Study Title: A randomised controlled trial of TRANSrectal biopsy versus Local Anaesthetic Transperineal biopsy Evaluation (TRANSLATE) of potentially clinically significant prostate cancer

Short title: The TRANSLATE Trial

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2. LAY SUMMARY

Prostate cancer (PCa) is the second most common cancer in men in the United Kingdom (UK), with ~45,000 cases diagnosed per year. When a man has symptoms that may indicate they have PCa such as increased frequency of urination, or when a man with no symptoms wishes to be tested for possible PCa, and consults their general practitioner (GP), the GP may perform a digital rectal examination (DRE) and a blood test to measure the level of a substance termed Prostate Specific Antigen (PSA). If either the DRE or PSA are abnormal then the GP may refer the man to a hospital for investigation. 100,000 men each year in the UK are referred to hospitals for investigation.

At hospital the patients' symptoms, DRE and PSA are reviewed, and if appropriate the patient may be offered further tests for possible PCa, such as a pre-biopsy MRI scan and a prostate biopsy. The MRI scan allows detailed images of the prostate gland to be obtained, which may visually identify a possible PCa within the prostate gland. The patient may also be offered a prostate biopsy in order to obtain multiple small samples of the prostate tissue in order to identify possible PCa. A biopsy may be offered regardless of the MRI result (as not all PCa is visible on the MRI scan), however if an abnormal area is seen on the MRI scan then targeted biopsies can be taken from that specific region of the prostate gland. Regardless of the MRI scan result, regularly spaced 'systematic' biopsies of the prostate gland may be taken during the biopsy process, to maximise the chance of finding PCa on the biopsy if it is present.

The way in which specialists take biopsies for possible PCa varies across the country; however, no clear evidence exists as to which method is best – both in terms of detecting the PCa, and in terms of the occurrence of serious infection and other common side-effects of the biopsy process.

The methods most commonly used to obtain prostate biopsies for possible PCa are called:

- A **Transrectal biopsy – known as a TRUS** – this is where a needle is inserted into the prostate gland through an ultrasound imaging probe placed in the rectum (back passage). The ultrasound probe uses sound waves to give the doctor or nurse a view of the prostate gland whilst doing the biopsy, and a needle inserted through the probe in the rectum is used to take prostate tissue biopsy samples.

- A **Transperineal biopsy – known as a TP** – this is where the biopsy needle is passed directly through the skin (perineum) between the anus and the scrotum in order to take prostate tissue biopsy samples. An ultrasound probe is placed in the rectum in order to visualise the prostate gland, but instead of the needle passing up the ultrasound probe and through the wall of the rectum, it passes directly through the skin of the perineum.

TP biopsies have historically been performed under general anaesthetic (GA) where patients are put to sleep – however, this is an involved procedure requiring day case surgery, with the associated risks of a GA. A recent medical advance has been to perform the TP biopsy procedure under local anaesthetic (LA) – termed an LATP biopsy – where the skin of the perineum and deeper area around the prostate is numbed using LA. In the TRANSLATE trial the LATP biopsy is being directly compared against the

longstanding TRUS biopsy, in terms of detection of clinically significant PCa (i.e. cases of PCa that are likely to require treatment), and in terms of complications and cost-effectiveness of the procedure.

The TRANSLATE study aims to recruit 1042 men from at least 9 large Urology departments from UK Hospitals. These men will be under investigation for possible PCa (based on either an abnormal DRE or PSA), and will not have received a prostate biopsy previously.

All men eligible for the study will have had a pre-biopsy MRI scan as part of the investigation for possible PCa. After obtaining informed consent they will be randomised (i.e. randomly allocated, as if 'by the toss of a coin') to either a TRUS biopsy or an LATP biopsy, with a 50% chance of being allocated to one or the other type of biopsy. Following the biopsy procedure, the study team will follow up the men in order to determine the rate of detection of clinically significant PCa in each biopsy group. The study team will also gather information on the occurrence of any post biopsy infections, and other patient reported biopsy-related complications such as bleeding, bruising, pain, and loss of erections and sexual function.

Additionally, the study team will record the details of any subsequent prostate biopsy procedures, which might be recommended if the first prostate biopsy has produced a possible 'false negative' result, where clinicians have concerns that the prostate biopsy result is inconsistent with the pre-biopsy MRI scan result and where there are concerns that a 'clinically significant' PCa may have been under-detected or 'missed'.

Data will be collected before the biopsy (baseline), immediately after the biopsy, and then at 7 days, 35 days and 4 months following the biopsy.

Timelines for delivery:
The total length of the study is 31 months (to include trial setup phase, recruitment phase, data analysis and write-up of reports and publications).

Recruitment of patients will last for 15 months. There will be a formal 'stop/go' review at the end of month 12 (i.e. after a full 6 months of recruitment) in order to ensure that a minimum of 140 patients has been randomised, and that at least 4 centres have been opened to recruitment. If the study team meets the 'stop/go' recruitment target, the trial will continue to recruit for a further 9 months. Data from all patients recruited in the 15-month period will be included in the final analysis.

3. SYNOPSIS

Study Title	A randomised controlled trial of TRANSrectal biopsy versus Local Anaesthetic Transperineal biopsy Evaluation (TRANSLATE) of potentially clinically significant prostate cancer		
Internal ref. no. / short title	The TRANSLATE Trial		
Study registration	ISRCTN98159689		
Sponsor	University of Oxford, Joint Research Office, 1st Floor, Boundary Brook House, Churchill Drive, Headington, OX3 7GB Tel: 01865 616480 ctrg@admin.ox.ac.uk		
Funder	National Institute for Health Research - Health Technology Assessment (HTA) Programme		
Study Design	Randomised controlled trial		
Study Participants	1042 biopsy-naïve men referred on the basis of a suspicion of PCa to a minimum of nine participating large NHS Urological Centres in the UK		
Sample Size	1042 men, randomised 1:1 to a TRUS biopsy or a LATP biopsy		
Planned Study Period	November 2021 to Oct 2024 A participant will remain in the study for 4 months post randomisation.		
Planned Recruitment period	November 2021 to Dec 2023		
	Objectives	**Outcome Measures**	**Time point(s)**
Primary	Does LATP biopsy improve the detection of clinically significant PCa (defined as Gleason Grade Group ≥2) compared to TRUS biopsy?	Detection of clinically significant PCa	Pathology reporting of biopsy samples
Secondary	What is the impact of LATP biopsy compared to TRUS biopsy on: 1) Rates of infection 2) HRQoL	 1) To include all symptoms of infection, GP prescribed treatment for infection, readmissions to hospital for infection, and microbiologically proven infection. 2) IIEF (Domain A) I-PSS EQ-5D-5L	 1) 7 days post procedure, 35 days post procedure, 4 months post procedure 2) Baseline, 7 days post procedure, 35 days post procedure,

			4 months post procedure
	3) Patient reported tolerability of the procedure	3) ProBE questionnaire (Perception part only)	3) Procedure
	4) Patient reported biopsy-related complications (including bleeding, bruising, pain, loss of erectile function)	4) ProBE questionnaire (General Symptoms part only)	4) 7 days post procedure
	5) Number of subsequent prostate biopsy procedures required and associated pathology results	5) Site completed post-biopsy radiology treatment and admissions form, and where a subsequent biopsy has occurred a pathology CRF	5) 35 days post procedure, 4 months post procedure
	6) Cost-effectiveness	6) Resource use questionnaire	6) Baseline, 7 days post procedure, 35 days post procedure, 4 months post procedure
	7) Histological parameters (ISUP grade group, cancer core length, core involvement, target biopsy cancer parameters)	7) Histology report	7) Histology reporting of biopsy samples
	8) Burden and rate of detection of clinically insignificant (Gleason Grade Group 1) PCa.	8) Histology report	8) Histology reporting of grading of biopsy samples
	9) Burden and rate of detection of additional definition of clinically significant (Gleason Grade Group ≥3) PCa	9) Histology report	9) Histology reporting of grading of biopsy samples
Intervention(s)	LATP prostate biopsy performed with an average of 12 biopsy cores in 6 sectors depending on prostate size, plus typically 4 target cores per MRI		

	lesion, using an ultrasound probe-mounted LATP needle guidance device (e.g. the "Precision-Point" access system, or BK UA1232, or any other which is used in a virtually identical fashion).
Comparator	TRUS prostate biopsy performed according to each hospital's standard practice, with an average of 12 biopsy cores, in two sectors with additional target pots (typically 4 target cores per MRI lesion).

4. ABBREVIATIONS

AE	Adverse event
AUA	American Urological Association
BAUS	British Association of Urological Surgeons
CCI	Charlson Comorbidity Index
CI	Chief Investigator
CRF	Case Report Form
csPCa	Clinically significant Prostate Cancer
DRE	Digital Rectal Examination
DSMC	Data Safety Monitoring Committee
EAU	European Association of Urology
eGFR	Estimated Glomerular Filtration Rate
GA	General Anaesthetic
GATP	General Anaesthetic TransPerineal
GCP	Good Clinical Practice
GP	General Practitioner
HEAP	Health Economics Analysis Plan
HES	Hospital Episode Statistics
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
ICF	Informed Consent Form
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
ISUP	International Society of Urological Pathology
ITT	Intention to treat

LATP	Local Anaesthetic TransPerineal biopsy
MDT	Multi-Disciplinary Team
MRI	Magnetic Resonance Imaging
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
OCTRU	Oxford Clinical Trials Research Unit
OPCSG	Oxfordshire Prostate Cancer Support Group
PCa	Prostate Cancer
PCUK	Prostate Cancer UK
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PI-RADS	Prostate Imaging Reporting And Data System
PP	Per protocol
PPI	Patient and Public Involvement
ProBE	Prostate Biopsy Effects (Questionnaire)
PROM	Patient Reported Outcome Measure
PSA	Prostate Specific Antigen
QALYs	Quality Adjusted Life Years
R&D	NHS Trust R&D Department
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance Team
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SITU	Surgical Intervention Trials Unit
SOP	Standard Operating Procedure
TIDieR	Template for Intervention Description and Replication
TMG	Trial Management Group
TP	TransPerineal
TRANSLATE	TRANSrectal biopsy versus Local Anaesthetic TransPerineal biopsy Evaluation
TRUS	TransRectal UltraSound-guided biopsy

TSC	Trial Steering Committee
UTI	Urinary Tract Infection

5. BACKGROUND AND RATIONALE

Health problem to be addressed:

PCa is the most common solid organ cancer, and the commonest cause of cancer-related death, in men in the UK. There are approximately 48,500 new PCa cases diagnosed in the UK each year, and around 11,700 men die from this malignancy each year, whilst the lifetime risk of being diagnosed with PCa is around 1 in 8 (1). PCa incidence is increasing due to wider use of PSA testing of asymptomatic men coupled with an ageing population. During investigation for suspected PCa, men currently receive a DRE and PSA test followed by an MRI scan and a prostate biopsy.

