wish to withdraw from ALL aspects of trial. In this case, you will stop taking study medication (finasteride), we will stop sending you the study questionnaires and we will not access national health registries to check if you had received further treatment for prostate cancer during the follow-up period, (passive follow-up).

Information and samples that have been collected up to the point of your withdrawal will remain part of the study. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. Research could go wrong if data is removed or changed.

Please ask the study doctor or nurse if you have any questions about this.

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

In this study, most of the research team will not need to know your name. In these cases, someone will remove your name from the research data and replace it with a code number. This is called coded data, or the technical term is pseudonymised data. For example, your blood test might be labelled with your

code number instead of your name. It can be matched up with the rest of the data relating to you by the code number. In the FINESSE study, this code number is called a Patient Identification Number (PIN). Your PIN will be used on most of your study records and samples instead of your name, wherever possible, to ensure information is kept confidential. Please see 'Who will have access to my data?' on page 18 for the exceptions.

Your medical records may be looked at by people who are authorised to check that the study is being carried out properly, and the quality of the research. Representatives of health regulatory authorities and the hospital NHS Trust, and auditors from the Trials Unit and Sponsor may have access to your medical records, and these people will be required to keep your information confidential. A responsible representative from Queen Mary University of London will also require access to records for the purpose of monitoring and auditing. By signing the consent form you are giving your permission for this to happen.

Your contact details and information collected about you will be stored on a secure database, and access will only be available to members of the trial team, other members of and Queen Mary University of London who may wish to monitor the study, and a third party based outside of the UK who will send text messages on our behalf. These details will also be required to send you study related information questionnaires, and to allow the study team to collect registry data during passive follow-up. Your personal identifiable data will never be stored outside of the UK.

19. Information for your General Practitioner

By signing the consent form, you give the study doctor permission to inform your family doctor (GP) that you will be taking part in this research. We feel that it is important because your GP should be aware of any treatment or medications that you receive so they have a more complete picture of your health. After you have joined the study, they will receive a letter that will include information about finasteride (if you are in the group taking it) and this information sheet for their records. We also encourage you to mention this trial the next time you see your GP.

20. Will any genetic tests be done?

No. We may decide to collect additional samples for testing in the future, but if this were to happen, the trial staff would let you know and discuss it with you. You would also be provided with an updated Patient Information Sheet. You may also be asked to sign an updated consent form.

21. What will happen to the results of this study?

It will take up to 5 years to complete this study, so it will be some time before any results are available. The findings from the trial will be shared with participants and may be reported at meetings, conferences, published in journals and shared with the medical community. If the results from this study are published, your identity will remain confidential and no personal identifiable information will be used.

22. Who is funding the study, and who else is involved?

The research is funded by Yorkshire Cancer Research, and the National Institute for Health Research (NIHR) provides support services within the NHS hospitals involved. The medicines for this trial are being sponsored by the NHS Commissioners.

The Chief Investigator of the study is Professor James Catto (University of Sheffield), and his co-investigator is Professor Peter Sasieni (Queen Mary University of London).

Sheffield Teaching Hospital NHS Foundation Trust (STHNFT) is organising this research, is the sponsor for the study and employs the Trial Radiologist.

Leeds Teaching Hospital NHS Foundation Trust employs the Trial Pathologist.

The University of Leeds employs the Trial Behavioural Scientist.

The study is being co-ordinated and managed by the Cancer Prevention Trials Unit at Queen Mary University of London.

None of the staff involved in the study will receive payment specific to their involvement in this research.

22. Data handling and confidentiality

This section outlines how your data will be used, stored, and accessed, during and after the trial.

What is patient data?

When you go to your GP or hospital, the doctors and others looking after you will record information about your health. This will include your health problems, and the tests and treatment you have had. They might want to know about family history, if you smoke, or what work you do. All this information that is recorded about you is called patient data or patient information and is also referred to as personal data.
When information about your health care joins together with information that can show who you are (like your name or NHS number) it is called identifiable patient information. It's important to all of us that this identifiable patient information is kept confidential to the patient and the people who need to know relevant bits of that information to look after the patient. There are special rules to keep confidential patient information safe and secure.

Will the use of my data meet UK GDPR rules?

UK GDPR stands for the United Kingdom General Data Protection Regulation. In the UK we follow the UK GDPR rules and have a law called the Data Protection Act. All research using patient data must follow UK laws and rules.

Universities, NHS organisations and companies may use patient data to do research to make health and care better. Universities and the NHS are funded from taxes, and they are expected to do research as part

of their job. They still need to be able to prove that they need to use patient data for the research. In legal terms this means that they use patient data as part of 'a task in the public interest'.

If they could do the research without using patient data, they would not be allowed to get your data.

Researchers must show that their research takes account of the views of patients and ordinary members of the public. They must also show how they protect the privacy of the people who take part. An NHS Research Ethics Committee (REC), an independent group of people, checks this before the research starts to protect your interests.

This study has been reviewed and given favourable opinion by the South-Central Oxford C Research Ethics Committee.

King's College London Data Protection Statement

King's College London has a responsibility to keep information collected about you safe and secure, and to ensure the integrity of research data. Specialist teams within King's College London continually assess and ensure that data is held in the most appropriate and secure way. This may include storage of personal data with a contracted GDPR compliant third-party storage provider within the UK, where they are assessed as the best data storage option. Employees of the third parties will have access to your data to fulfil their role as a third-party service providers, but your records and information will be kept strictly confidential.

The QMUL Data Protection Statement can be found here: https://www.qmul.ac.uk/governance-and-legal-services/governance/information-governance/data-protection

FINESSE Study Data Protection Statement

Your data will be processed under the terms of UK data protection law [including the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018]. The sponsor, Sheffield Teaching Hospitals NHS Foundations Trust, is the Data Controller and is responsible for looking after your information and using it properly. The KCL Data Protection Officer provides oversight of KCL activities involving the processing of personal data, and can be contacted at info-compliance@kcl.ac.uk. The QMUL Data Protection Officer provides oversight of QMUL activities involving the processing of personal data and can be contact via data-protection@qmul.ac.uk .

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' Special category personal data is personal data that reveals racial or ethnic origin, political opinions, religious or philosophical beliefs, trade union membership, health (the physical or mental), sex life or sexual orientation, genetic or biometric data. The lawful basis used to process *special category personal data* will be for scientific and historical research or statistical purposes.

If you would like more information about how your data will be processed in accordance with UK GDPR, please visit the links below:

https://www.kcl.ac.uk/research/support/research-ethics/kings-college-london-statement-on-use-of-personal-data-in-research

https://arcs.qmul.ac.uk/governance/information-governance/data-protection

What data will be collected?

In this study we will collect data from five different sources:

1. Clinical data - When you have medical treatment or visit a clinic, a nurse will collect data about your prostate cancer diagnosis and treatment, and other medical conditions which are relevant to the trial. All research should only use the patient data that it really needs to do the research. You can ask what parts of your health records will be looked at.

2. Directly from you - We will ask you to provide your date of birth (DOB), and your NHS and hospital ID numbers to help us locate your MRI scans, pathology, PSA results and other relevant reports. We will also ask you to provide your email address, home address and mobile phone number so that we can contact you and send you online questionnaires. We will always make sure that as few people as possible can see this sort of information that can show who you are.

The online questionnaires will ask about your quality of life, symptoms you experience, your emotional state, and your treatment. If you are in the finasteride group, we will also ask if you took the pill every day and if you are having any issues with taking the drug. All research should only use the patient data that it really needs to do the research. You can ask what parts of your health records will be looked at.

3. Biological tissue - As standard in the NHS, during a prostate biopsy small samples of tissue are taken from the prostate. Once the doctors finish their diagnosis, the trial pathologist may review the biopsy tissue and/or digital images of the tissue where available. This is known as 'central review', and it is carried out to ensure the local radiologists at each of the study sites are reporting results in a similar way. It is a quality control exercise. The comments from their review will not be traceable back to you. With your permission, we will store these images with your study data. You will not be asked to provide any additional prostate tissue for the study. All samples will be managed in accordance with the requirements of the Human Tissue Act (2004).

4. Medical imaging (bpMRI/mpMRI) – You will undergo a diagnostic imaging procedure (magnetic resonance imaging, MRI), as part of your active surveillance, whereby an MRI scanner will scan your prostate. The number of scans you have will be dependent on your individual needs and is something you will discuss with the urologist treating you. You will not have any additional scans as part of this study. Your doctors will look at the results of this imaging. With your permission, the Trial Radiologist will also centrally review and store these images with your study data. They will be a valuable research resource.

As with the pathology samples the comments from the Trial Radiologist's review will not be traceable back to you.

5. Health data registries – This data is protected by data laws and strict access requirements. With your permission we will use these data registries to learn about your long-term health, such as any further treatment you may have for prostate cancer.

If you take part in the additional telephone interview at the end of the trial, your call will be recorded and typed out in a transcript.

Where possible, we will anonymise or pseudonymise the personal data you provide. Pseudonymisation is a technique that replaces information in a data set that identifies an individual, with an artificial identifier. In the case of FINESSE study, this artificial identifier will be a Patient Identification Number or PIN. We will always minimise the processing of personal data wherever possible.

You can find out more about how we use your information at www.hra.nhs.uk/information-about-patients

How will my data be stored?

Prostate tissue samples will be held within Leeds Teaching Hospital NHS Foundation Trust, where the Trial Pathologist is based and bpMRI/mpMRI images will be held by Sheffield Teaching Hospital NHS Foundation Trust (STHNFT), where the Trial Radiologist is based. Digitised images of the tissue samples and copies of the MRI scans will be stored in the Data Safe Haven (DSH). The DSH will be maintained by a contracted GDPR compliant third-party storage provider based within the UK.
It is a secure place we use to store all personal, sensitive, pseudonymised electronically captured data, and other confidential study data, e.g., your questionnaire responses, for access exclusively by approved researchers and clinicians only. In addition, your identifiable patient information will be kept separately from your clinical data.

Who will have access to my data?

Only authorised members of the research team at Queen Mary University of London will have access to your identifiable data. The exceptions to this are:

Your mobile number, since the third party responsible for sending you reminder text messages is based outside of the UK. The sharing of this data will be in accordance with UK GDPR, and your data will never be stored by this third party.

Your MRI scans and associated reports as it is not possible to anonymise these for this study. However, these will be transferred electronically from one NHS hospital to another NHS hospital using an established and secure transfer process, so the associated risk is considered to be low. We have recommended that where possible, sites use only your NHS number and year of birth to identify you.

Anonymous or pseudonymised data will be viewed by the trial oversight committees and auditors who regulate the trial and ensure everything is done to protect you and your data.

When information is anonymised, it means that data is processed in a manner that makes it impossible to identify individuals from them. Pseudonymisation means that it can no longer be linked to a specific person without the use of additional information. Such additional patient identifiable information (e.g., name and address) must be kept separately from the pseudonymised personal data.

The research nurses/team at your hospital will have access to your medical records to make sure you are suitable for this trial.

Stored, pseudonymised and anonymised data and samples may be used by other researchers, for future medical and health-related research, but only if they have relevant approval from a Research Ethics Committee who look after your interests and ensure the integrity of potential research. Data will not be shared outside of Europe.