Currently, most PCa cases are diagnosed by TRUS biopsy performed in the outpatient clinic setting (2). However, whilst TRUS biopsy has been performed for decades to sample the prostate gland, it can be difficult to biopsy the anterior and apical regions of the prostate using the TRUS biopsy technique, making targeting and comprehensive sampling difficult in some cases. It is therefore recognised that TRUS biopsy can miss ~30% of clinically significant PCa cases (3), meaning ~15,000 men per year in the UK may be falsely reassured by an initial negative TRUS biopsy result. These men may need to undergo further biopsies as a follow-up procedure. Moreover, TRUS biopsy has a reported 3-5% associated risk of urinary infection due to the transrectal nature of the biopsy, and there is ~1-2% risk of urosepsis and hospitalisation based on National data, despite antibiotic prophylaxis (4), and a small but important risk of intensive care admission, and in rare serious cases, death.

TP biopsy, in general, has an advantage over TRUS in that the anterior region of the prostate gland can be more readily biopsied due to the 'in-line' or 'parallel' approach that the biopsy needle takes to the long axis of the prostate gland. The available evidence suggests that LATP has a high rate of PCa detection, both in targeting MRI-detected lesions and through systematic biopsy of the entire prostate gland. Overall, the reported detection rate of clinically significant PCa, defined as Gleason grade group ≥2 (i.e. any Gleason pattern 4) disease, is 50-65% (5-7). The ability of LATP to increase the detection rate of anterior zone PCa compared with TRUS is an important consideration of these two biopsy techniques. In one study, 52.7% of PCa cases had some element of anterior gland involvement, and 9.7% of cases had tumours exclusive to the anterior zone (5). However, given differences in biopsy techniques in reported observational cohort series and the lack of Randomised Controlled Trials (RCTs), there is no level one evidence that LATP leads to a higher detection rate of clinically significant PCa versus TRUS biopsy.

Serious infection is a main concern of TRUS biopsy, mandating the prophylactic use of broad-spectrum antibiotics such as fluoroquinolones which are associated with drug toxicity (8) and are controlled in their use. Unfortunately, the incidence of urosepsis continues to rise worldwide due to antibiotic resistance (9) and it remains critical to follow guidance on antibiotic stewardship wherever possible. In contrast to TRUS biopsy, TP biopsy allows the needle to avoid contamination from rectal flora by taking a transcutaneous route to the prostate. The infection rate from LATP biopsy in observational series is low

at <1% (4,7). A recent report of LATP as the primary biopsy technique in 1287 consecutive individuals demonstrated only 4 patients (0.3%) had lower urinary tract symptoms suggestive of infection post-procedure, only 1 had a positive urine culture, and only 1 required hospital admission for persistent hypotension post-biopsy (5). In Oxford we reported our initial experience using LATP in other settings (repeat biopsy, and in active surveillance). We have observed a low post-LATP infection rate of 0.6% (7). A recent audit of our last 6 months of TRUS demonstrated a post-procedure urinary infection rate of 3.7%, and risk of hospitalisation for urosepsis of 1.7%, despite antibiotic prophylaxis in accordance with contemporary published series. Taken together the available evidence suggests that the infection rate from LATP is likely to be lower than for TRUS, however to date this has not been demonstrated in an RCT. The absence of level one evidence comparing LATP with TRUS biopsy means that the introduction of the LATP biopsy technique is being undertaken on an *ad hoc* basis at various UK centres, resulting in geographical variation in availability of this technique across the UK.

It is possible that there are other differences between TRUS and LATP biopsy in terms of complications post-procedure. The rate of acute urinary retention requiring catheterisation was reported to be 1.6% in a recent observational series of LATP biopsy (5). Moreover, the rate of transient erectile dysfunction after LATP biopsy may be different following LATP compared to TRUS biopsy. However, like TRUS, LATP is generally well tolerated by most patients (5-7), with only mild levels of discomfort during the procedure (6,7), demonstrating that it is feasible in the outpatient clinic setting.

The lack of RCT-based evidence means that the National Institute for Health and Care Excellence (NICE) in the UK, and similar bodies globally, is unable to make robust recommendations regarding the optimal form of prostate biopsy technique, highlighting the urgent need for the primary research described in this proposal. It is imperative to investigate whether LATP biopsy, with potentially better prostate sampling and fewer potential infection-related side effects but perhaps higher economic costs (although this may in part be mitigated by a reduction in the need for repeat biopsies), is superior to TRUS biopsy which may have higher infection-related complications but fewer other side effects.

Why is this research needed now?

Over 95% of NHS prostate biopsies are currently undertaken using the TRUS approach. However, some NHS centres have recently replaced TRUS with LATP, leading to geographical variation in biopsy techniques in the UK. Approximately 30% of clinically significant PCa cases are missed by TRUS (3), requiring repeat biopsies to be performed, which are often performed as a TP procedure (either under GA in the operating theatre, or as a LATP procedure in clinic). A repeat biopsy has significant implications for the patient and the NHS, as the financial burden of prostate biopsy is substantial.

LATP biopsies may sample the prostate gland more comprehensively than TRUS biopsies, thus delivering a more accurate representation of the presence or absence of clinically significant PCa. However, there may be a trade-off between the detection rate of clinically significant PCa between the two biopsy approaches and issues around delivery of the biopsy procedure, such as rates of post-procedure complications including infection, erectile dysfunction and urinary retention, and the tolerability of the biopsy procedure by the patient. Moreover, there may be a financial cost difference between the two

biopsy techniques, and differences in the rate of re-biopsy in the context of concerns regarding a false negative initial biopsy result.

Serious post-biopsy infection requiring hospital admission reportedly occurs in 1-2% of TRUS biopsy cases, requiring intravenous antibiotics, and, rarely, Intensive Care Unit admission. Worldwide sepsis rates are high and rising, due to antibiotic resistance (9). Re-admission for infection following TRUS biopsy reportedly results in ~37,000 extra "bed days" at a cost of £7.7-11.1 million per year to the NHS (11,12).

There is no well-designed RCT comparing TRUS to any form of TP biopsy for clinically significant PCa detection.

LATP biopsy is now an alternative procedure to TRUS in the outpatient setting. Cohort studies suggest LATP biopsy provides more comprehensive sampling than TRUS, which may give greater confidence in the result if the biopsy is performed via the LATP approach, thus reducing the need for subsequent biopsies. The literature reports lower infective complications with LATP compared to TRUS. Until recently, TP biopsy required a GA and time in the operating theatre with high consequent cost, time and logistical implications. However, the use of LATP as a clinic procedure has been pioneered in recent years, without the need for GA/spinal anaesthetic. There are potential advantages of using the LATP approach, for example higher rates of accuracy in terms of detection of clinically significant PCa, and potentially lower rates of significant post-procedure infection. There may also be disadvantages of LATP compared with TRUS, including a higher rate of post-procedure urinary retention, potential for transient erectile dysfunction, and possible reduced tolerability, although current evidence regarding the latter is conflicting. LATP may also take longer to perform than TRUS in the outpatient clinic setting; however, this might be offset by a reduced need for repeat biopsy due to fewer missed significant PCa cases, and higher confidence in the initial sampling from LATP compared to TRUS.

Some NHS centres have already transitioned from TRUS to LATP, initially driven by a need to reduce infection-related complications in centres such as those in London where rates of antibiotic resistance are higher than elsewhere in the UK, but there have been no RCTs or economic evaluations comparing these two biopsy techniques.

The TRANSLATE study is therefore particularly timely, as there is considerable interest in the urological community in the UK and other countries regarding the emergence and uptake of LATP as a feasible clinic-based procedure. There is a need to provide the high-quality level one evidence to inform a potential change of biopsy technique, given that most UK centres await such evidence before deciding whether to transition to the LATP approach as the sole method of prostate biopsy, or to continue the current practice of using TRUS biopsies as the predominant method in the primary diagnostic setting.

The TRANSLATE study aims to definitively investigate the detection rate of clinically significant PCa, along with the tolerability, cost-effectiveness, and health-related quality of life (10) of LATP versus TRUS biopsy in the investigation of possible PCa in a robust phase III RCT.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Time point of evaluation of this outcome measure
Primary Objective		
To compare the TRUS biopsy versus LATP biopsy evaluation in detecting clinically significant PCa (defined as Gleason Grade Group ≥2, i.e. any Gleason pattern ≥4 disease)	Detection rate of clinically significant PCa, defined as Gleason Grade Group ≥2, i.e. any Gleason pattern ≥4 disease	This is a pathology-based endpoint. (Generally, this is usually available within 7 days of the initial biopsy having been undertaken, but difficult cases or other pathway delays may result in a longer period of time being taken).
Secondary Objectives		
Rates of infection	Questionnaires to include all symptoms of infection, GP prescribed treatment for infection, readmissions to hospital for infection, and microbiologically proven infection.	7 days post procedure, 35 days post procedure, 4 months post procedure
HRQoL	IIEF (Domain A) I-PSS EQ-5D-5L	Baseline, 7 days post procedure, 35 days post procedure, 4 months post procedure
Patient reported tolerability of the procedure	ProBE questionnaire (perception part only)	Immediately post procedure
Patient reported biopsy-related complications (including bleeding, bruising, pain, loss of erectile function)	ProBE questionnaire (General symptoms part only)	7 days post procedure
Number of subsequent prostate biopsy procedures required, and details of the subsequent biopsies (including Pathology results)	Patient questionnaire Subsequent pathology CRF	35 days post procedure, 4 months post procedure 4 months post procedure
Cost-effectiveness	Resource use questionnaire	Baseline, 7 days post procedure, 35 days post procedure, 4 months post procedure
Histological parameters (ISUP grade group, cancer core length, core involvement, target biopsy cancer parameters)	Histology report	Histology reporting of biopsy samples as per local reporting practices –

		generally within 7 days of procedure
Burden and rate of detection of clinically insignificant (Gleason Grade Group 1) PCa.	Histology report	Histology reporting of grading of biopsy samples as per local reporting practices – generally within 7 days of procedure
Serious adverse events incidence	Patient questionnaires	Up to 4 months post procedure

7. STUDY DESIGN

TRANSLATE has been designed as a two-stage study. The first stage aims to demonstrate the feasibility of identifying and randomising men with a suspicion of PCa to a RCT comparing LATP against TRUS. Including this first stage internal pilot randomised phase will provide insights into the optimisation of recruiting to this type of trial, and will highlight key lessons that are important for recruitment in the second stage main trial. For example, the first stage internal pilot may highlight logistical issues regarding how best to optimally schedule the prostate biopsy "lists" at each hospital centre (LATP or TRUS) in order to ensure that each centre can perform the necessary randomised biopsy in a timely fashion. The internal pilot phase may also identify factors that may help to optimise recruitment, such as whether men are willing to discuss the trial with a member of the recruiting team via a phone call consultation or face-to face consultation (given that clinical practice is shifting toward a greater number of telephone-based consultations). This information will not be formally captured, but the initial experience of recruitment in the initial opened centres will inform other centres as they open. The second stage comprises the main full definitive trial, which aims to assess the effectiveness of LATP versus TRUS biopsy in terms of diagnosing clinically significant PCa, and will additionally investigate the two biopsy techniques in terms of their risk of significant infection-related and other complications, tolerability, impact on quality of life, and cost-effectiveness.

The overall aim is to assess whether LATP biopsy improves detection of clinically significant PCa compared to TRUS biopsy, while remaining tolerable to men and reducing rates of infection in a UK-based multicentre RCT.

Stage 1 (internal pilot study):
The purpose of this pilot phase is to evaluate the willingness of men to consent to recruitment and randomisation in this RCT. This will be assessed as a 'stop/go' criterion at the end of month 12 (i.e. after 6 months of recruitment, with at least 4 centres open and recruiting by the end of the internal pilot study). We aim to recruit at least 140 men during this period.

Stage 2 (main RCT):
Contingent upon a successful Stage 1 recruitment, the full RCT will continue on from the internal pilot, and will include the results of all the men recruited in stage 1.

Population:
1042 biopsy-naïve men referred with suspected PCa on the basis of an elevated age-specific PSA or abnormal DRE, and suitable for investigation with a pre-biopsy MRI and prostate biopsy.

Inclusion criteria: See section 8.2.
Exclusion criteria: See section 8.3.

Intervention: LATP prostate biopsy. See section 12.1.1.
Comparator: TRUS prostate biopsy. See section 12.1.2.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

1042 biopsy-naïve men referred with suspected PCa on the basis of an elevated age-specific PSA or abnormal DRE, and suitable for investigation with a pre-biopsy MRI and prostate biopsy.

8.2. Inclusion Criteria

All biopsy-naïve men aged 18 years and over who, during investigation for suspicion of possible PCa, require a prostate biopsy. This includes:

- A PSA value above the age-adjusted upper limit of normal, regardless of the MRI result
  OR
  An abnormal pre-biopsy MRI on a 1.5 Tesla or higher MRI scanner
  OR
  An abnormal prostate DRE (regardless of serum PSA or MRI result)
- Considered suitable to tolerate an LATP biopsy procedure by the local clinical team
- Able to give informed consent
- Able to understand written English to enable completion of study validated patient reported outcome measures (questionnaires)

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Any previous prostate biopsy
- Dysuria on the day of biopsy or untreated urinary tract infection (UTI)
- Immunocompromised (due to history of prior immunocompromising medical condition, or medications e.g. steroids or methotrexate)
- May need enhanced antibiotic prophylaxis: Indwelling catheter, recurrent UTIs
- Previous abdomino-perineal resection (i.e. absent rectum)
- Unable to recline adequately in Lloyd-Davis / lithotomy position (e.g. hip surgery, contractures)

- Unable to have a pre-biopsy MRI (e.g. pacemaker, eGFR<50, claustrophobia)
- PSA >50ng/ml (>25ng/ml if patient is on Finasteride). This excludes patients with locally advanced/metastatic PCa, easily detectable by TRUS.

Note: *The location of the radiological lesion on the pre-biopsy MRI scan is not an exclusion criterion, as anterior lesions can be accessed by TRUS biopsy by many who perform a TRUS biopsy, especially if the lesion extends either side of the anatomical midline. It is therefore felt that it is important to randomise patients with an anterior radiological lesion on MRI to either a TRUS or LATP biopsy.*
Note: Participants of the TRANSLATE trial may be recruited into other ethically approved trials/ research whilst participating in TRANSLATE.

9. SCHEDULE OF STUDY PROCEDURES

			Post procedure		
	Routine Hospital referral appointment Screening and pre-biopsy	**Biopsy procedure – LATP or TRUS**	**7 days**	**35 days**	**4 months**
Screening/ eligibility	x				
Approach for consent	x				
Informed consent taken	x				
Randomisation	x				
Demographics and baseline questionnaires	x				
Medical history	x				
Biopsy procedure details ¥		x			x
ProBE questionnaire – perception part		x (immediately post procedure)			
Biopsy reporting (pathology) (as per standard NHS practice)**			x*		
Biopsy-related complications including the ProBE§ questionnaire and pain, bruising, infection and erectile function questions			x	x	x
HRQoL questionnaires	x		x	x	x
Resource use questionnaire	x		x	x	x
Adverse event assessments		x	x	x	x

¥ *There will usually be no more than 4 weeks between randomisation and biopsy – if there is more than 4 weeks then the baseline data will be reviewed to ensure it is all still correct.*

§ProBE questionnaire (General Symptoms) only undertaken at 7 days after procedure

**This will generally be within 7 days of the procedure – but different cancer pathways or a difficult biopsy may result in later reporting*

*** Note this will include reporting of the study primary outcome but this is not a study specific procedure - detection of any clinically significant PCa, defined as Gleason Grade Group ≥2, i.e. any Gleason pattern ≥4 disease.*

10. RECRUITMENT AND SELECTION OF SITES

10.1. Sites

A minimum of nine urological centres across the UK will participate in the study. A centre must have equipoise over the research question, and therefore have specialist nurses and clinicians that are willing to randomise their patients into the study.

Additionally, sites need to agree that patients for recruitment to TRANSLATE should have had either a biparametric or multiparametric pre-biopsy MRI on a 1.5 Tesla or higher MRI scanner, with a radiology report from a suitably qualified radiologist.

For a site to participate in the trial, the site PI needs to confirm equipoise for that site, and there needs to be confirmation from the lead radiologist and MRI Superintendent that the hospital scanner is able to achieve the scanning parameters. All pre-biopsy MRI scans will need to be reported according to PI-RADS v2.1 Guidelines or using a Likert scale if this is local protocol.

10.2. Inclusion criteria for participating clinicians at a site

Either a clinician or a specialist nurse, depending on local practice at each recruiting centre, may perform the TRUS and LATP biopsies. All participating centres will have performed many thousands of TRUS biopsies, and many LATP biopsies. Clinician and/or specialist nurse participation in performing a biopsy will be determined on a '*competency*' basis, determined by the site PI, in discussion with the Chief Investigators. However, indicative numbers are provided below to assist with this:

1. To ensure that a high quality of delivery of the biopsies occurs in both arms, for a clinician or specialist nurse to undertake a study TRUS biopsy they individually must have:
    - Already undertaken at least 50 previous TRUS biopsies

2. For a clinician or specialist nurse who has extensive experience of GA TP biopsy to undertake a study LATP biopsy they individually must have:
    - Already undertaken at least 50 previous GA TP biopsies, and have performed at least 20 LATP biopsies

3. For a clinician or specialist nurse without prior experience of GA TP biopsy to undertake a study LATP biopsy they individually must have:
    - Already undertaken at least 50 previous LATP biopsies.

11. RECRUITMENT AND SELECTION OF PATIENTS

11.1. Patients

All biopsy naïve patients referred for prostate biopsy, and who meet the eligibility criteria, will be approached for potential inclusion in the trial. There will be minimal deviation for participants from the standard care pathway for patients with suspected PCa undergoing a biopsy.

Where local NHS polices allow - paper or electronic posters may be used at a research site to highlight the presence of the study. The posters state for those interested to ask their clinical care team as to

whether they might be a suitable candidate for the TRANSLATE study. Patients will be provided with a patient information sheet (PIS), which will be included in the referral form and/or provided at the time of initial consultation for suspected PCa (depending on local 2 week wait practice), and given time to decide whether to take part in the study. Patients will give informed consent ahead of the prostate biopsy and enrolment into the study.

Patients will be randomised in a 1:1 ratio to either an LATP biopsy or a TRUS biopsy prior to, or on, the day that they are due to receive their procedure. Each research site has the ability to undertake either an LATP or a TRUS biopsy. Once participants accept their biopsy allocation, the biopsy will be performed by a competent clinician or nurse specialist in one of the participating centres (depending on local practice and expertise).