How will my data be used?

We will keep all information about you confidential, safe and secure. We will link data about you collected during this trial with other existing health data collected in the UK, such as The National Cancer Registration and Analysis Service (NCRAS). NCRAS collects data on all cases of cancer that occur in people living in England. In order to link your data with other health data, we will use your personal details, such as your NHS number, to link to information in the NCRAS.

Health data collected from any health or social care provider will be securely transferred to the trial team and uploaded onto the trial database. Restricted access to this data will be given to authorised and trained personnel working on the study, and the identifiable personal information will be stored on a secure, restricted access server DSH maintained by a contracted GDPR compliant third-party storage provider based within the UK.

Your personal data will be processed so long as it is required for the research project. Researchers from the Sheffield Teaching Hospitals NHS Foundations Trust (STH NHS), Sheffield University, the University of Leeds and Queen Mary University of London will analyse your data, to see if:

- Taking the drug finasteride results in reduced rates of radical or advanced cancer treatments
- Taking finasteride helps men stay on active surveillance safely, for longer.
- Prostate cancer progresses more slowly in men taking finasteride compared with men not taking finasteride
- Participants have any difficulties sticking to finasteride treatment
- The trial has any impact on participants' wellbeing
- Taking finasteride reduces the number of men receiving treatment for prostate cancer that has spread

The findings will be written up into research papers and published alongside the data, as well as presented at meetings and conferences. However, the reports about the study will be written and presented in a way that no-one can work out that you took part in the study. This personal data will be stored for a minimum of 5 years after the completion of this study in case we need to check it or use it for future research. In addition, the hospital where you are taking part in the study will keep a copy of the research data along with your name. You can ask about the hospital who will keep it, whether it includes your name, and how long they will keep it.

Future Research

If you agree to take part in this research study, you will get the choice for us to keep your contact details and some of your health information, so we can invite you to take part in future clinical trials or other studies. Your data will not be used to sell you anything. It will not be given to other organisations or companies except for research.

Thank you for reading this information leaflet. Should you now decide to proceed with your participation in this study, you will be asked to sign a consent form. Please note that you will be given a copy of this information leaflet and a copy of the signed consent form to keep.

[Please print on local headed paper & add contact details of the local research

CONSENT FORM

FINESSE: ***A medical research study to improve treatment for men with early prostate cancer***

Name of Principal Investigator:

PIN:							

Please **initial** box

1. I confirm that I have read and understood Parts 1 and 2 of the Participant Information Sheets, Version no: X Dated: DD/MM/YYYY for the above study. I have had the opportunity to ask questions, and these have been answered to my satisfaction. I understand how to raise a concern or make a complaint. ☐

2. I understand that my participation is voluntary, and that I am free to withdraw from the study at any time, without giving a reason, and without my medical care or legal rights being affected. ☐

3. I understand that relevant extracts from my medical notes, data and tissue collected, may be looked at by the clinical trials unit co-ordinating this research, researchers from the Universities of Sheffield and Leeds, the Sponsor, Sheffield Teaching Hospital NHS Trust, and also by the regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that even if I withdraw from the study, the information and samples collected from me up to that point will be used in the analysis of the results, and my identity will remain anonymous within this analysis. ☐

5. I understand that my name and contact details will be collected and securely stored on a secure, restricted access server Data Safe Haven maintained by a contracted GDPR compliant third-party storage provider based within the UK, who are retained by Kings College London or Queen Mary University of London. My details will be used to send me relevant information relating to the study, to track my health long-term via relevant health data registries e.g. The National Cancer Registration and Analysis Service (NCRAS), and to request additional information relevant to the trial, from local health information sources, e.g., my treating hospital.
   As detailed in the PIS, I am aware that employees of third-party providers, based outside of the UK, and contracted by the research team, may require access to my personal-identifiable data to fulfil their role as a third-party service provider. However, my personal-identifiable data will be kept strictly confidential and never be stored outside of the UK. ☐

6. I understand that where relevant, slides of tissue collected for standard care biopsies & corresponding pathology reports, may be sent from my hospital's Pathology Department to the Pathology Department at Leeds Teaching Hospital NHS Foundation Trust, for ☐

[Please add contact details of the local research team]

central review by the FINESSE Lead pathologist. Slides & reports will be pseudo-anonymised, and the pathology samples will be returned to the sites once the review is complete, and in accordance with the site's pathology release conditions.

7. I understand that pseudonymised and anonymised data generated from the Trial may be made publicly available and shared with commercial/overseas researchers within Europe or organisations, to support other research in the future, and may be shared anonymously with other researchers or organisations which may include those in the commercial sector, here or within Europe. ☐

8. I agree to update the FINESSE Coordinating Centre of any relevant changes to my personal details e.g., a change to my email address, or a new telephone number. ☐

9. I agree to my General Practitioner being informed of my participation in the study. ☐

10. I agree to take part in the above study. ☐

Optional interview consent	*Please **initial** relevant box below*	
1. I agree to be approached by the research team and invited to participate in a 60-minute telephone interview exploring my experience of taking part in this study. I understand that my participation in the interview is voluntary and that I am free to withdraw at any time without giving any reason.	Yes	
	No	

Optional future contact consent	*Please **initial** relevant box below*	
2. I agree to be contacted about future studies using the contact details I have provided.	Yes	
	No	

Name of Participant: *Date:* *Signature:*

Name of Person taking consent if not PI: *Date:* *Signature:*

Name of PI/Delegated Investigator: *Date:* *Signature/Countersignature:*

*1 copy for the participant; 1 copy for Investigator Site File (ISF); 1 (original) to be kept in medical notes.

BMJ Open

Protocol for a randomised phase 3 trial evaluating the role of Finasteride in Active Surveillance for men with low and intermediate-risk prostate cancer: The FINESSE Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-096431.R1
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Protocol for a randomised phase 3 trial evaluating the role of Finasteride in Active Surveillance for men with low and intermediate-risk prostate cancer: The FINESSE Study

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Abstract

Background

Prostate cancer (PCa) is the commonest male malignancy in the western world. Many men (40%) are diagnosed with localised low or intermediate-risk PCa, which is suitable for Active Surveillance (AS). AS affords careful monitoring to identify changes in otherwise non life-threatening cancers. Whilst AS reduces overtreatment (and quality of life impact), long term compliance can be poor, with many men undergoing radical treatment after starting AS.

Methods and analysis

FINESSE is a prospective, open label, two-arm, phase 3 trial, in which men with low or intermediate PCa are randomised (1:1) to receive AS with or without finasteride (5mg once a day for 2 years). Randomisation is stratified by age and PCa risk. AS includes regular Prostate Specific Antigen (PSA) testing, Magnetic Resonance Imaging (MRI) scans and the offer of repeat biopsy (at 3 years, or if imaging suggests progression). Additional MRI scans and/or biopsies will be performed for biochemical or clinical indications. We aim to recruit 550 men (aged 50 to 75-years) from up to 8 sites. Active outpatient follow up will be for 3-5 years (depending upon date recruited), followed by passive registry-based follow up for up to 10 years. Primary outcome is adherence to AS. Secondary outcomes include rates and type of disease progression, treatments received (for PCa and benign prostatic enlargement), overall and PCa-specific mortality, an understanding of patients/professionals views of this approach, and health-related quality of life. An external panel of experts blinded to allocation, will review all AS cessation and progression events. Trial pathologist's and radiologist's, blinded to allocation, will review representative cases. Analysis is Intention to Treat.

Ethics and dissemination

The study received Health Research Authority and South-Central Oxford Research Ethics Committee (14/12/2021: 21/SC/0349) and CTA/MHRA (29/12/2021: 21304/0274/001-0001) approvals. Results will be made available to providers and researchers via publicly accessible scientific journals.

Trial registration: ISRCTN16867955

Article summary

Strengths and limitations

- Whilst active surveillance is an established method of managing men with prostate cancer, few studies have attempted to improve compliance with this regimen.
- Finasteride is widely available, has a known safety profile, is well tolerated and is used in a similar patient population for benign prostate enlargement.
- This study will determine AS outcomes in a contemporary cohort of intermediate-risk cancers.
- There remains some scepticism about the role of pharmacological PSA manipulation for AS patients.
- Pre-biopsy MRI may reduce the pool of eligible men and hamper recruitment.

Introduction

Prostate cancer (PCa) is the commonest male malignancy in the western world [1]. Prostate Specific Antigen (PSA) screening of asymptomatic men has been used to reduce mortality from the disease. However, most men diagnosed through this route have clinically localised disease and may not benefit from treatment as their cancers are indolent, with a long natural history, or metastatic at diagnosis [2]. There has yet to be a universally accepted screening program for PCa and most men are diagnosed through 'case-finding' using PSA testing for lower urinary tract symptoms or known risk factors (e.g. family history). The detection and radical treatment of PCa 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. Radical treatment is reserved for men whose tumours progress biochemically, clinically, or radiologically.

In men with low-risk PCa undergoing AS, the risk of disease-specific mortality is small (e.g., 0.3% at 8 years and lower than that from competing diseases [5]). AS is popular amongst men with localised PCa [6, 7] and recommended by NICE guidelines in the United Kingdom [https://www.nice.org.uk/guidance/ng131]. However, there are concerns regarding the accuracy of PCa risk stratification and the reliability of monitoring tools [8-10]. Clinicians and patients fear that deferring radical treatment could reduce the chance of cure and lead to higher morbidity [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 the Toronto trial 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. Therefore, many men with rising PSA values may not have disease progression and may not need radical treatment. For 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], highlighting the potential for overtreatment.

Various approaches have been tried to improve compliance with AS, including pharmacological interventions. The REDEEM study group randomised 302 men with low-risk PCa 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). The ENACT study group randomised 227 men with low or intermediate-risk PCa to AS with or without 160mg daily Enzalutamide [17]. The addition of Enzalutamide reduced progression (pathological or therapeutic) by 46% at 12 months, although no difference was present at 2 years, there were side effects with this agent and its cost poses financial challenges to healthcare providers (especially if for long term AS regimens).

Contemporary AS cohorts include many men with intermediate-risk PCa, as MRI may have changed the spectrum of PCa's diagnosed. Many men with small, low risk PCas are often no longer diagnosed either because they do not have a biopsy or there is less random prostate sampling [18, 19, 20]. Within the PRECISION trial, 38% of men with mpMRI guided biopsy (versus 24% in ultrasound Scan (USS) guided-biopsies) had Gleason 3+4 PCa [18]. Van der Leest et al. found mpMRI guided biopsy reduced the rate of insignificant PCa diagnosis from 25% to 14% [19]. Therefore, the focus to improve the care of men with PCa is shifting to using AS in men with intermediate-risk PCa [21-26]. This population is common and includes more men with lethal cancer than in the low-risk cohorts [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 PCa management [Question #1: What is the most suitable surveillance protocol? [https://www.nice.org.uk/guidance/ng131]. Given the positive signals from the REDEEM and ENACT trials, this study aims to test if the drug Finasteride can increase men's adherence to AS and reduce radical treatment rates, using a more contemporary cohort.

Methods and analysis

Design

FINESSE is a randomised, prospective, non-blinded, open-label, parallel group, phase 3 trial. Men will be randomised 1:1 to receive Active Surveillance plus finasteride (5 mg) for 2 years or Active Surveillance alone.