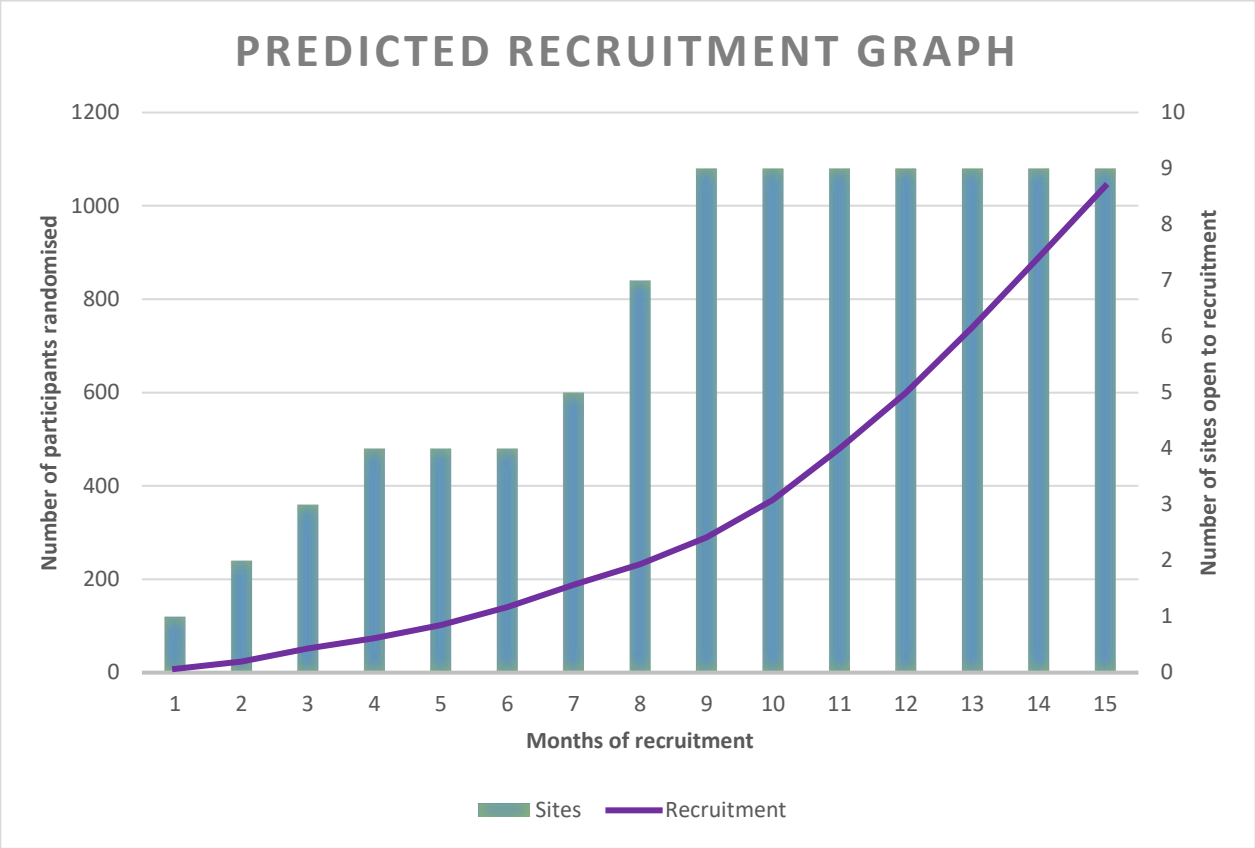
11.2. Recruitment predictions

This table shows estimated recruitment across 9 of the NHS centres that have confirmed participation in the trial to date:

Centre	Number of eligible men undergoing biopsy per year	Estimated 15-month recruitment number*¥
Oxford University Hospitals NHS Foundation Trust	750	328
Kent & Canterbury Hospitals NHS Foundation Trust	675	237
Maidstone & Tonbridge Wells NHS Trust	375	164
Milton Keynes University Hospital NHS Foundation Trust	450	197
Buckinghamshire Healthcare NHS Trust	500	219
Western General Hospital, NHS Lothian Board	375	164
University Hospitals Coventry and Warwickshire NHS Trust	300	132
Sheffield University Hospitals NHS Foundation Trust	690	302
Cardiff and Vale University Health Board	550	241

*Assuming 35% of eligible patients consent to participate in the trial.

Allowing for the fact that some men opt to not receive a prostate biopsy in the context of a 'normal' pre-biopsy MRI (e.g. a PSA density <0.15ng/ml^2 and a PI-RADs score of 1-2 for their MRI). We estimate that approximately 75% of patients will meet the eligibility criteria for the trial, and that approximately 30-40% of eligible patients will consent to take part in the trial (which we consider is a conservative but realistic estimate). Therefore, once all sites are open, we expect recruitment of 75-100 patients per month.



11.3. Screening and eligibility

Patients will be screened by clinical teams for eligibility. Anyone screened will be added to the trial screening log by anyone listed on the site study delegation log. There will be no exceptions made regarding eligibility, i.e. that each participant must satisfy all the approved inclusion and exclusion criteria of the protocol.

* Note that changes to the approved inclusion and exclusion may only be made by substantial amendment.

11.4. Informed Consent

Informed consent from each patient will be obtained before enrolment into the study, by a member of the study team listed on the delegation log for this purpose. A member of the patient's local clinical care team will ask the patient's verbal permission for a member of the site research team to come to speak to them about the study; either in person, or over the phone. Patients referred to each recruiting centre with suspected PCa will be informed of the study at their routine consultation (which may be a telephone, video or face to face appointment, depending on local practice), and they will be offered to receive a copy of the PIS. We will offer electronic or paper versions of the written PIS and Informed Consent form to the participants, detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. Participants will have the opportunity to discuss the PIS and consent form with a

member of the study team; either in person, or over the phone. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

Note: Approaches for the study may be made either in the face-to-face clinic appointment, or in a telephone or video consultation, depending on local practice at each research site. The PIS will either be emailed to the potential participant with their approval (if the initial consultation was a telephone or video consultation), or the patient can receive a hard copy if seen in a face-to-face clinic.

Consent will be requested after presentation of the trial PIS and a discussion has been had with the patient. We will seek informed consent for inclusion in the trial ahead of the prostate biopsy procedure, with the potential participants allowed as much time as desired to consider the information, and having had the opportunity to ask questions from the clinical trial team and/or research nurse, and contact their GP or other independent parties to decide whether they wish to participate in the trial. Consent for inclusion in the study may be obtained either on the day of the biopsy (as many patients may not have a routine clinic appointment between the initial referral consultation and the biopsy), or in the days leading up to the biopsy (to help aid scheduling of patients to the appropriate TRUS or LATP 'list', depending upon randomisation outcome).

Consent may be obtained in person in clinic, or remotely. The Informed Consent Form will be offered to participants in clinic as an electronic form on a tablet device (with the consent form being filled in directly on REDCap), or on paper if specifically requested. Where it is not possible for a consent form to be completed in clinic (For example; If a participant has only had telephone appointments), electronic (remote) informed consent may also be obtained by means of an eConsent form emailed to the participant as a link via the trial's instance of REDCap. This emailed link will direct the participant to an electronic consent form on REDCap, which is identical to the electronic consent form used in clinic on a tablet device. The electronic consent form will include a participant dated signature and the researcher taking consent will countersign using a 'Consent Confirmation' form on REDCap.

The paper consent form (if requested by the participant) will include a participant dated signature and dated name of the person who presented and obtained the Consent. Scottish sites will make use of a separate Scottish consent form (with Scottish-specific requirements) and this will be paper-based only. The person who obtains the consent using any of the described methods above must be suitably qualified and experienced and have been authorised to take consent by the site's Principal Investigator. If electronic informed consent is obtained, a copy of the signed Consent Form will be emailed securely as a PDF to the participant (or a printed version provided if requested), a copy placed in the medical notes, and the original will be retained securely on REDCap.

Note: TRANSLATE aims to be a paperless trial, but Scottish sites will make use of Scottish-specific paper consent forms. If necessary, paper PIS and/or Consent forms can also be used for non-Scottish sites. The paper and electronic informed consent forms will have identical content and consent points.

11.5. Randomisation

Randomisation will take place on or before the day of the prostate biopsy, depending upon logistics regarding scheduling of the prostate biopsy on a suitable clinic 'list' for either the TRUS or LATP procedure.
Note: Sites should only randomise if there are the facilities and local agreements in place for both LATP or TRUS biopsies to take place.

We will randomise eligible patients using the centralised validated computer randomisation program through a secure (encrypted) web-based service, RRAMP (https://rramp.octru.ox.ac.uk), provided by the Oxford Clinical Trials Research Unit (OCTRU), accessed via the study's REDCap instance, with a minimisation algorithm to ensure balanced allocation across treatment groups, stratified in a 1:1 ratio to either TRUS biopsy or LATP biopsy using:

- research site, and
- location of the MRI lesion (i.e. 'No significant lesion', 'Significant lesion, including anterior', 'Significant lesion, but not anterior'.

To ensure the unpredictability of treatment allocation, the minimisation algorithm will include a probabilistic element and a small number of participants randomised by simple randomisation. Stratification by centre will help to ensure that any centre-effect will be equally distributed in the trial arms and enable practical issues associated with the active intervention to be overcome.

There is some evidence that MRI lesion location can affect PCa progression, therefore it is important for the two prostate biopsy techniques to be balanced across this potentially important prognostic factor.

The following information will be recorded on a secure web-based form in the study randomisation system (RRAMP) by the attending clinician or delegate including a member of research team to enable follow-up:

- Patient details e.g. name, Hospital number, address, NHS/CHI number, date of birth, telephone number, email address, GP name and GP address

Note: *These data fields will allow sites to check their local hospital records to for any admissions/further biopsies. The GP details are required to allow the central trial team to send a letter to the patient's GP informing them of their TRANSLATE participation. The email address will enable a copy of the completed consent form to be sent to the patient or at their request a different individual for safekeeping. Depending upon patient preference the email /postal address and/or telephone may be utilised for follow up questionnaires.*

11.6. Blinding and code-breaking

Due to the nature of the intervention, both the patients and the clinical team will not be blind to the allocated biopsy.

12. TRIAL INTERVENTIONS

12.1. Description of study intervention(s), comparators and study procedures (clinical)

Currently in the NHS, an LATP biopsy procedure is not the standard routinely offered option in all diagnostic centres when men are referred from primary care with suspected prostate cancer. The "gold standard" procedure for the last 3 decades has been a TRUS prostate biopsy. However, LATP has become popular in some hospitals, and LATP has been chosen to replace TRUS in some individual centres, despite absence of level one evidence that it is superior to TRUS. The protocol regarding performance of LATP (e.g. regarding the number of biopsy cores taken) can vary in the hospitals where it is becoming offered. The classical Ginsburg protocol described 24 systematic biopsies being taken for LATP, which is higher than the average number of biopsies taken for TRUS (12 – 16, depending on prostate size). It is a particularly important issue in the context of the TRANSLATE RCT to have equivalence of the average number of biopsy cores taken for each biopsy procedure type, so as not to introduce bias in terms of cancer detection, and in terms of secondary outcome measures (such as infection risk). In the TRANSLATE trial a modified Ginsburg LATP sampling will be performed, with an equivalent mean number of systematic prostate biopsies taken as would have been taken for TRUS (i.e. 12 systematic biopsy cores in 6 sectors), and the same mean number of target biopsies (3-5 per target) if a lesion is present.

Participants will be randomised 1:1 to LATP prostate biopsy or TRUS prostate biopsy.

Note: The number of individual biopsy cores taken at each biopsy procedure will be equivalent on average across the study, regardless of whether acquired by an LATP or TRUS biopsy approach.

12.1.1. Description of study intervention – LATP biopsy

LATP biopsy protocol:

This should be performed with an average of 12 systematic biopsy cores in 6 sectors, i.e. a modified Ginsburg protocol with x2 biopsy cores per anterior, mid, and posterior gland sector, left and right-sided, depending on prostate size, using an ultrasound probe-mounted LATP needle guidance device (e.g. the "Precision-Point" access system, or BK UA1232, or any other which is used in a virtually identical fashion). Preliminary cohorts using the "Precision-Point" access system, or BK UA1232 devices, reveal that detection, infection and tolerability rates are almost identical.

An additional 3-5 (average 4) target biopsy cores will be taken for each significant target lesion seen on the pre-biopsy MRI. Clinicians should use their judgment as to whether same sector systematic biopsies are required or not depending on size of lesion and size of prostate gland. Centres will follow their local procedures regarding sending the biopsy cores to pathology in pots but the target biopsy cores must, at least, be in a separate pot.

The LATP biopsy should be performed in the outpatient setting with the patient reclined in the Lloyd-Davis / lithotomy position, using LA infiltration of the perineum after chlorhexidine-based skin preparation, and should be performed without antibiotics.

Each centre will use its existing LATP biopsy technique and ultrasound probe-mounted LATP needle guide devices, in order to reflect "real world" clinical practice (given that there are some minor variances in LATP biopsy technique from centre to centre already using this technique across the UK).

12.1.2. Description of comparator – TRUS biopsy

TRUS biopsy protocol: Depending on prostate size, this should be performed with an average of 12 systematic biopsy cores (6 per side i.e. x2 biopsy cores per base, mid, and apical regions of the prostate gland, left and right-sided) using a TRUS probe. An additional 3-5 (average 4) target biopsy cores will be taken for each significant target lesion seen on the pre-biopsy MRI. Clinicians should use their judgement as to how many additional systematic biopsies are required on the side of a target lesion. Centres will follow own local procedures regarding sending the biopsy cores to pathology in pots, but the target biopsies must, at least, be in a separate pot.

The TRUS biopsy should be performed in the outpatient setting with the patient in the left lateral position, using LA infiltration of the prostate, and with a pre-procedure dose of antibiotics followed by post-procedure antibiotics (typically for 48 hours, but may vary according to local guidelines and/or clinician preference) according to local guidelines in each centre.

Each centre will use its existing TRUS biopsy technique in order to reflect 'real world' clinical practice (given that there are some minor variances in TRUS biopsy technique from centre to centre across the UK).

12.1.3. Description of study procedure(s)

After giving informed consent, patients will be asked to complete some baseline questionnaires and a member of the local research team will complete a clinical CRF to describe the patient's demographics, medical history and PCa pathway to date. Participants will then be asked to complete further data/questionnaires immediately after their biopsy, 7 days post procedure, 35 days post procedure, and 4 months post procedure.

The validated questionnaires to be used in this trial are:

- The International Index of Erectile Function (IIEF): Erectile Function Domain A only (Questions 1, 2, 3, 4, 5 and 15).
- International prostate symptom score (IPSS)
- The 5-level EQ-5D version (EQ-5D-5L)
- Prostate Biopsy Effects (ProBE): ProBE Perception and ProBE General Symptoms only.

These questionnaires will be available to participants as an electronic form, either emailed directly to the participants by the REDCap database or completed on an iPad in clinic. Participants who are not able to complete the electronic version will be offered to receive their questionnaire over the phone or in the post.

Time point	Data	Data collection method
Baseline	Patient demographics IIEF questionnaire (Domain A) I-PSS questionnaire EQ-5D-5L questionnaire	Research nurse administers baseline data collection – completing baseline CRF and patient completes the questionnaires
Immediately post-procedure	ProBE questionnaire (Perception part)	Patient completes questionnaire in clinic

		Immediately after biopsy procedure.
7 days post-procedure	ProBE questionnaire (General Symptoms part) IIEF questionnaire (Domain A) I-PSS questionnaire EQ-5D-5L questionnaire Resource use questionnaire to include any GP visits, medication use for infections and pain, outpatient visits and in-patient stays Complications and SAEs	Patient completes information/questionnaires either electronically or via a phone call or a posted pack. This will be sent to the participant 24h before the 7-day timepoint and will be due 48h after the 7-day timepoint.
35 days post-procedure	IIEF questionnaire (Domain A) I-PSS questionnaire EQ-5D-5L questionnaire Resource use questionnaire to include any GP visits, medication use for infections and pain, outpatient visits and in-patient stays Complications and SAEs Number of subsequent prostate biopsy procedures	Patient completes information/questionnaires either electronically or via a phone call or a posted pack. This will be sent to the participant 48h before 35-day timepoint and will be due 7 days after the 35-day timepoint.
4 months post-procedure	IIEF questionnaire (Domain A) I-PSS questionnaire EQ-5D-5L questionnaire Resource use questionnaire to include any GP visits, medication use for infections and pain, outpatient visits and in-patient stays Complications and SAEs Number of subsequent prostate biopsy procedures, and associated pathology results	Patient completes information/questionnaires either electronically or via a phone call or a posted pack. This will be sent to the participant 7 days before the 4-month timepoint and will be due 14 days after the 4-month timepoint. Site staff collect data on complications, SAEs and any subsequent biopsies from hospital notes.

Note: Histology (pathology) and radiology reporting will also produce data but these are not study specific procedures. The histology reporting includes the primary outcome measure (detection of clinically significant PCa, defined as Gleason Grade Group ≥2, i.e. any Gleason pattern ≥4 disease)

After the allocated biopsy, the results of the MRI and biopsy of all trial participants will be reviewed on a weekly basis as a standard of care as part of the 'Suspected Prostate Cancer Pathway' at the regional Uro-Oncology Multidisciplinary Team (MDT) meeting at each centre.

Decisions regarding whether or not to recommend a repeat prostate biopsy, where there may be a concern that the initial RCT-determined biopsy may have under-sampled radiologically significant lesions (PI-RADS 4-5 lesions) within the prostate, will be taken on a case-by-case basis by the MDT as part of routine clinical care.

Note: Teams may know that an individual is in the TRANSLATE study and will not be blinded to the method of biopsy.

It is anticipated that most cases where a repeat prostate biopsy is indicated will typically be original TRUS biopsies where there are concerns that a radiologically significant anterior lesion may not have been adequately sampled via the TRUS approach. Occasionally, however, the repeat biopsy cases may be original LATP procedures where there is subsequent concern that a clinically significant PCa may have not been sampled, or may have been 'under-sampled', at the original LATP biopsy procedure, *Note: If there is any concern that any RCT-determined biopsy may have under-detected a clinically significant PCa, then the MDT may recommend a repeat biopsy procedure, and this data will be captured.*

Where a repeat biopsy is recommended, the aim will be for this to be performed within 12 weeks of the original TRANSLATE RCT randomised biopsy, unless a newly-arising clinical condition precludes the repeat biopsy being performed as an LATP procedure, or unless the repeat biopsy needs to be performed under GA.

12.2. Baseline Assessments

The following information will be recorded on the web-based form (which goes straight into the password protected study database) by the attending clinician or delegate including a member of research team:

- Ethnicity
- BMI (height/weight)
- Charlson Comorbidity Index (CCI)
- Family history of PCa (first degree relatives only)
- Family history of Breast Cancer (first degree relatives only)
- Major comorbidity and medical history
    - cardiovascular disease
    - diabetes
    - chronic lung disease
    - asthma
    - hypertension
    - ongoing cancer treatment
    - previous cancer treatment
- Concomitant medications (specifically anticoagulants and Finasteride)

  Note: Based on our previous published biopsy-naïve cohorts (23) we estimate that ~3% of participants will be taking 5-alpha reductase inhibitors (Finasteride). We expect these patients to be equally distributed across the two trial arms through randomisation, and we will not specifically stratify for patients taking this medication. The balance of this across the groups will be monitored throughout the trial to ensure that no adjustments are needed to the randomisation schedule.
- Date and result of latest pre-biopsy PSA level
- Date and result of latest DRE
- Date of most recent MRI
- Location of lesion on MRI (anterior or posterior lesion or no lesion detected)

- Questionnaire preference (email/telephone and/or telephone)
- Questionnaires – IIEF, I-PSS, EQ-5D-5L

12.3. Biopsy

The following information will be recorded on the web-based form (which goes straight into the password protected study database) by the attending clinician or specialist nurse or research nurse (or a delegate who is a member of the research team):

- Type of biopsy
- Date of biopsy
- Result of pre-biopsy DRE
- Was the biopsy conducted the biopsy allocated? If No, the reason for the deviation
- Who conducted the biopsy
- Local anaesthetic used (strength and volume)
- Antibiotics used (Note – it is recommended these are used for TRUS biopsies only)
- Cleaning fluid used
- Number of MRI-visible lesions
- Site (anterior or posterior) and size (mm) and PI-RADs V2.1 or Likert score for each MRI visible lesion
- Number of systematic cores taken for each side
- Number of lesions target cores taken from
- Number of cores taken for each targeted radiological lesion

12.4. Pathology findings

Prostate biopsies will be reported at local recruitment sites, each of which has specialist uropathology teams as per standard NHS practice. Standard practice at some sites may include the use of Artificial Intelligence (AI) and/or digital pathology. Cases will be reported according to standards set in the Royal College of Pathologists' ''dataset for histopathology reports for prostatic carcinoma'' (current version – June 2016). Grading will be based on the ISUP guidance issued in 2005 and 2014, which is gold standard in the UK and internationally.

Where centres have digital pathology capability, they will be encouraged to routinely scan the pathology slides, which may enable later centralisation of images subject to further funding. Study consent forms and PIS sheets will be worded accordingly.