Randomisation and population

Randomisation is through a web-based tool bespoke to the King's Clinical Trials Unit (KCTU). Once participants have completed a signed consent form (Supplementary figure 1. example Finesse Consent form, Version 5.0 from 27th Mar 2024) their data will be stored on the system. The randomisation process is at the individual level using the method of permuted block randomisation with block sizes stratified by PCa risk (low vs. intermediate), and participant age (<65 vs. >65 yrs).

Blinding

This is an open label study. Both participants and clinicians will be aware of the study arm to which they are randomised. Whilst test results e.g. MRI scans and PSA values can make it obvious that a participant is taking finasteride, the following will be blinded (not informed) to treatment allocation:

1) Lead Trial Radiologist responsible for reviewing MRI scans.
2) Lead Trial Pathologist responsible for reviewing histopathology.
3) Independent PCa Progression Review Panel (PCPP), made up of three urologists.

Study setting

The FINESSE trial is recruiting in secondary care sites. The trial is funded by Yorkshire Cancer Research, a charity whose remit is to fund research which will save lives in Yorkshire, and so initial sites have been established within the Yorkshire region. Non-Yorkshire centres will be included to expedite recruitment. Eligible patients are identified by secondary care clinicians (urologist) in outpatient clinics and multi-disciplinary team meetings (MDTs). Research nurses will support the screening, consent and follow-up processes.

Recruitment

We aim to recruit 550 men over 24 months. The trial management group (TMG) will monitor this in real time and recommend action if recruitment is behind projections (such as opening additional sites, extending recruitment duration or adjusting eligibility (e.g. removing biopsy restrictions, increasing the time since diagnosis)). PPI representatives and behavioural scientists will be involved from the outset to ensure the research questions and study design are relevant to the needs of PCa patients, to inform the patient facing literature, and to facilitate effective recruitment. Patients may self-refer by contacting their local FINESSE investigator. Informed consent will be obtained by recruiting physicians (supplemtary files 1-2).

Eligibility criteria

1). Male subjects aged 50 to 75 years, with an estimated life expectancy of 10 years or more, who have opted for AS as their preferred PCa management option.

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.

5). A histological diagnosis of Gleason grade group ≤ 2 (i.e. Gleason grade 3+3=6 or 3+4=7) PCa within the last 6 months.

6). Radiological stage ≤T2b cN0 cM0 as defined by mpMRI imaging within the last 6 months (from the date of the mpMRI scan to the date of the patient's randomisation). A copy of the mpMRI scan, and report confirming eligibility will be required.

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

8). PSA Density ≤0.2ng/ml/ml. The result must be within 3 months of the date of the patient's randomisation

9). Biopsy criteria (via either trans-rectal or trans-perineal routes) within the last 6 months of the patient's randomisation date):

- If targeted biopsy then the maximum cancer core length is ≤10mm
- If targeted and systematic sampling biopsy then the maximum cancer core length should be ≤10mm, and ≤2 or ≤15% of non-targeted cores involved with cancer.

- If non-targeted biopsy (i.e. USS template or sampling irrespective of lesions) then maximum cancer core length is ≤10mm AND ≤3 or ≤20% of total number of cores involved with cancer.

Ineligibility criteria

1). Previously received treatment for PCa (including radiotherapy, hormone therapy, brachytherapy or surgery). Of note, men who have received treatment for benign prostate enlargement are eligible.

2). Current or recent (≤12 months) 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 dutasteride.

6). Known allergy to any excipients of finasteride.

7). Any malignancy (other than non-melanoma skin cancer and/or PCa) 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.

12). High-risk disease.

Usual care: Active surveillance

Men randomised to usual care will receive AS (see figure 1). Patients will not receive a placebo, as PSA and MRI changes make masking impossible, 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, know they are independent of the treatment, participants unaware they are taking finasteride may opt for radical treatment earlier, and placebo controlled trials are expensive. Concerns regarding PSA

changes or digital rectal examination (DRE) changes will lead to MRI scans outside the schedule. Changes in MRI and PSA will lead to either a re-biopsy (to detail histological grade) or radical treatment. Radical treatment without radiological or pathological evidence of progression is discouraged, but not prohibited.

Finasteride plus Active surveillance

Men randomised to the intervention group will receive finasteride (oral 5 mg) to be taken once a day for 2 years, in addition to AS (as above). Participants will be prescribed finasteride on a 3-monthly basis and this will be dispensed from their recruiting hospital pharmacy. Compliance will be measured using pill counts and patient questionnaires.

Study aims

1. To understand whether the addition of finasteride to AS increases adherence in men with low/intermediate-risk PCa.
2. To understand the tolerability and compliance with finasteride within an AS regimen.
3. To understand whether the addition of finasteride to AS reduces disease progression in these men.

Objectives and outcomes

The primary and secondary objectives, with matching outcomes, are detailed in tables 1-2. We will also detail health related quality of life, over time, using validated Patient Reported Outcome tools, including decision regret and conflict findings (table 3).

Sample size

We estimate finasteride will reduce AS cessation rates by 50% (from 20% to 10%) after an average of 4 years follow-up. 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. We assume that 50% of control participants will progress (or be treated) during follow-up and that the hazard ratio is 0.65. The exact number needed is 271 per arm. We believe we will need to screen 1,500 men to obtain 550 eligible, consenting recruits.

Statistical methods

Participant population

The main endpoint analysis of progression from AS will be performed on all participants who have been randomised on an intention-to-treat (ITT) basis. 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 Schemper's weighted model. The analysis of QOL questionnaires will be performed on the set of men who complete the questionnaires. Tolerability of Finasteride analysis will be performed on all participants randomised to Finasteride.

Procedure(s) to account for missing or spurious data

We anticipate the dropout level will 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.

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.

Other statistical considerations

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

Prostate cancer progression panel (PCPP)

Some of the progression events in PCa or reasons for cessation of AS can be open to investigator bias. Given that this trial is open label, to minimise bias and inform broader clinician agreement regarding progression, an independent panel of urologists will review each case of progression or AS cessation. Members of this panel were selected based on recognition of their expertise in managing PCa and knowledge of AS. The panel will agree to the presence (or absence) of progression and classification (e.g. radiological, pathological, biochemical). It was considered optimal to have a panel that is independent of the NHS.

Data collection, monitoring and harms

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 electronic data capture system (EDC, referred to as simply the EDC within the protocol): a web-based EDC system designed, using the InferMed Macro 4 system for collection screening log information, trial eCRFs and generating prescriptions.

3). REDCAP: used to collect patient identifiable data, participant surveys, PROMs, and registry data.

Several methods will be implemented to maximise data completeness. The Finesse EDC has in-built validation checks to alert for missing or unusual data. There will also be manual reviews where data monitoring queries can be raised. There will be league tables for posting metrics on completeness of data from each site. Lastly, there will be automated phone Short Text Messages (SMS) and email reminders to participants to optimise Quality of Life questionnaires completion.

A formal risk assessment has been undertaken for the trial to identify and propose mitigation strategies for the main 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 DM/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. The PI will be met at each visit, where possible.

Ethics and dissemination

Approval, protocol amendments, consent

The study received approval from the Health Research Authority and South-Central Oxford Research Ethics Committee (14/12/2021: 21/SC/0349) and CTA/MHRA (29/12/2021: 21304/0274/001-0001). The study is sponsored by Sheffield Teaching Hospitals NHS Foundation Trust. The sponsors have no role in the collection, interpretation or dissemination of the trial findings. 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 Patient Information Sheet (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 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 NHS Digital 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.

Informed consent will be obtained prior to randomisation (Supplementary figure 1. Finesse Consent form).

Results will be made available to providers and researchers via publicly accessible scientific journals and presentations at academic meetings. Results will be shared with patient groups through the funders (Yorkshire Cancer Research) and relevant patient groups.

Confidentiality and 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. 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.

Amendments to protocol since recruitment started

Several amendments to the protocol have been completed since the initial protocol and the trial opened to recruitment. Please see these detailed in Supplementary Appendix 1.

Trial Status:

The trial opened to recruitment in August 2022 with the first participant randomised at St. James's University Hospital, Leeds on the 23rd September. The study is in the active recruitment phase.

Acknowledgements:

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Authors contributions:

MGC - construction, critical review of the protocol and writing of the manuscript

BN - statistics and critical review of the manuscript

RK – protocol and study document development, trial management and critical review of the manuscript

SGS - behavioural science and critical review of the manuscript

RH – development of radiological manual and critical review of the manuscript

SK – development of radiological manual and critical review of the manuscript

SB – development of the pathological manual and critical review of the manuscript

WC - critical review of the manuscript

RC - critical review of the manuscript

RJB - critical review of the manuscript

ADL - critical review of the manuscript

MDD - critical review of the manuscript

SF - critical review of the manuscript from the PPI view point

PS - concept, funding, trial design, statistics and writing of the manuscript

JWFC - concept, funding, trial design, protocol development and writing of the manuscript

JWFC is responsible for the overall content as guarantor.

Competing interests statement:

MGC has received speaker fees from Ipsen and Pfizer. JWFC has received reimbursement for consultancy from Astra Zeneca, BMS, Ipsen, Janssen and Roche, speaker fees from BMS, Ipsen, MSD, Nucleix and Roche, honoraria for membership of advisory boards from Astra Zeneca, Ferring, Roche and Janssen, and research funding from Roche. PS is a paid member

of the Scientific Advisory Board of GRAIL and the medical advisory board of NSV. The remaining authors declare no potential conflicts of interest.

Participant Consent for Publication:

Not required. No identifiable personal data will be used in publications.

Data Availability:

All information related to participants will be kept confidential and managed in accordance with UK General Data Protection Regulation (GDPR), Data Protection Act (2018), NHS Caldicott Principles, UK Policy Framework for Health and Social Care Research (2017), and the conditions of Research Ethics Committee Approval. Upon reasonable requests to the study team, only deidentified participant data will be available after publication of the study outcomes. Use and projects need approval by the Trial Steering Committee. Data will be shared via secure NHS email or a secure data sharing platform. Robust data sharing agreements will be put in place with all collaborating organisations as necessary to ensure the confidentiality and appropriate data handling. No identifiable personal data will be shared with organisations or individuals outside of these collaborating organisations.

Ethics and regulatory approvals:

The study received the following approvals: Health Research Authority and South-Central Oxford Research Ethics Committee (14/12/2021: 21/SC/0349) and CTA/MHRA (29/12/2021: 21304/0274/001-0001). The trial is registered as ISRCTN16867955.

Open access

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

References:

1. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. *Eur Urol 2020;77(1):38-52.*

2. Martin RM, Turner EL, Young GJ, et al. Prostate-Specific Antigen Screening and 15-Year Prostate Cancer Mortality: A Secondary Analysis of the CAP Randomized Clinical Trial. *JAMA* 2024;331(17):1460–1470.