Prostate biopsy CRFs for the TRANSLATE study need to be completed by sites by extracting the data from pathology reports and entered into the central trial REDCap database. Pathologists, the site PI or another suitable individual such as a research nurse can fill in the data.

12.5. Radiology findings

MRI findings CRFs for the TRANSLATE study need to be completed by sites by extracting the data from radiology reports and entered into the central trial database. Radiologists, the site PI or another suitable individual such as a research nurse can fill in the data.

12.6. Subsequent Visits

No other research-related visits will be required for the study by participants, and they will follow their local PCa pathway if PCa is diagnosed (and follow local practice of the biopsy does not reveal PCa), and the patients will receive their biopsy result according to local practice.
Note: A follow up period of 4 months per patient represents a sufficient period to capture all adverse effects of the first prostate biopsy (LATP or TRUS biopsy), and to identify any patients requiring a repeat biopsy, (for example, due to discrepancy between the pre-biopsy MRI findings and the prostate biopsy result), in order to provide the relevant information for the cost-effectiveness analysis.

12.7. Sample Handling

No additional research-specific prostate biopsy samples are to be taken for the TRANSLATE study, above and beyond those obtained as part of the patient's diagnostic procedure.

12.8. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw from the study investigation/ follow-up at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable SAE.
- Inability to comply with study procedures
- Participant decision

Participants may choose to stop investigation and/or study assessments but may remain on study follow-up.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely.

In the case of withdrawal from both investigation and active follow up, the following options may be considered for a tiered withdrawal from the study. Not all options may be relevant to this study. The options elected for use in the study must be covered in the PIS.

According to the design of the study, participants may have the following three options for withdrawal:

1) Participants may withdraw from active follow-up and further communication, but allow the study team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care, i.e. Scans, blood results and disease progression data etc.

2) Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.

3) Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis.

In addition, the Investigator may discontinue a participant from the study investigation at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with the investigation or study requirements
- Clinical decision including a decision that it is unsafe to proceed to biopsy

Withdrawn participants will not be replaced.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an Adverse Event (AE), the Investigator will arrange for follow-up visits or telephone calls until the SAE has resolved or stabilised.

12.9. Definition of End of Study

The end of study is the point at which all the study data has been entered and queries resolved.

13. SAFETY REPORTING

The trial will be run in accordance with OCTRU's Standard Operating Procedures (SOPs) and operational policies, which all adhere to applicable UK regulatory requirements.

An independent Data and Safety Monitoring Committee (DSMC) and Trial Steering Committee (TSC) will be appointed. The DSMC will monitor data arising from the trial, review confidential interim reports of accumulating data, and recommend whether there are any ethical or safety reasons why the trial should not continue. The TSC will monitor the trial's progress and will provide independent advice. Both committees will comprise independent clinicians, statisticians, health service researchers and patient representatives. (See sections 16.4.1 and 16.4.2)

13.1. Definition of Serious Adverse Events (SAEs)

A SAE is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity

- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

13.2. Reporting Procedures for Serious Adverse Events (SAEs)

A SAE occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of SAE form (see HRA website).

It is important to consider the natural history of PCa affecting each participant enrolled, the expected sequelae of the illness, and the relevance of these complications to the trial intervention (i.e. prostate biopsy). Consequently, only SAEs will be recorded in this trial. This is limited to SAEs, which might reasonably occur as a consequence of the trial intervention (i.e. not events that are part of the natural history of the primary disease process or expected complications of PCa).

SAEs, as defined above, experienced by a participant from their enrolment until their completion of the trial must be reported in the participant's medical notes, on the trial CRF, and reported to the CTU using the SAE Reporting Form, within 24 hours of observing or learning of the SAE(s). All sections of the SAE Reporting Form must be completed.

A SAE occurring to a participant will be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of either of the two types of prostate biopsy procedure) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of SAE form

13.2.1. Events exempt from being reported as SAEs

The following hospitalisations are not considered a SAE:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- admissions as per protocol for a planned medical/surgical procedure
- admissions for planned surgery and/or chemotherapy and/or radiotherapy and any related sequelae
- routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the

study
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- admission for administration of anti-cancer therapy in the absence of any other SAEs (applies to oncology protocols)
- disease progression where not considered to be related to study intervention

14. STATISTICS AND ANALYSIS

14.1. Statistical Analysis Plan (SAP)

Full details of the statistical analysis will be detailed in a separate statistical analysis plan (SAP) which will be drafted early in the trial and finalised prior to the interim analysis data lock, and will receive review and input from the TSC and DSMC. Stata (StataCorp LP) or other appropriate validated statistical software such as R (R Core Team) will be used for analysis. A summary of the planned statistical analysis is included here.

14.2. Description of the Statistical Methods

All analyses will be carried out on the intention-to-treat population (ITT) (i.e. all patients will be analysed in the group they were randomised to regardless of actual intervention received). It is not anticipated that there will be any protocol deviations, but in the event that any occur we will repeat the primary analysis for the per protocol (PP) population (patients excluded from the PP population will be pre-specified in the SAP).

Standard descriptive statistics will be used to describe the demographics between the two biopsy groups, reporting means and standard deviations or medians and interquartile ranges as appropriate for continuous variables and numbers and percentages for binary and categorical variables. All comparative outcomes will be presented as summary statistics and reported together with 95% confidence intervals and all tests will be carried out at a 5% two-sided significance level.

The primary outcome is the proportion of patients with a prostate biopsy positive for clinically significant PCa (defined as Gleason Grade Group ≥2, i.e. any Gleason pattern ≥4 disease), and this will be compared across the 2 randomised groups using a logistic regression model adjusted for the stratification factors (research site and site of prostatic lesion on pre-biopsy MRI). As supporting analyses we will also carry out an unadjusted analysis, and a further analysis adjusting for additional important prognostic factors (such as Gleason grade, PSA level, tumour stage and cancer risk group). The proportion of patients in each randomised group with positive and negative biopsy results will be tabulated, and the difference between groups reported as odds ratios and absolute differences together with 95% confidence intervals.

Secondary outcomes will be analysed using logistic regression for binary data and linear regression for continuous data, with adjustment for the stratification variables. Multilevel models will be used for variables measured at multiple time points.

Where an additional non-study prostate biopsy is performed during the 4-month follow-up period in TRANSLATEW, we will collect additional data regarding the pathology details, and biopsy type details, of that subsequent prostate biopsies reported by site staff. The rationale for collecting this additional pathology data for any additional prostate biopsies in this 4-month clinical follow up period, is to provide further descriptive data pertaining to the existing Secondary Outcome regarding the need for additional follow-up biopsies. The intention is to tabulate the content (cancer versus benign, and grade of cancer) of the repeat biopsy (this being a non-study biopsy) as descriptive data in the primary results analysis paper, and to be 'armed' with this data, in the event that it may be requested by an expert reviewer.

In addition, there is a planned 'methodological add-on' to the main trial where we will re-analyse the trial dataset using an adaptive Bayesian methodology to explore the relative efficiency savings of running the trial using a Bayesian analysis with planned interim analyses, rather than the frequentist analysis which forms the *actual* primary outcome analysis (see SAP for full details). We will initially use noninformative priors for the Bayesian analysis, and may consider informative priors also (elicited from experts and/or data). We will calculate a Bayesian sample size and estimate the final treatment effect, comparing both the sample size and treatment estimates with that gained from the primary analysis. In addition, we will simulate fictional interim analyses and stopping criteria to model how the trial's conduct would have taken place, had the Bayesian analysis been the true primary outcome analysis (for example assessing whether the trial may/may not have stopped earlier than it truly did, and why).

14.3. Sample Size Determination

Data collected from 792 patients in Oxford over a 12-month period suggests that the detection rate of clinically significant PCa in previously biopsy naïve individuals through TRUS biopsy following a pre-biopsy MRI is 45% (14), in line with the reported literature. We consider a 10% improvement (from 45% to 55%) in this rate of detection of clinically significant PCa (defined as Gleason Grade Group ≥2, i.e. any Gleason pattern ≥4 disease) through LATP to be clinically meaningful. To detect this primary outcome difference with 90% power and 5% significance, we need to recruit 1,042 men over a 15-month period across the nine (at least) participating centres.

14.4. Analysis populations

The principal analysis will be performed once data collection is completed and on the ITT population, whereby participants will be analysed according to their randomisation allocation, irrespective of compliance with the protocol. If appropriate, additional analysis population, such as a PP population, will be defined in the SAP. A PP population may exclude participants who deviate from specific aspects of the protocol.

14.5. Decision points

Built into the trial is an internal pilot of recruitment to the RCT (Stage 2). There will be a formal 'stop/go' review after 6 months of recruitment to the RCT to review the number of randomisations over the pilot period. If the target of at least 140 randomisations has been met, the trial will continue to recruit for a further 9 months. Data from the 140 patients will be included in the final analysis. All Stage 2 patients will be followed up to 4 months after randomisation.

The following 'stop-go' criteria are proposed for the Trial Steering Committee (TSC) after 6 months of recruitment:

Target	**Actual recruitment in 6 months**		
140	> 140 men	110-140 men	<110 men
'Stop-Go' criteria	• Recruitment feasible • Proceed with study	• Review recruitment strategies • Report to TSC • Continue but modify and monitor closely	• Recruitment not feasible • Decision not to proceed

Recruitment will last for 15 months; there will be a formal 'stop/go' review of the internal pilot at the end of month 12 (i.e. after 6 months of recruitment) to ensure a minimum of 140 patients have been randomised and 4 centres have been opened (based on 10 patients per month; centre 1 opening at the start of month 1 of the pilot, centre 2 at the start of month 3, and centres 3 and 4 at the start of month 5; i.e. 60+40+20+20=140 patients). If the target of at least 140 patients is met, the trial will continue to recruit for a further 9 months, with all 9 (at least) centres open and recruiting ~12 patients/month (i.e. a further 972 patients in the main trial period). Data from the internal pilot phase will be included in the final analysis.

14.6. Stopping rules

Given the nature of the primary, and key secondary, outcomes and the planned study length, no formal interim analyses with stopping guidelines are planned. An independent DSMC will review the accumulating data at regular intervals and may recommend pausing or stopping the trial in the event of safety concerns.

14.7. The Level of Statistical Significance

All principal analyses will be performed at the 2-sided 5% significance level.