3. Loeb S, Bjurlin MA, Nicholson J et al. Overdiagnosis and overtreatment of PCa. *Eur Urol 2014;65(6):1046-1055.*

4. Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, Jain S, Yamamoto T, Mamedov A, Loblaw A. Long-term follow-up of a large active surveillance cohort of patients with PCa. *J Clin Oncol 2015;33(3):272-277.*

5. Yamamoto T, Musunuru HB, Vesprini D, Zhang L, Ghanem G, Loblaw A, Klotz L: Metastatic PCa in Men Initially Treated with Active Surveillance. *J Urol 2016;195(5):1409-1414.*

6. Cooperberg MR, Carroll PR. Trends in Management for Patients With Localized PCa, 1990-2013. *JAMA 2015;314(1):80-82.*

7. Loeb S, Folkvaljon Y, Curnyn C, Robinson D, Bratt O, Stattin P: Uptake of Active Surveillance for Very-Low-Risk PCa in Sweden. *JAMA Oncol 2017;3(10):1393-1398.*

8. Tosoian JJ, Trock BJ, Landis P, Feng Z, Epstein JI, Partin AW, Walsh PC, Carter HB: Active surveillance program for PCa: an update of the Johns Hopkins experience. *J Clin Oncol 2011;29(16):2185-2190.*

9. van den Bergh RC, Steyerberg EW, Khatami A, Aus G, Pihl CG, Wolters T, van Leeuwen PJ, Roobol MJ, Schröder FH, Hugosson J: Is delayed radical prostatectomy in men with low-risk screen- detected PCa associated with a higher risk of unfavorable outcomes? *Cancer 2010;116(5):1281-1290.*

10. Simpkin AJ, Tilling K, Martin RM, Lane JA, Hamdy FC, Holmberg L, Neal DE, Metcalfe C, Donovan JL: Systematic Review and Meta-analysis of Factors Determining Change to Radical Treatment in Active Surveillance for Localized PCa. *Eur Urol 2015;67(6):993-1005.*

11. Johansson E, Steineck G, Holmberg L, Johansson JE, Nyberg T, Ruutu M, Bill-Axelson A. Long- term quality-of-life outcomes after radical prostatectomy or watchful waiting: the Scandinavian PCa Group-4 randomised trial. *Lancet Oncol 2011;12(9):891-899.*

12. Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, Martin RM, Young GJ, Walsh EI, Bryant RJ, Bollina P *et al*. Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. *N Engl J Med 2023;388(17):1547-1558.*

13. Bokhorst LP, Valdagni R, Rannikko A, Kakehi Y, Pickles T, Bangma CH, Roobol MJ: A Decade of Active Surveillance in the PRIAS Study: An Update and Evaluation of the Criteria Used to Recommend a Switch to Active Treatment. *Eur Urol 2016;70(6):954-960.*

14. Godtman RA, Holmberg E, Khatami A, Pihl CG, Stranne J, Hugosson J: Long-term Results of Active Surveillance in the Göteborg Randomized, Population-based PCa Screening Trial. *Eur Urol 2016;70(5):760-766.*

15. Hong SK, Sternberg IA, Keren Paz GE, Kim PH, Touijer KA, Scardino PT, Eastham JA: Definitive pathology at radical prostatectomy is commonly favorable in men following initial active surveillance. *Eur Urol* 2014;66(2):214-219.

16. Fleshner NE, Lucia MS, Egerdie B, Aaron L, Eure G, Nandy I, Black L, Rittmaster RS: Dutasteride in localised PCa management: the REDEEM randomised, double-blind, placebo- controlled trial. *Lancet 2012;379(9821):1103-1111.*

17. Shore ND, Renzulli J, Fleshner NE, et al. Enzalutamide Monotherapy vs Active Surveillance in Patients With Low-risk or Intermediate-risk Localized Prostate Cancer: The ENACT Randomized Clinical Trial. *JAMA Oncol* 2022;8(8):1128–1136.

18. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, Briganti A, Budäus L, Hellawell G, Hindley RG *et al*: MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med 2018;378(19):1767-1777.*

19. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, Zamecnik P, Bakker D, Setiasti AY, Veltman J *et al*: Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naïve

539 Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical
540 Study. *Eur Urol 2019;75(4):570-578.*

541 20. Kasivisvanathan V, Stabile A, Neves JB, Giganti F, Valerio M, Shanmugabavan Y,
542 Clement KD, Sarkar D, Philippou Y, Thurtle D *et al*: Magnetic Resonance Imaging-
543 targeted Biopsy Versus Systematic Biopsy in the Detection of PCa: A Systematic Review
544 and Meta-analysis. *Eur Urol 2019;76(3):284-303.*

545 21. Cooperberg MR, Cowan JE, Hilton JF, Reese AC, Zaid HB, Porten SP, Shinohara K,
546 Meng MV, Greene KL, Carroll PR: Outcomes of active surveillance for men with
547 intermediate-risk PCa. *J Clin Oncol 2011;29(2):228-234.*

548 22. Ahmed HU, Arya M, Freeman A, Emberton M: Do low-grade and low-volume PCas
549 bear the hallmarks of malignancy? *Lancet Oncol 2012;13(11):e509-517.*

550 23. Overland MR, Washington SL, 3rd, Carroll PR, Cooperberg MR, Herlemann A: Active
551 surveillance for intermediate-risk PCa: yes, but for whom? *Curr Opin Urol*
552 *2019;29(6):605-611.*

553 24. Kim SP, Shah ND, Meropol NJ, Tilburt JC, Nguyen PL, Yu JB, Abouassaly R, Kim A,
554 Gross CP: Recommendations of Active Surveillance for Intermediate-risk PCa: Results
555 from a National Survey of Radiation Oncologists and Urologists. *Eur Urol Oncol*
556 *2019;2(2):189-195.*

557 25. Tosoian JJ, Carter HB: Patients with Intermediate-risk PCa May be Good Candidates
558 for Active Surveillance: Con. *J Urol* 2017;198(5):997-999.

559 26. Nyame YA, Almassi N, Haywood SC, Greene DJ, Ganesan V, Dai C, Zabell J, Reichard
560 C, Arora H, Zampini A *et al*: Intermediate-Term Outcomes for Men with Very Low/Low
561 and Intermediate/High Risk PCa Managed by Active Surveillance. *J Urol 2017;198(3):591-*
562 *599.*

563 27. Francis JJ, Johnston M, Robertson C, Glidewell L, Entwistle V, Eccles MP, Grimshaw
564 JM. What is an adequate sample size? Operationalising data saturation for theory-based
565 interview studies. *Psychol Health 2010;25(10):1229-1245*

566 28. C. Englman, D. Maffei, C. Allen, A. Kirkham, P. Albertsen, V. Kasivisvanathan, *et al*.
567 PRECISE Version 2: Updated Recommendations for Reporting Prostate Magnetic

Resonance Imaging in Patients on Active Surveillance for Prostate Cancer. *Eur Urol 2024;86(3):240-255*

Figure legends

Figure 1. Recruitment and participant flow within the FINESSE study. Follow up within Active Surveillance includes PSA testing, MRI Scans and the offer of a repeat biopsy (times in months (m) shown).

Tables

Table 1. Primary objectives and outcomes within the Finesse trial.

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)	Additional Information
Primary Objective: To compare adherence with AS in men with low or intermediate PCa 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. - Rate of other treatment for PCa. - Rate of participant death from PCa. - Rate of men discontinuing AS for any other reason.	- 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. - Later analysis will use passive follow up (up to 10 years after trial closure).	- Rates in each arm will be measured by patient self-reporting. - Participants who are lost to follow up, or who die of a cause unrelated to PCa will be taken as censored.

585 **Table 2. Secondary objectives and outcomes within the Finesse trial.**

1. To compare between Finasteride with AS and AS alone, the rates of cessation of AS due to: i. ADT and/or chemotherapy initiation ii. Radical Prostatectomy iii. Radical Radiotherapy initiation. iv. Other treatment including watchful waiting V. Death from prostate cancer **Outcome Measures** Time until cessation of AS due to initiation of: i. ADT and/or chemotherapy ii. Radical Prostatectomy or iii. Radical Radiotherapy **Timepoint(s) of evaluation of this outcome measure (if applicable):** All occurrences of cessation of AS events due to i) ADT initiation, chemotherapy, ii) Radical Prostatectomy iii) Radical Radiotherapy, iV) Other treatment including watchful waiting, and v) death from prostate cancer during participant follow-up, 4 years on average, will be included in the analysis. The listed reasons for AS cessation will be treated as competing events. 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. **Outcome Measures** Progression is defined as either: - Increase in MRI stage from T2a to ≥T2c, T2b to ≥T2c, or T2x to ≥T3b [28] - Increase in grade from Gleason 3+3 to ≥3+4 or 3+4 to ≥4+3 - RARP histology revealing 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. - Death from prostate cancer. - Clinical DRE deterioration* - Extra-prostatic disease (note *DRE results alone will not be considered a definitive endpoint). **Timepoint(s) of evaluation of this outcome measure (if applicable):**
3. To measure PCa mortality. **Outcome Measures** Participant death from PCa. **Timepoint(s) of evaluation of this outcome measure (if applicable):** All deaths from PCa occurring during the 3-5 years follow-up of the study will be analysed.
4. To study the changes in MRI appearances of the prostate over time in men with/without finasteride. **Outcome Measures** bpMRI/mpMRI scan results at baseline (the diagnostic MRI), 12 and 36 months. (Please note, a 36-month MRI scan is strongly recommended). **Timepoint(s) of evaluation of this outcome measure (if applicable):** Baseline, 12 and 36 months. **Additional Information:** We will record: - Prostate volume from (height, width, length). - PCa stage: Using the Prostate Imaging Reporting and Data System (version 2) and Tumour, Nodes, Metastasis staging.

- PCa size: Taken as the maximum diameter on an axial slice from the MRI acquisitions. The pMRI/mpMRI images will be quality controlled centrally by the Lead radiologist. 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 AS for this disease. **Outcome Measures** Semi-structured one-to-one interviews led by a trained interviewer, with selected individuals during the follow- up phase. **Timepoint(s) of evaluation of this outcome measure (if applicable):** Months 48 to 60
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 similar). **Outcome Measures** Patient self-reporting. **Timepoint(s) of evaluation of this outcome measure (if applicable):** All symptoms during the follow up of between 3 and 5 years until trial end. **Additional Information:** Determined from new prescriptions for 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 similar).
7. Overall (all cause) mortality. **Outcome Measures** Death eCRF completed by sites. **Timepoint(s) of evaluation of this outcome measure (if applicable):** All deaths during the follow up of between 3 and 5 years until trial end. **Additional Information:** Cause of death will be decided by note review (and CRF completion) and death certificates.