14.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

The procedure for handling spurious or missing data will be described in the Statistical Analysis Plan, and the Data Monitoring Plan. The trial will attempt to collect data as completely as possible.

Missing data will be minimised by careful data management. Missing data will be described with reasons given where available; the number and percentage of individuals in the missing category will be presented by intervention arm. All data collected on data collection forms will be used, since only essential data items will be collected. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis.

The nature and mechanism for missing variables and outcomes will be investigated, and if appropriate multiple imputation will be used. In this situation sensitivity analyses will be undertaken assessing the underlying missing data assumptions. Any imputation techniques will be fully described in the Statistical Analysis Plan.

14.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

A detailed statistical analysis plan will be drawn up early in the trial with review and appropriate sign-off following OCTRU SOPs. Any changes to the statistical analysis plan during the trial will be subject to the same review and sign-off procedure with details of changes being included in the new version. Any changes/deviations from the original SAP will be described and justified in protocol and/or in the final report, as appropriate should these occur.

14.10. Health Economics Analysis

We will conduct a within-trial analysis to assess the cost-effectiveness of implementing LATP biopsy, conducted using an ultrasound probe-mounted LATP needle guidance device (e.g. the “Precision-Point” access system, or BK UA1232, or any other which is used in a virtually identical fashion), compared to TRUS biopsy as a diagnostic test for clinically significant PCa. Resource utilisation, cost and cost-effectiveness of implementing LATP with each of these LATP devices compared with the current practice of TRUS will be assessed, adhering to good economic evaluation practice with a NHS and Personal Social Services perspective (15,16).

A detailed health economics analysis plan (HEAP) will be prepared in the first 4 months of the programme, setting out the proposed analyses in detail. The health economists will work with the project team to identify and design the best ways of collecting resource use information and HRQoL data, using our experience from previous PCa trials (17,18). It is envisaged that a self-complete resource use questionnaire will be used to collect all resource events associated with the diagnostic tests, side-effects/complications and follow-up primary care consultations, hospitalisations and treatment. The self-complete resource use questionnaire will be administered at various time-points through an online interface, but if needed this could be undertaken by mail, telephone, face to face in clinic, or e-mail. Site teams may also contribute data regarding resource use. It will take place at baseline (T0), 7 days post procedure (F1), 35 days post procedure (F2), and 4 months post procedure (F3) to indicate health care resource use from baseline to 7 days, from 7 days to 35 days, and from 35 days to 4 months. Where possible, resource utilisation items will be valued using national unit cost schedules (e.g. NHS Reference costs) and medication costs calculated using British National Formulary pricing. Where unit costs are unavailable (e.g. intervention costs) bottom-up micro-costing will be undertaken. CRFs will be completed at each participating site to capture the time taken for each procedure, disposable equipment

used. Information on capital and reusable equipment will be obtained from the relevant manufacturers. Number of work/usual activity days lost due to the diagnostic process and any related complications and any over-the-counter medications purchased by patients will also be captured by the questionnaire. These patient and societal costs will not be included in the base-case cost-effectiveness and their inclusion and impact on the base case results will be explored as part of a sensitivity analysis.

To determine quality-adjusted life-years (QALYs) (18), the EQ-5D-5L (20) will be used to measure HRQoL at baseline (T0), and at 7 days (F1), 35 days (F2), and 4 months (F3) post procedure. Each time interval will be weighted by the utility scores apportioned to that time with linear interpolation between data collection time points. Acceptable methods of administering the EQ-5D-5L will be explored in collaboration with our PPI group (the Oxfordshire Prostate Cancer Support Group, OPCSG): this could include mailing, face-to-face, telephone, text messaging and/or web-based collection. At present EQ-5D-5L responses would be cross-walked to the EQ-5D-3L and the existing UK valuation set applied, in line with NICE recommendations, but an approved UK value set for the EQ-5D-5L may be available by the later stages of this trial. We will test for baseline difference in utilities between the trial arms and if required adjust for these differences using the most appropriate recommended method.

Incremental cost-effectiveness ratios (ICERs) will be estimated by dividing the difference in costs by the difference in effects. The ICERs will be compared against the threshold used to establish value for money in the NHS (currently in the region of £20,000 to £30,000 per QALY) (15). Uncertainty around the ICER will be explored using non-parametric bootstrapping. All cost-effectiveness results will be presented on the cost-effectiveness plane and as cost-effectiveness acceptability curves, indicating where the results fall in relation to a given cost-effectiveness threshold. The impact of each of the two available devices to conduct LATP will be explored in a sensitivity analysis.

Resource events and corresponding costs will be scaled-up to ascertain the national NHS cost/budget impact.

If the LATP intervention proves to be more effective in identifying clinically significant PCa, without an excess morbidity or poorer tolerability compared with TRUS, then we will extrapolate the results beyond the ‘within-trial’ analysis in order to estimate lifetime costs, benefits and cost-effectiveness arising from any observed within-trial differences. This would be undertaken in line with current recommended practice (21,22).

We are not assessing long-term HRQoL as part of this trial. Specifically, we are not assessing the impact of a missed PCa diagnosis as we consider this to be beyond the scope of this trial, and would require long-term follow-up (>12 months). However, we will be able to capture the HRQoL changes associated with the need for second biopsy in either the TRUS or LATP biopsy arm, which will be captured within the 4-month follow-up period. A secondary outcome measure of TRANSLATE is to assess the short term HRQoL issues relevant to the conduct of each type of biopsy (TRUS or LATP), and the tolerability of the procedure.

15. DATA MANAGEMENT

A data management and sharing plan will be produced for the trial in accordance with OCTRU Standard Operating Procedures (SOPs), and this will include reference to confidentiality, access and security arrangements.

All data will be processed following the SOPs, which have been written in line with all applicable regulatory requirements. All trial-specific documents, except for the signed consent form and follow-up contact details, will refer to the participant with a unique study participant number/code and not by name. Participant identifiable data will be stored separately from study data, and in accordance with OCTRU SOPs. All trial data will be stored securely in offices only accessible by swipe card by the central coordinating team staff in Oxford, and authorised personnel.

Data will be collected from participants via questionnaires and CRFs that will be returned to the central trial office in Oxford, via post using a pre-addressed freepost envelope, or NHS email as appropriate, or directly into an online secure database – the study's dedicated instance of REDCap. In addition, participant pathology biopsy histology images where these exist in digital format will be stored in a secure electronic database in the Oxford Histopathology Department.

Participant data will be stored in REDCap (containing demographic and clinical data, such as age, PSA, MRI scan result, prostate biopsy pathology result, and TNM stage of PCa etc) and will be transported in accordance to SOPs. Future ethically approved research data repositories may apply to link with the TRANSLATE demographic and clinical data, so that de-identified patient characteristics, and MRI images can be used for scientific research (subject to acquisition of future funding, with all due governance in place). A cohort such as that in TRANSLATE will be of significant, unique interest to the prostate cancer research community, even though TRANSLATE is not acquiring extra research specific samples. Upon completion of the trial, fully de-identified research data may be shared with other organisations at the behest of the funder.

15.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and histology records, and radiographs.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent and follow-up contact details, the participant and proxy will be referred to by the study participant/proxy number/code, not by name.

15.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution to permit trial-related monitoring, audits and inspections.

Where data is submitted directly to the trial office, contemporaneous access by local research teams to the online database will enable the local research teams at sites to download copies of their participants' data.

15.3. Data Recording and Record Keeping

The data will be stored and used in compliance with the relevant, current data protection laws (Data Protection Act 2018; UK General Data Protection Regulation). The processing of participant personal data will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). The trial data (including data for SAEs) and e-consent forms will be entered during the study onto a validated REDCap study database developed and maintained by OCTRU and which can only be accessed by authorised users via the application. The application resides on a webserver hosted and managed by Oxford University's IT Services division. The server is on the university's backbone network and is backed up nightly to a secure off-site location.

After closure of the trial and data analyses, the data will be made publicly available at the time of publication. The Trial Master File will be archived for at least three years from the publication of the study. The Investigators will maintain appropriate medical and research records for this trial, in compliance with the principles of GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The Chief Investigator, site teams and central study team will have access to records. The Investigators will permit authorised representatives of the Sponsor, as well as ethical and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

It is aimed for all study data to be captured directly in the study's instance of REDCap or the study instance of their randomisation system RRAMP. There are no paper CRFs or worksheets to be completed by sites, however participants who wish to complete the follow up questionnaires via paper will be sent paper CRFs/questionnaires to be returned to the trial office and then entered into the study's instance of REDCap.

Identifiable information will be recorded on a secure web-based form in the study randomisation system (RRAMP) and Clinical database (REDCap) by the attending clinician or delegate including a member of research team to enable follow-up:

- Patient details e.g. name, Hospital number, date of birth, telephone number, email address and GP details

Note: These data fields will allow sites to check their local hospital records to check for any admissions/further biopsies. The GP details are required to allow the central trial team to send a letter to the patient's GP informing them of their TRANSLATE participation. The email address will enable a copy of the completed consent form to be sent to the patient or at their request a different individual for safe-keeping. Depending upon patient preference the email/postal address and/or telephone may be utilised for follow up questionnaires.

The Investigator and/or Sponsor must retain copies of the essential electronic documents for 5 years following the publication of the study. Site investigators will always have contemporaneous access to all

data entered into the system for patients from their site including any direct patient completed questionnaires.

The Investigator will inform the Sponsor of the storage location of the essential documents and of any changes in the storage location should they occur. The Investigator must contact OCTRU for approval before disposing of any documentation. The Investigator should take measures to prevent accidental or premature destruction of these documents.

15.4. Collection of data

Data will be collected by a member of the clinical or study team. Data will also be collected from EPR/medical notes and NHS Spine, and directly from patients.

16. QUALITY ASSURANCE PROCEDURES

The study may be monitored or audited in accordance with the current approved protocol, GCP, relevant regulations and CTU standard operating procedures. This research will be coordinated by the Surgical Interventional Trials Unit (SITU), which falls under the Oxford Clinical Trials Research Unit (OCTRU) and SITU personnel work according to OCTRU SOPs. The OCTRU SOPs and related quality assurance and control procedures will be used by SITU to ensure that the study procedures are assessed and carried out as defined in this protocol.