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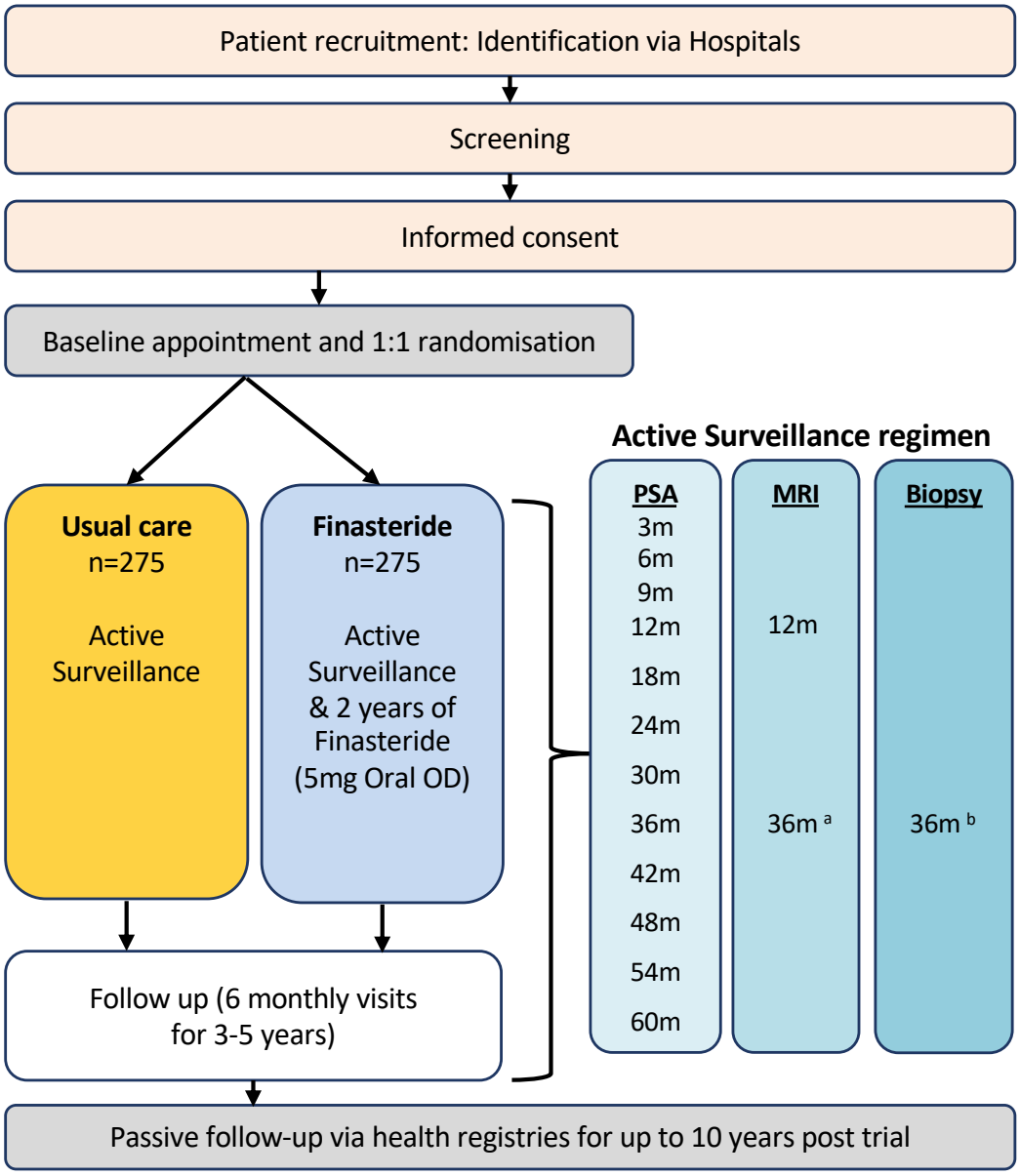
Table 3: Schedule of events for quality-of-life measures (collected through eCRFs (electronic Case Report Forms)) during the FINESSE trial.

		TREATMENT PHASE (Years 1-2)									FOLLOW UP PHASE *(Years 3-5)*						
		Timepoint in months (visit can be +/- 2 weeks).															
	Completed by participants on FINESSE web-based EDC, (REDCap)	Randomisation	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]

Footnote: 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



Footnote
a. Strongly recommended
b. Offered as a routine to all men. Also strongly recommended for changing MRI appearances and/or where indicated by the MRI scan

Figure 1. Recruitment and participant flow within the FINESSE study. Follow up within Active Surveillance includes PSA testing, MRI Scans and the offer of a re-biopsy (times in months (m) shown).

Appendix 1: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1). (Non-substantial)	2.0	03.03.2022	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.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
2). (Substantial)	3.0	18.05.2022	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.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
3). (Substantial)	4.0	19.06.2023	Roseann Kealy	The following significant changes have been made to the protocol: • Eligibility criteria updated to increase the time since PCa 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 PCa', 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.
4). (Non-substantial)	4.0	27.09.2023	Roseann Kealy	The following changes have been made to the protocol to address three sections where updates to the timelines were missed within the recently approved substantial amendment: • The trial summary table states, "Men aged 50 to 75 years diagnosed with low/intermediate-risk localised prostate cancer in the 6 months preceding their date of randomisation". This has been corrected to, "Men aged 50 to 75 years diagnosed with low/intermediate-risk localised prostate cancer in the 24 months

				preceding their date of randomisation". • Section 5.1 states, “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”. This has been corrected to read, Eligible men aged 50 – 75 years with low or intermediate-risk prostate cancer diagnosed within the last 24 months will be invited to join the trial”. • Section 6.1b states “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.” This has been corrected to read, “Prior active surveillance populations: Recruiting hospitals can assess their databases to identify potentially eligible patients already managed by active surveillance, diagnosed within the last 24 months.”
Substantial	5.0	17. 10.24	Harriet Strachan & Roseann Kealy	• Change of institution of the Cancer Prevention Trials Unit from King’s College London to Queen Mary University of London. • Change of institution for Peter Sasieni (Co- Lead Applicant & Trial Statistician), Bernard North (Independent Trial Statistician) and Roseann Kealy (FINESSE Study Trial Manager) from King’s College London to Queen Mary University of London. • Update to indemnity section to add Queen Mary University of London. • Clarification: ○ That the secure restricted access server Data Safe Haven maintained by a contracted GDPR compliant third-party storage provider that stores patient identifiable data for the study will now be retained by King’s College London and Queen Mary University of London.

				○ Of the IMP destruction policy. ○ Of the requirements for a valid PSA density result. ○ Of the 'outcome measures' for the secondary objective 'To compare between Finasteride with AS and AS alone, the rates of cessation of AS due to initiation of ....' • Removal of the limit on number of cores and maximum cancer core length, from inclusion criterion 10, to increase the pool of potentially eligible men. • Additional advice for Investigators and research staff to improve awareness of the potential risk of psychiatric and sexual dysfunction side effects, and to highlight the need to monitor these closely, within section 7.10.

[FINESSE STUDY LOGO]

[Please print on local headed paper & add contact details of the local research

CONSENT FORM

FINESSE: ***A medical research study to improve treatment for men with early prostate cancer***

Name of Principal Investigator:

PIN:							

Please **initial** box

1. I confirm that I have read and understood Parts 1 and 2 of the Participant Information Sheets, Version no: X Dated: DD/MM/YYYY for the above study. I have had the opportunity to ask questions, and these have been answered to my satisfaction. I understand how to raise a concern or make a complaint. ☐

2. I understand that my participation is voluntary, and that I am free to withdraw from the study at any time, without giving a reason, and without my medical care or legal rights being affected. ☐

3. I understand that relevant extracts from my medical notes, data and tissue collected, may be looked at by the clinical trials unit co-ordinating this research, researchers from the Universities of Sheffield and Leeds, the Sponsor, Sheffield Teaching Hospital NHS Trust, and also by the regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that even if I withdraw from the study, the information and samples collected from me up to that point will be used in the analysis of the results, and my identity will remain anonymous within this analysis. ☐

5. I understand that my name and contact details will be collected and securely stored on a secure, restricted access server Data Safe Haven maintained by a contracted GDPR compliant third-party storage provider based within the UK, who are retained by Kings College London or Queen Mary University of London. My details will be used to send me relevant information relating to the study, to track my health long-term via relevant health data registries e.g. The National Cancer Registration and Analysis Service (NCRAS), and to request additional information relevant to the trial, from local health information sources, e.g., my treating hospital.
   As detailed in the PIS, I am aware that employees of third-party providers, based outside of the UK, and contracted by the research team, may require access to my personal-identifiable data to fulfil their role as a third-party service provider. However, my personal-identifiable data will be kept strictly confidential and never be stored outside of the UK. ☐

6. I understand that where relevant, slides of tissue collected for standard care biopsies & corresponding pathology reports, may be sent from my hospital's Pathology Department to the Pathology Department at Leeds Teaching Hospital NHS Foundation Trust, for central review by the FINESSE Lead pathologist. Slides & reports will be pseudo-anonymised, and the pathology samples will be returned to the sites once the review is complete, and in accordance with the site's pathology release conditions. ☐

[FINESSE Study Logo]

[Please add contact details of the local research team]

7. I understand that pseudonymised and anonymised data generated from the Trial may be made publicly available and shared with commercial/overseas researchers within Europe or organisations, to support other research in the future, and may be shared anonymously with other researchers or organisations which may include those in the commercial sector, here or within Europe. ☐

8. I agree to update the FINESSE Coordinating Centre of any relevant changes to my personal details e.g., a change to my email address, or a new telephone number. ☐

9. I agree to my General Practitioner being informed of my participation in the study. ☐

10. I agree to take part in the above study. ☐

Optional interview consent	*Please **initial** relevant box below*	
1. I agree to be approached by the research team and invited to participate in a 60-minute telephone interview exploring my experience of taking part in this study. I understand that my participation in the interview is voluntary and that I am free to withdraw at any time without giving any reason.	Yes	
	No	

Optional future contact consent	*Please **initial** relevant box below*	
2. I agree to be contacted about future studies using the contact details I have provided.	Yes	
	No	

Name of Participant: *Date:* *Signature:*

Name of Person taking consent if not PI: *Date:* *Signature:*

Name of PI/Delegated Investigator: *Date:* *Signature/Countersignature:*

*1 copy for the participant; 1 copy for Investigator Site File (ISF); 1 (original) to be kept in medical notes.

[Please print on local headed paper and add contact details of the local research team & Trust Logo]

Short Title: FINESSE – A research study to improve treatment for men with early prostate cancer

Scientific Title: 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.

You are being invited to take part in the FINESSE study. This is a clinical trial for men diagnosed with prostate cancer. To help you decide whether to take part you need to understand why the research is being carried out and what it would involve.

For the purposes of this information sheet, the term 'we' refers to the Cancer Prevention Trials Unit at King's College London, who are responsible for co-ordinating and running this study on behalf of the Sponsor and the Chief Investigator. Please see section 21.

If this information sheet and consent form contain words you do not understand, please ask the study doctor or nurse to explain anything unclear. Please take time to read the information carefully. You will be able to take a copy of this sheet home so you can read it again. If you want to, you can discuss it with family or friends before deciding. If you choose not to take part, your healthcare will not be affected.

You should not sign the consent form until you have read this information sheet carefully, asked any questions you might have, and received satisfactory answers.

Part 1

1. What is the purpose of this study?

This trial will try to find out if a drug called finasteride can support men to continue with active surveillance after they have been diagnosed with localised prostate cancer. If this works, it will increase the number of men who avoid or delay the need for further treatment, and the side-effects accompanying this.

One of the popular treatment options for low or intermediate risk prostate cancer is active surveillance. Active surveillance means, rather than treating you with surgery or radiotherapy, your doctor will monitor you for signs that your cancer is changing. That way you would only need further treatment if you and

your doctor agree you do. Active surveillance is used because some prostate cancers never progress beyond the stage they are at when they are found, and so do not need further treatment.