16.1. Risk assessment

A risk assessment will be conducted according to OCTRU's process and a monitoring plan will be drafted to include all central monitoring activities. The trial will be conducted in accordance with the current approved protocol, Principles of GCP, relevant regulations and OCTRU standard operating procedures.

16.2. Study monitoring

Regular monitoring will be performed according to the study specific Monitoring Plan. Monitoring will be limited to central monitoring activities – there will be no site monitoring, missing data will be queried with sites where mandatory. Monitoring of the data will occur as the data is being entered into the database.

16.3. Quality assurance

The Sponsor or its designated representative will assess each study site to verify the qualifications of each Investigator and the site staff and to ensure that the site has all of the required equipment. A virtual study Initiation meeting will occur where among other things the Investigator will be informed of their responsibilities and procedures for ensuring adequate and correct study documentation.

16.4. Study Committees

16.4.1 Data Safety Monitoring Committee (DSMC)

The DSMC is a group of independent experts external to the trial who assess the progress, conduct, participant safety and critical endpoints of the study. The study DSMC will adopt a DAMOCLES based charter, which defines its terms of reference and operation in relation to the oversight of the trial. The DSMC will meet regularly throughout the trial at time-points agreed by the Chair of the Committee and the CI. At a minimum this will be on an annual basis. The DSMC will review the safety data generated, including all adverse events, and make recommendations as to whether the protocol should be amended to protect patient safety. Recommendations of the DSMC will be discussed between the CI, TSC, and the Sponsor.

16.4.2 Trial Steering Committee (TSC)

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. The TSC will monitor trial progress and conduct, and will advise on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DSMC and ultimately carries the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy. The TSC includes independent members and members of the research team, and provides overall supervision of the trial on behalf of the funder. Its terms of reference will be agreed and will be recorded in a TSC charter.

16.4.3 Core Trial Management Group (TMG)

The Trial Management Group (TMG) consists of those individuals responsible for the operational management of the trial such as the co-chief investigators, SITU trial development lead, SITU operational lead, the trial manager, the trial statistician, the trial health economist. Other specialities/ individuals will be invited as required for specific items/issues.

The TMG will meet at least every month throughout the lifetime of the study and will:

- Supervise the conduct and progress of the study, and adherence to the study protocol
- Assess the safety as compiled by SITU and assessed by the DSMC
- Evaluate the quality of the study data
- Review relevant information from other sources (e.g. related studies)
- Escalate any issues for concern to OCTRU, specifically where the issue could compromise patient safety or the integrity of the study or quality of the study data.

17. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

18. SERIOUS BREACHES

A ‘serious breach’ is a breach of the protocol, or of the conditions or principles of GCP, which is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

19. ETHICAL AND REGULATORY CONSIDERATIONS

19.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

19.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with the principles of GCP.

19.3. Approvals

Following Sponsor approval, the protocol, informed consent form, PIS and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

19.4. Other Ethical Considerations

None

19.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

19.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

19.7. Participant Confidentiality

The study will comply with the UK General Data Protection Regulation and UK Data Protection Act 2018, which require data to be anonymised as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the storage of patient and their GP contact details to enable follow-up of the participants. This data is stored in an encrypted form. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

Instances of missing, discrepant, or uninterpretable data will be queried with the Investigator for resolution. Any changes to study data will be documented in an audit trail, which will be maintained within the clinical database.

In compliance with the principles of ICH GCP and regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies or Independent Ethics Committees (IEC) may conduct quality assurance audits at any time during or following a study. In the event of monitoring, the Investigator must agree to allow monitoring of the study according to ICH GCP requirements.

The Investigator should also agree to allow auditors direct access to all study-related documents including source documents. They must also agree to allocate their time and the time of their study staff to the auditors in order to discuss findings and issues.

19.8. CTU Involvement

This study will be coordinated by the UKCRC registered OCTRU at the University of Oxford, the affiliated SITU will lead the study on a day-to-day basis.

19.9 Expenses and Benefits

Study visits at the hospital have been scheduled to coincide with routine clinical appointments to avoid additional expenses for participants.

20. FINANCE AND INSURANCE

20.1. Funding

The study is supported by the National Institute for Health Research – Health Technology Assessment programme under the reference NIHR131233. The views expressed in this document are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

20.2. Insurance

The University has a specialist insurance policy in place, which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting

Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

20.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

21. PUBLICATION POLICY and OUTPUTS

The trial has been prospectively registered, prior to ethics approval, on the International Standard Randomised Controlled Trial Number register. The trial protocol will be published in an open-access peer-reviewed journal in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT, www.spirit-statement.org/). The trial results will be published in an open-access journal, in accordance with the NIHR's policy on open-access research. The study will be reported following the Consolidated Standards of Reporting Trials guideline (CONSORT, www.consort-statement.org), in particular the extensions for non-pharmacological interventions, patient-reported outcomes and pilot and feasibility studies. The Template for Intervention Description and Replication (TIDieR) statement will be used for reporting the intervention, ensuring that replication is possible.

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by National Institute for Health Research – Health Technology Assessment Programme. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.
All trial materials, including the clinician training materials and patient materials will be made freely available via the trial website.

22. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable.

23. ARCHIVING

During the clinical trial and after trial closure the Investigator will maintain adequate and accurate records to enable the conduct of the clinical trial and the quality of the research data to be evaluated and verified. All essential documents will be stored in such a way that ensures that they are readily available, upon request for the minimum period required by national legislation or for longer if needed. The medical files of trial subjects will be retained in accordance with applicable national legislation and the host institution policy.

It is the University of Oxford's policy to store data for 5 years from publication. Investigators may not archive or destroy study essential documents or samples without written instruction from the trial office.

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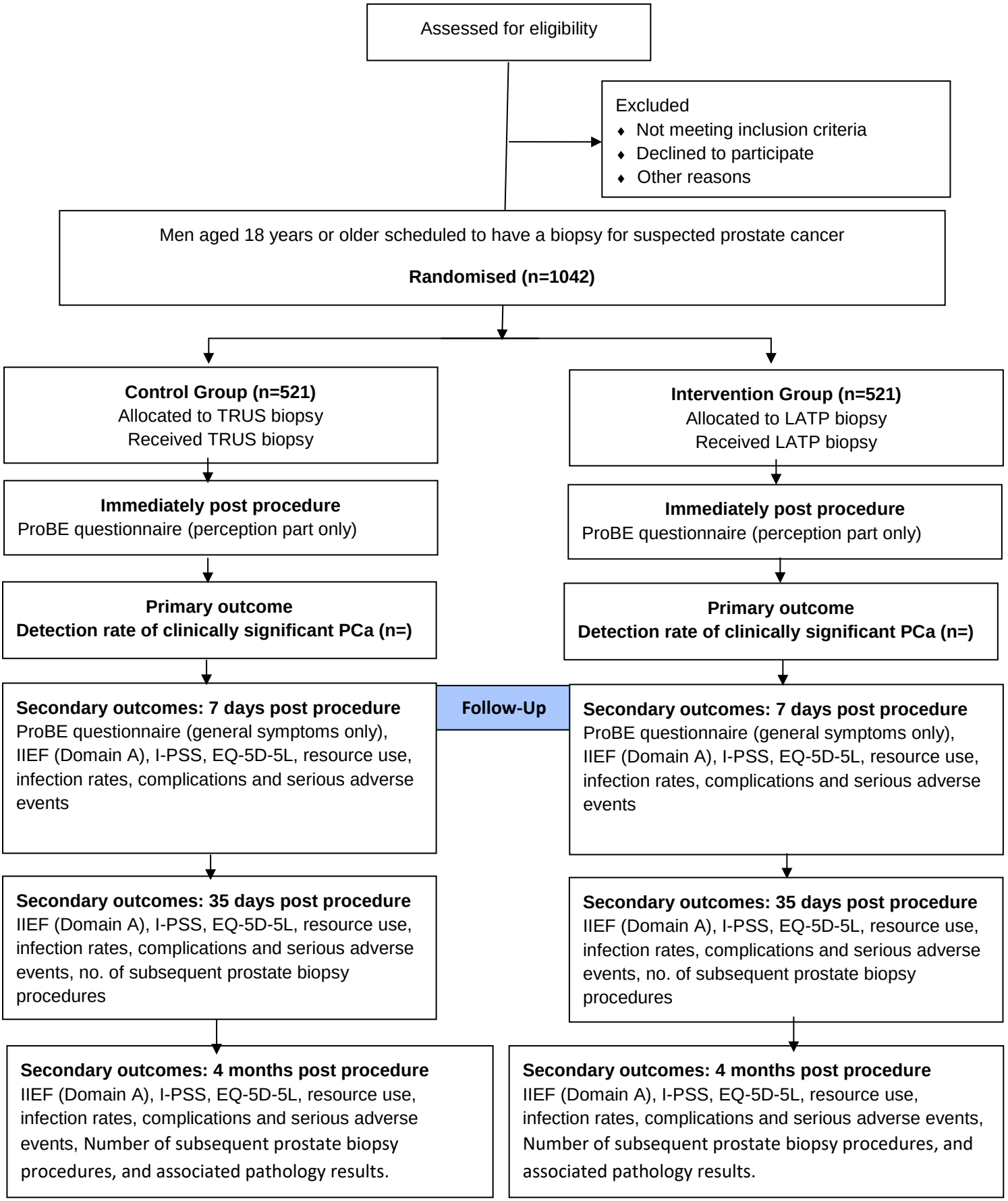
25. APPENDIX A: STUDY FLOW CHART



26. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	27 Oct 2021	Roxanne Williams	1) "Site teams may also contribute data regarding resource use." added to page 38, to allow site teams to contribute to resource use data collection. 2) Confidentiality statement removed from page 2, as requested by the funder.
2	3.0	14 Nov 2022	Roxanne Williams	1) Additional wording clarifying Electronic/ modified questionnaires. 2) Removed 'Subsequent Biopsies' from Day 7 timepoint. 3) Bayesian methodology trial design updated to allow for non-informative priors and fictional interim analyses to be defined after the trial has started. 4) Clarify PSA Exclusion criteria to include Finasteride. 5) Added details about the emailed consent form being countersigned using the Consent
3	4	29 Feb 2024	Roxanne Williams	1) Additional data collection around details of subsequent biopsies reported by site staff. This will include details of the pathology report for the subsequent biopsies.