Once active surveillance begins, you'll have regular tests to check on the cancer. One of the tests is a prostate specific antigen (PSA) test. This test measures the amount of PSA in your blood. PSA is produced by normal cells in the prostate and also by prostate cancer cells. A raised PSA level may suggest a problem in your prostate, but not necessarily cancer. PSA tests can be unreliable and can suggest prostate cancer is present when no cancer exists. They can also incorrectly indicate that a man does not have prostate cancer when they in fact do. PSA levels in men with prostate cancer can vary and can go up even when cancer is not progressing. Most men with low or intermediate risk prostate cancer do not require further treatment, but higher PSA levels may make men worry and this is a common reason why men decide to have further treatment.

We aim to improve what is offered for men like you so that you feel more confident in safely staying on active surveillance, using a drug called finasteride. Finasteride is used to improve symptoms of enlarged prostates, but also reduces PSA levels. We think that reducing PSA levels with finasteride might help your clinician to assess your prostate cancer more accurately by stopping it from rising due to factors that are not related to your prostate cancer (such as inflammation or normal enlargement associated with ageing). The decision regarding the need for further treatment will be more focused on the results of a prostate biopsy and prostate MRI, rather than fluctuating PSA levels. However, PSA levels will still be considered by your doctor because if your cancer is progressing, they can still rise, even if you are taking finasteride.

This is a randomised controlled trial, which means if you take part, you will be allocated to one of two study arms chosen at random. You and your medical team cannot choose which group you are put into. Half of the men will be placed into the active surveillance AND finasteride group (intervention arm) and half into active surveillance ONLY (control arm). We will recruit 550 men and allocate them to these groups. You and your doctor will both know which group you are in. This is what we call an 'open label' study. The study will run for five years, but if you are randomised to the intervention arm you will only take finasteride tablets for two of those years. Please note, if you are randomised to the control arm but are then prescribed finasteride for another medical reason by your treating clinician or GP, you will have to be withdrawn from the study.

2. What does taking part in this study involve?

Men who choose active surveillance for further treatment are seen regularly in a hospital clinic. Most of the time, the clinic and research appointments will be at the same time. However, participants will be required to attend up to three additional appointments as part of the trial, including a consent and randomisation visit at the start and two additional visits during the second year of the study. You can claim up to £25 per visit for your travel expenses to attend these extra visits. Please note, if current pandemic

policies change during the study, your study appointments may happen by telephone or video call, and your study drug if you are randomised to the finasteride arm may be posted to you.

Consent and randomisation visit – consent and random allocation to the study group can take place on the same day for men who have had a PSA test done in the last 3 months.

First year of the study – Local staff have been asked to ensure as far as possible, that research appointments coincide with regular active surveillance appointments, so that no extra study appointments are required during this period. Men allocated to the treatment arm will also take one tablet of finasteride (5mg) every day during this year.

Second year of the study - during the second year of active surveillance, men are usually seen every 6 months in their regular active surveillance Clinic. Finesse study visits will continue to be scheduled every 3 months so participants will be asked to attend **two extra visits, one at month 15** and the other **at month 21,** during this period. Men in the treatment arm will continue to take one tablet of finasteride (5mg) every day during this year. The treatment will be stopped after two years.

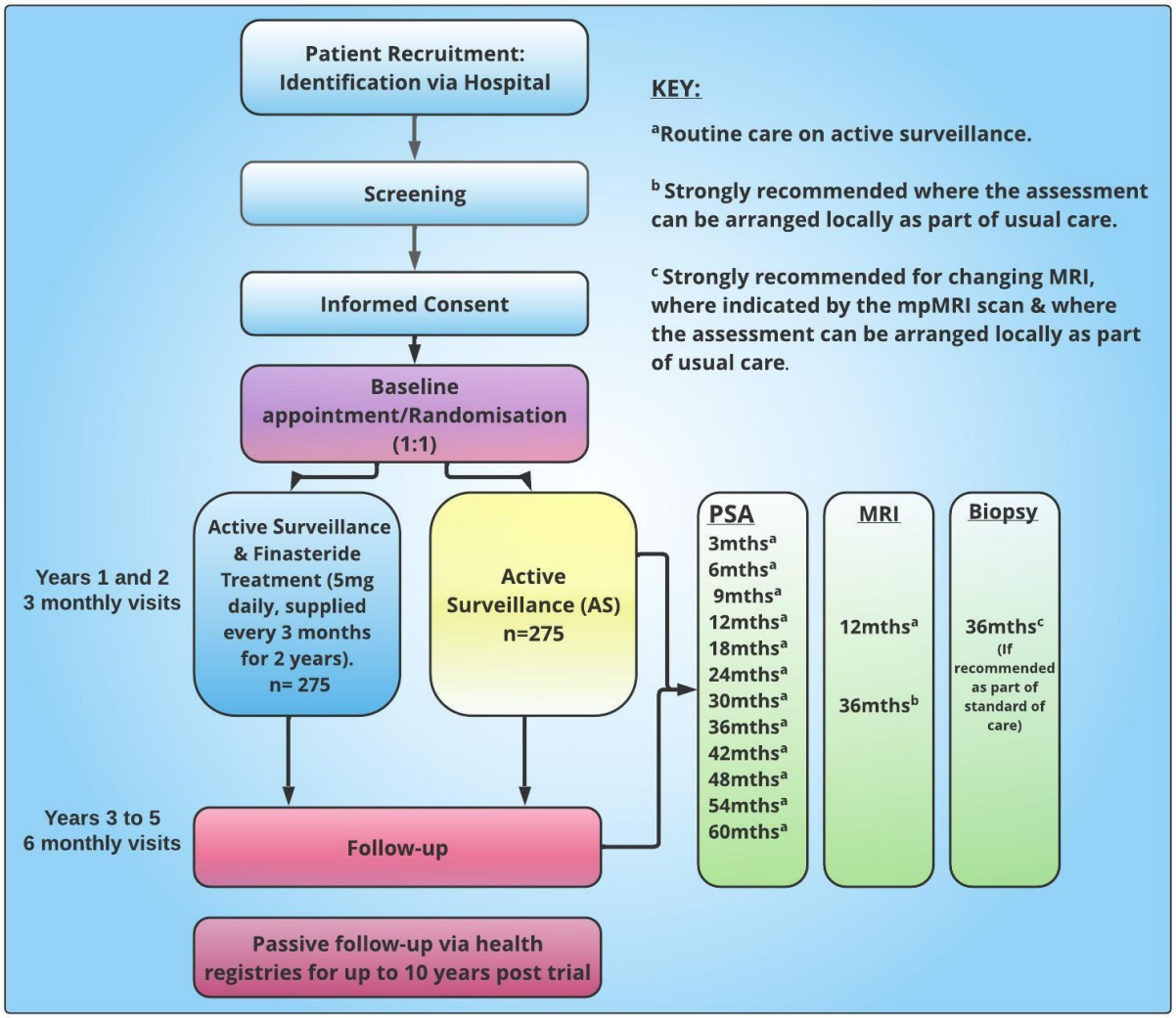
Third, fourth and fifth year of the study - men will continue to attend routine active surveillance appointments every 6 months and all study appointments will take place at the same time. Men allocated to the treatment arm will no longer take finasteride tablets during this period.

All men in the trial will be asked to complete questionnaires approximately every three months, which should take between 20 and 30 minutes in total to complete. This is to check how you are getting on, as we want to keep track of how your health and treatment may affect your quality of life.

These questionnaires will be emailed to you in between your visits. For this reason, we will collect your personal contact details, with your permission.

Some men will be invited to take part in a telephone interview at the end of the trial. Questions in this interview will relate to their experiences of taking part in the trial. The interview is optional.

Flow Diagram of Order of Events:



3. Why have I been invited?

You are being invited to take part in this study because your doctor believes your type of prostate cancer and treatment makes you suitable.

You **are potentially able** to take part in this trial if you:	You are **not able** to take part in this trial if you: • have previously received treatment for prostate cancer

• have been diagnosed with prostate cancer in the last 12 months • have not received previous treatment for prostate cancer • have opted for active surveillance for prostate cancer • are fit and suitable for radical treatment • are aged 50-75 years old at diagnosis	• are currently taking or have been taking finasteride or dutasteride in the last 12 months • you are planning to father a child • you have been told you have a terminal illness

There are some additional eligibility criteria related to your diagnosis and other medical conditions you may have. A research nurse will ask you questions in person at the clinic, or over the phone, and look at your medical records, to check that you are suitable.

If you are interested in the trial, but unsure whether you can take part, please contact your research nurse (contact details on the front page).

4. I am transgender or a non-binary person, can I still take part?

Yes. Whilst the terms 'men' and 'male' are used throughout the study documents, 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. Do I have to take part if I am suitable?

No. It is completely up to you whether you take part or not. If you do not wish to take part, your healthcare will not be affected in any way. If you do decide to take part, you will be asked to read and sign a consent form. Even if you consent to taking part in this trial, you can change your mind and leave the study at any time, without giving a reason.

6. What is the medicine being tested?

The medicine being tested is finasteride. Finasteride will be in tablet form, 5mg in a single tablet, taken once a day. Ideally this will be around the same time every day, with water. The tablet will be coated to avoid irritating the stomach lining. All men in the treatment arm will be asked to take finasteride for 2 years.

Finasteride is also known by the brand names Proscar and Propecia. It is a type of medicine called a 5-alpha reductase inhibitor which works by stopping testosterone (a sex hormone) turning into another hormone called dihydrotestosterone (DHT), which can cause your prostate to grow bigger. Finasteride

stops DHT being produced which helps shrink your prostate. It is therefore used to treat men with an enlarged prostate (benign prostate enlargement). It can help ease symptoms such as frequent and urgent urination, difficulty completely emptying the bladder or starting urination. Some studies have suggested that it **MAY** shrink the prostate tumour, but this is not the main objective of the FINESSE study.

In this study, finasteride is being used 'off label' which means the medicine is being used in a way that is different to that described in the licence.

7. Are there any alternative treatment to the study?

For men who have already made the decision to join an active surveillance programme, your alternative to this study is not to take part. There are alternatives to active surveillance which your doctor will have discussed with you, including surgery. However, if you are unsure what those alternatives are, or you would like to discuss them again, please ask your doctor, who will talk you through them in detail.

8. What are the possible side effects of taking part?

Like all medicines, finasteride can cause side effects, but not everyone will get them. Finasteride is well tolerated and does not normally cause serious side effects.

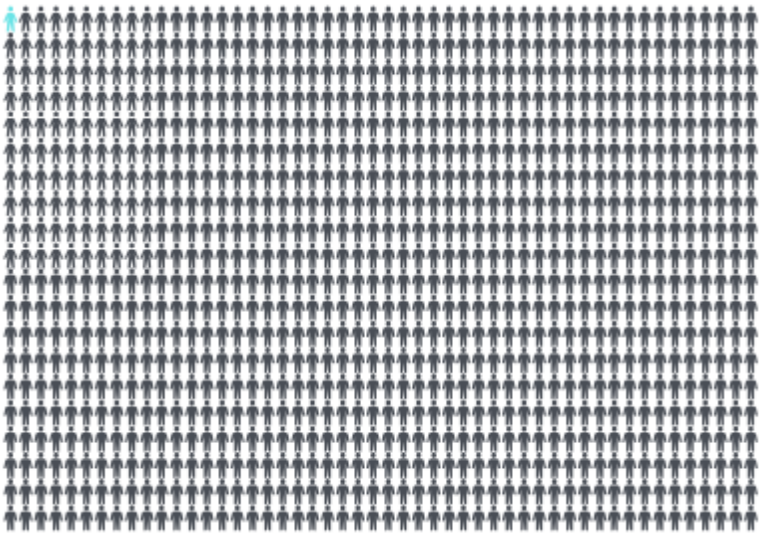
Common Side Effects (happen in more than 1 in 100 people):

These usually improve after a while, but they should be discussed with a doctor if they bother you or do not go away:

- less interest in having sex (decreased libido/sex drive)
- trouble getting or keeping an erection.
- problems with ejaculating, such as little or no semen

- increase in breast size and tenderness.
- skin rash

Serious side effects:



Serious side effects are rare and happen in less than 1 in 1,000 people. Some people may notice these side effects after taking finasteride for a few months. These should always be reported to a doctor.

- Lumps, pain or swelling in your chest area or discharge from your nipples
- Unusually low mood (depression) or thoughts of harming yourself
- Allergic reaction- in rare cases, finasteride may cause a serious allergic reaction (anaphylaxis), in which case immediate action such as calling 999 or going to A&E, would be required

A full list of side effects will be provided inside the medicine packet.

Special note on pregnancy:

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:

1) Men trying for a baby or with a pregnant partner will not be allowed to take part in the trial.
2) Participants taking finasteride will be advised to:
    a. Use a condom when having sex. 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's any chance they could be pregnant. Finasteride can get into your bloodstream through your skin if you handle **broken** tablets. This is why the tablets come with a protective coating.

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.

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

If you have already chosen to have active surveillance a disadvantage is that some of your appointments might take a little longer than normal. You will need to remember to take a tablet every day, unless advised otherwise. Completing the online questionnaires may also take some time.

10. What are possible benefits of taking part?

- You may avoid or delay more intensive treatment for prostate cancer, which may have benefits for your quality of life.
- The growth of your prostate cancer **MAY** be slowed down (with the drug), although further research is needed to see if this is definitely true, and this is not the main objective of the FINESSE study.
- You may help improve the care of men with prostate cancer who opt for active surveillance and help us better manage the disease e.g., by promoting the use of other technologies in active surveillance such as MRI scans.
- If you have benign disease in addition to prostate cancer, you may see improvements in this.
- You will have more regular follow-ups than is standard practice.

11. What happens at the end of the trial?

The study will run for five years (two years to cover the treatment period, and three years of follow-up). Men taking finasteride will be asked to stop taking the drug after two years. The trial is not funded to offer

finasteride treatment after two years. Because the drug is being used 'off-label' in this study, you will need to consult your urologist if you wish to continue taking finasteride after your two years' trial treatment.

Men whose prostate cancers have remained unchanged at that point will continue to be followed up as part of the normal active surveillance programme. In addition, during years 3, 4 and 5 of the study, you will continue to complete study questionnaires every 12 months.

If at any stage your cancer shows signs of change and you need further treatment, your doctor will advise you to stop the study treatment. You can still complete the study questionnaires.

With your permission, once you have finished your trial appointments, the research team will continue to collect information from your doctor or from central NHS records for up to ten years to track your health, including whether you have received further treatment for prostate cancer. This is sometimes called 'Passive follow-up' because it takes place without requiring any involvement from study participants. If you do not want this to happen, you can say you want to stop any more information being collected.

At the end of the trial, your data will be stored securely and used to answer our research questions. The findings from the trial may be reported at meetings, conferences, and published in journals in a way that no-one can work out who took part in the study. More information on the storage and use of your data can be found on in section 23. Data handling and confidentiality.

12. What if something goes wrong?

You should contact your doctor or nurse if you have a question or a problem while taking part in the research. Their contact details can be found in section 13 of this information sheet. If you are seen by a doctor outside the study, you should remind them you are taking part in FINESSE. In case of emergency, you should act in the same way you would if you were not on the study. It is unlikely that you will need emergency hospital treatment as a result of this trial. However, you should always inform any doctor treating you that you are taking finasteride 5mg.

The overall sponsor of the trial is the Sheffield Teaching Hospitals NHS Foundations Trust (STHNHSFT), and the trial is coordinated by the Cancer Prevention Trials Unit at King's College London (KCL).

NHS indemnity will provide cover for negligent harm relating to STHNHSFT's role as trial sponsor. As employers of the authors, KCL and the University of Sheffield (UoS) provide indemnity to cover negligence only liabilities arising from the design of the research. You may be able to claim compensation if you can prove that STH NHS, KCL and/or the University of Sheffield has been negligent.

However, as this clinical trial is being carried out in hospital, the hospital continues to have a duty of care to you. STHNHSFT, KCL & 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.

If you sustain injury as a result of negligence and wish to make a claim for compensation, you should do so in writing in the first instance to the Chief Investigator via the CPTU. Address details can be found on the trial website. 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.

13. Will my taking part in the study be confidential?

Yes. All the information about your participation in the study will be kept confidential. Further details about this can be found in Part 2.

14. Who should I call if I have questions, queries and/or complaints?

- You can ask more questions about the study at any time, and you can contact the following people for more information: 'local PI name' and 'research study nurse' – the study doctor and research nurse

  Telephone: [Sites to enter local number]
- You can also visit the FINESSE study website at: www.finessetrial.org
- For independent advice on taking part in a clinical trial please contact 'local' Health Patient Advice and Liaisons Service (PALS) on Sites to enter local PALS number] or email: [Sites to enter local PALS email]

  The PALS service is available [Sites to add local PALS opening hours]
- If you want to complain about how researchers have handled your information, you should contact the research team. If you are not happy after that, you can contact the Data Protection Officer on info-compliance@kcl.ac.uk

If you are not happy with their response or believe they are processing your data in a way that is not right or lawful, you can complain to the Information Commissioner's Office (ICO) (www.ico.org.uk or 0303 123 1113).

This completes part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering taking part, please continue to read the additional information in Part 2 before making any decision.

FINESSE Patient Information Sheet:	**V5.0 22nd May 2023**	**REC Ref:**	**21/SC/0349**	**ISRCTN:**	**ISRCTN16867955**
IRAS Project No:	**1004290**	**Chief Investigator:**	**Prof. James Catto**	**EudraCT No:**	**2021-004004-17**

Part 2

15. What should I do if I want to take part?

If you have received this leaflet from one of the urological clinics at participating NHS centres please contact the research nurse working on the trial (see section 13).

If you have found this Patient Information Sheet on the FINESSE website, or elsewhere on the Internet, please register your interest by emailing finesse@kcl.ac.uk

If you are interested in taking part, the next steps include the research nurse:

- Checking that you are suitable (if they have not already done so), by asking you a series of questions about your health
- Booking a consent and randomisation visit. During this visit you will be asked to complete a consent form indicating that you understand what the trial involves and that you agree to take part. Once all of these have been completed, you will then be randomised to one of two groups.

Please only agree to take part in this study if you are willing to accept allocation to either group. Participation in both groups is important to help us find out whether finasteride can reduce the number of men who receive radical treatment for prostate cancer.

16. What if new information becomes available?

Sometimes, during a research study, new or important information about the medicine(s) being studied becomes available. If this were to happen, the trial staff would let you know and discuss it with you. Depending on what the information is, you may wish to withdraw from the study, or your doctor may advise you to withdraw. If you withdraw you would continue to be seen in the normal active surveillance clinics. If you decided to continue in the study, you may be asked to sign an updated consent form.

A special group of experts, known as a Data Monitoring Committee, who are independent from the trial staff and doctors, has been set up to oversee the study on a regular basis to make sure any issues are looked into properly and that the men taking part are informed about any relevant new information. The information sheet and other study documents will also be updated with any new details.

17. What will happen if I don't want to carry on in the study?

You are completely free to leave the study any time you wish and for any reason. The standard of care you receive will not be affected. However, the more men we have on the study, the more data we collect, and the better our chances of answering our research questions accurately. Your participation is important to us and valued. Therefore, we would encourage you to talk to us before making your final decision, to see if we can address any problems that you may be having and improve your trial experience.

If you change your mind about taking part in the study, you can withdraw at one of three levels:

1. It is possible for you to stop the study medication (finasteride), and remain in the study, under follow-up clinic, or by telephone. In this case, you will be asked to continue completing the study questionnaires. During follow-up, and for up to ten years after the trial has finished, the research team will continue to collect some information from central NHS records to track your health, in particular if you had received further treatment for prostate cancer during that period. This type of follow-up is often called 'passive follow-up' because trial participants are not actively involved or inconvenienced.

2. You can decide to stop the study medication (finasteride) AND stop completing the study questionnaires. During follow-up, and for up to ten years after the trial has finished, the research team will access central NHS records to check if you had received further treatment for prostate cancer during that period, (passive follow-up).

3. Alternatively, you may wish to withdraw from ALL aspects of trial. In this case, you will stop taking study medication (finasteride), we will stop sending you the study questionnaires and we will not access national health registries to check if you had received further treatment for prostate cancer during the follow-up period, (passive follow-up).

Information and samples that have been collected up to the point of your withdrawal will remain part of the study. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you. Research could go wrong if data is removed or changed.

Please ask the study doctor or nurse if you have any questions about this.

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

In this study, most of the research team will not need to know your name. In these cases, someone will remove your name from the research data and replace it with a code number. This is called coded data, or the technical term is pseudonymised data. For example, your blood test might be labelled with your

code number instead of your name. It can be matched up with the rest of the data relating to you by the code number. In the FINESSE study, this code number is called a Patient Identification Number (PIN). Your PIN will be used on most of your study records and samples instead of your name, wherever possible, to ensure information is kept confidential. Please see 'Who will have access to my data?' on page 18 for the exceptions.

Your medical records may be looked at by people who are authorised to check that the study is being carried out properly, and the quality of the research. Representatives of health regulatory authorities and the hospital NHS Trust, and auditors from the Trials Unit and Sponsor may have access to your medical records, and these people will be required to keep your information confidential. A responsible representative from King's College London will also require access to records for the purpose of monitoring and auditing. By signing the consent form you are giving your permission for this to happen.

Your contact details and information collected about you will be stored on a secure database, and access will only be available to members of the trial team, other members of King's College London who may wish to monitor the study, and a third party based outside of the UK who will send text messages on our behalf. These details will also be required to send you study related information questionnaires, and to allow the study team to collect registry data during passive follow-up. Your personal identifiable data will never be stored outside of the UK.

19. Information for your General Practitioner

By signing the consent form, you give the study doctor permission to inform your family doctor (GP) that you will be taking part in this research. We feel that it is important because your GP should be aware of any treatment or medications that you receive so they have a more complete picture of your health. After you have joined the study, they will receive a letter that will include information about finasteride (if you are in the group taking it) and this information sheet for their records. We also encourage you to mention this trial the next time you see your GP.

20. Will any genetic tests be done?

No. We may decide to collect additional samples for testing in the future, but if this were to happen, the trial staff would let you know and discuss it with you. You would also be provided with an updated Patient Information Sheet. You may also be asked to sign an updated consent form.

21. What will happen to the results of this study?

It will take up to 5 years to complete this study, so it will be some time before any results are available. The findings from the trial will be shared with participants and may be reported at meetings, conferences, published in journals and shared with the medical community. If the results from this study are published, your identity will remain confidential and no personal identifiable information will be used.

FINESSE Patient Information Sheet:	**V5.0 22nd May 2023**	**REC Ref:**	**21/SC/0349**	**ISRCTN:**	**ISRCTN16867955**
IRAS Project No:	**1004290**	**Chief Investigator:**	**Prof. James Catto**	**EudraCT No:**	**2021-004004-17**

22. Who is funding the study, and who else is involved?

The research is funded by Yorkshire Cancer Research, and the National Institute for Health Research (NIHR) provides support services within the NHS hospitals involved. The medicines for this trial are being sponsored by the NHS Commissioners.

The Chief Investigator of the study is Professor James Catto (University of Sheffield) and his co-investigator is Professor Peter Sasieni (King's College London).

Sheffield Teaching Hospital NHS Foundation Trust (STHNFT) is organising this research, is the sponsor for the study and employs the Trial Radiologist.

Leeds Teaching Hospital NHS Foundation Trust employs the Trial Pathologist.

The University of Leeds employs the Trial Behavioural Scientist.

The study is being co-ordinated and managed by the Cancer Prevention Trials Unit at King's College London.

None of the staff involved in the study will receive payment specific to their involvement in this research.

22. Data handling and confidentiality

This section outlines how your data will be used, stored, and accessed, during and after the trial.

What is patient data?

When you go to your GP or hospital, the doctors and others looking after you will record information about your health. This will include your health problems, and the tests and treatment you have had. They might want to know about family history, if you smoke or what work you do. All this information that is recorded about you is called patient data or patient information and is also referred to as personal data.
When information about your health care joins together with information that can show who you are (like your name or NHS number) it is called identifiable patient information. It's important to all of us that this identifiable patient information is kept confidential to the patient and the people who need to know relevant bits of that information to look after the patient. There are special rules to keep confidential patient information safe and secure.

Will the use of my data meet UK GDPR rules?

UK GDPR stands for the United Kingdom General Data Protection Regulation. In the UK we follow the UK GDPR rules and have a law called the Data Protection Act. All research using patient data must follow UK laws and rules.

Universities, NHS organisations and companies may use patient data to do research to make health and care better. Universities and the NHS are funded from taxes, and they are expected to do research as part of their job. They still need to be able to prove that they need to use patient data for the research. In legal terms this means that they use patient data as part of 'a task in the public interest'.

If they could do the research without using patient data, they would not be allowed to get your data.

Researchers must show that their research takes account of the views of patients and ordinary members of the public. They must also show how they protect the privacy of the people who take part. An NHS Research Ethics Committee (REC), an independent group of people, checks this before the research starts to protect your interests.

This study has been reviewed and given favourable opinion by the South-Central Oxford C Research Ethics Committee.

King's College London Data Protection Statement

King's College London has a responsibility to keep information collected about you safe and secure, and to ensure the integrity of research data. Specialist teams within King's College London continually assess and ensure that data is held in the most appropriate and secure way. This may include storage of personal data with a contracted GDPR compliant third-party storage provider within the UK, where they are assessed as the best data storage option. Employees of the third parties will have access to your data to fulfil their role as a third-party service providers, but your records and information will be kept strictly confidential.

FINESSE Study Data Protection Statement

Your data will be processed under the terms of UK data protection law [including the UK General Data Protection Regulation (UK GDPR) and the Data Protection Act 2018]. The sponsor, Sheffield Teaching Hospitals NHS Foundations Trust, is the Data Controller and is responsible for looking after your information and using it properly. The KCL Data Protection Officer provides oversight of KCL activities involving the processing of personal data, and can be contacted at info-compliance@kcl.ac.uk

Data protection regulation requires that we state the legal basis for processing information about you. In the case of research, this is 'a task in the public interest.' Special category personal data is personal data that reveals racial or ethnic origin, political opinions, religious or philosophical beliefs, trade union membership, health (the physical or mental), sex life or sexual orientation, genetic or biometric data. The lawful basis used to process *special category personal data* will be for scientific and historical research or statistical purposes.

If you would like more information about how your data will be processed in accordance with UK GDPR, please visit the link below:

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https://www.kcl.ac.uk/research/support/research-ethics/kings-college-london-statement-on-use-of-personal-data-in-research

What data will be collected?

In this study we will collect data from five different sources:

1. Clinical data - When you have medical treatment or visit a clinic, a nurse will collect data about your prostate cancer diagnosis and treatment, and other medical conditions which are relevant to the trial. All research should only use the patient data that it really needs to do the research. You can ask what parts of your health records will be looked at.

2. Directly from you - We will ask you to provide your date of birth (DOB), and your NHS and hospital ID numbers to help us locate your MRI scans, pathology, PSA results and other relevant reports. We will also ask you to provide your email address, home address and mobile phone number so that we can contact you and send you online questionnaires. We will always make sure that as few people as possible can see this sort of information that can show who you are.

The online questionnaires will ask about your quality of life, symptoms you experience, your emotional state, and your treatment. If you are in the finasteride group, we will also ask if you took the pill every day and if you are having any issues with taking the drug. All research should only use the patient data that it really needs to do the research. You can ask what parts of your health records will be looked at.

3. Biological tissue - As standard in the NHS, during a prostate biopsy small samples of tissue are taken from the prostate. Once the doctors finish their diagnosis, the trial pathologist may review the biopsy tissue and/or digital images of the tissue where available. This is known as 'central review', and it is carried out to ensure the local radiologists at each of the study sites are reporting results in a similar way. It is a quality control exercise. The comments from their review will not be traceable back to you. With your permission, we will store these images with your study data. You will not be asked to provide any additional prostate tissue for the study. All samples will be managed in accordance with the requirements of the Human Tissue Act (2004).

4. Medical imaging (mpMRI) – You will undergo a diagnostic imaging procedure (magnetic resonance imaging, MRI), as part of your active surveillance, whereby a MRI scanner will scan your prostate. The number of scans you have will be dependent on your individual needs, and is something you will discuss with the urologist treating you. You will not have any additional scans as part of this study. Your doctors will look at the results of this imaging. With your permission, the Trial Radiologist will also centrally review and store these images with your study data. They will be a valuable research resource. As with the pathology samples the comments from the Trial Radiologist's review will not be traceable back to you.

5. Health data registries – This data is protected by data laws and strict access requirements. With your permission we will use these data registries to learn about your long-term health, such as any further treatment you may have for prostate cancer.

If you take part in the additional telephone interview at the end of the trial, your call will be recorded and typed out in a transcript.

Where possible, we will anonymise or pseudonymise the personal data you provide. Pseudonymisation is a technique that replaces information in a data set that identifies an individual, with an artificial identifier. In the case of FINESSE study, this artificial identifier will be a Patient Identification Number or PIN. We will always minimise the processing of personal data wherever possible.

You can find out more about how we use your information at www.hra.nhs.uk/information-about-patients

How will my data be stored?

Prostate tissue samples will be held within Leeds Teaching Hospital NHS Foundation Trust, where the Trial Pathologist is based and mpMRI images will be held by Sheffield Teaching Hospital NHS Foundation Trust (STHNFT), where the Trial Radiologist is based. Digitised images of the tissue samples and copies of the MRI scans will be stored in the Data Safe Haven (DSH). . The DSH will be maintained by AIMES, a contracted GDPR compliant third-party storage provider based within the UK.
It is a secure place we use to store all personal, sensitive, pseudonymised electronically captured data, and other confidential study data, e.g., your questionnaire responses, for access exclusively by approved researchers and clinicians only. In addition, your identifiable patient information will be kept separately from your clinical data.

Who will have access to my data?

Only authorised members of the research team at King's College London will have access to your identifiable data. The exceptions to this are:

Your mobile number, since the third party responsible for sending you reminder text messages is based outside of the UK. The sharing of this data will be in accordance with UK GDPR, and your data will never be stored by this third party.

Your MRI scans and associated reports as it is not possible to anonymise these for this study. However, these will be transferred electronically from one NHS hospital to another NHS hospital using an established and secure transfer process, so the associated risk is considered to be low. We have recommended that where possible, sites use only your NHS number and year of birth to identify you.

Anonymous or pseudonymised data will be viewed by the trial oversight committees and auditors who regulate the trial and ensure everything is done to protect you and your data.

When information is anonymised, it means that data is processed in a manner that makes it impossible to identify individuals from them. Pseudonymisation means that it can no longer be linked to a specific person without the use of additional information. Such additional patient identifiable information (e.g., name and address) must be kept separately from the pseudonymised personal data.

The research nurses/team at your hospital will have access to your medical records to make sure you are suitable for this trial.

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Stored, pseudonymised and anonymised data and samples may be used by other researchers, for future medical and health-related research, but only if they have relevant approval from a Research Ethics Committee who look after your interests and ensure the integrity of potential research. Data will not be shared outside of Europe.

How will my data be used?

We will keep all information about you confidential, safe and secure. We will link data about you collected during this trial with other existing health data collected in the UK, such as The National Cancer Registration and Analysis Service (NCRAS). NCRAS collects data on all cases of cancer that occur in people living in England. In order to link your data with other health data, we will use your personal details, such as your NHS number, to link to information in the NCRAS.

Health data collected from any health or social care provider will be securely transferred to the trial team and uploaded onto the trial database. Restricted access to this data will be given to authorised and trained personnel working on the study, and the identifiable personal information 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.

Your personal data will be processed so long as it is required for the research project. Researchers from the Sheffield Teaching Hospitals NHS Foundations Trust (STH NHS), Sheffield University, the University of Leeds and King's College London will analyse your data, to see if:

- Taking the drug finasteride results in reduced rates of radical or advanced cancer treatments
- Taking finasteride helps men stay on active surveillance safely, for longer.
- Prostate cancer progresses more slowly in men taking finasteride compared with men not taking finasteride
- Participants have any difficulties sticking to finasteride treatment
- The trial has any impact on participants' wellbeing
- Taking finasteride reduces the number of men receiving treatment for prostate cancer that has spread

The findings will be written up into research papers and published alongside the data, as well as presented at meetings and conferences. However, the reports about the study will be written and presented in a way that no-one can work out that you took part in the study. This personal data will be stored for a minimum of 5 years after the completion of this study in case we need to check it or use it for future research. In addition, the hospital where you are taking part in the study will keep a copy of the research data along with your name. You can ask about the hospital who will keep it, whether it includes your name, and how long they will keep it.

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Future Research

If you agree to take part in this research study, you will get the choice for us to keep your contact details and some of your health information, so we can invite you to take part in future clinical trials or other studies. Your data will not be used to sell you anything. It will not be given to other organisations or companies except for research.

Thank you for reading this information leaflet. Should you now decide to proceed with your participation in this study, you will be asked to sign a consent form. Please note that you will be given a copy of this information leaflet and a copy of the signed consent form to keep.