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Original Article

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Protocol for the TRANSLATE prospective, multicentre, randomised clinical trial of prostate biopsy technique

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Objectives

Primary objectives: to determine whether local anaesthetic transperineal prostate (LATP) biopsy improves the detection of clinically significant prostate cancer (csPCa), defined as International Society of Urological Pathology (ISUP) Grade Group ≥2 disease (i.e., any Gleason pattern 4 disease), compared to transrectal ultrasound-guided (TRUS) prostate biopsy, in biopsy-naïve men undergoing biopsy based on suspicion of csPCa. Secondary objectives: to compare (i) infection rates, (ii) health-related quality of life, (iii) patient-reported procedure tolerability, (iv) patient-reported biopsy-related complications (including bleeding, bruising, pain, loss of erectile function), (v) number of subsequent prostate biopsy procedures required, (vi) cost-effectiveness, (vii) other histological parameters, and (viii) burden and rate of detection of clinically insignificant PCa (ISUP Grade Group 1 disease) in men undergoing these two types of prostate biopsy.

Patients and Methods

The TRANSLATE trial is a UK-wide, multicentre, randomised clinical trial that meets the criteria for level-one evidence in diagnostic test evaluation. TRANSLATE is investigating whether LATP biopsy leads to a higher rate of detection of csPCa compared to TRUS prostate biopsy. Both biopsies are being performed with an average of 12 systematic cores in six sectors (depending on prostate size), plus three to five target cores per multiparametric/bi-parametric magnetic resonance imaging lesion. LATP biopsy is performed using an ultrasound probe-mounted needle-guidance device (either the 'Precision-Point' or BK UA1232 system). TRUS biopsy is performed according to each hospital's standard practice. The study is 90% powered to detect a 10% difference (LATP biopsy hypothesised at 55% detection rate for csPCa vs 45% for TRUS biopsy). A total of 1042 biopsy-naïve men referred with suspected PCa need to be recruited.

Conclusions

This trial will provide robust prospective data to determine the diagnostic ability of LATP biopsy vs TRUS biopsy in the primary diagnostic setting.

Keywords

Prostate cancer, transrectal prostate biopsy, transperineal prostate biopsy, local anaesthetic, clinically significant prostate cancer, #PCSM, #ProstateCancer, #uroonc

Introduction

The pathway of investigation for possible clinically significant prostate cancer (csPCa) is usually triggered by a raised age-specific PSA assay result, or the finding of a clinically suspicious feeling prostate on DRE. In the UK men referred with either of these abnormalities usually undergo a multiparametric MRI (mpMRI) followed by a prostate biopsy [1,2]. Over the last three decades prostate biopsy techniques under local anaesthetic (LA) in the clinic setting have become increasingly refined [3], progressing from digitally guided 'Tru-Cut' biopsies to TRUS-guided systematic biopsies, to targeting of MRI-visible lesions with or without systematic cores. Refinements of TRUS biopsy during this time [3] have included use of LA [4], povidone-iodine rectal cleansing [5], rectal swabs to guide antibiotic prophylaxis [6], appropriate use of antibiotic prophylaxis based on local microbiology guidelines and microbial resistance patterns [7], standardisation of the appropriate numbers of prostate biopsy cores with which to sample the prostate based on gland volume [8], and use of pre-biopsy mpMRI [2], along with targeted biopsy based on cognitive or image-fusion guidance [9–11].

Despite these improvements, it is known that TRUS biopsy can under-sample the prostate gland, particularly the anterior zone and apex [12] which can be difficult to access via the TRUS route. TRUS biopsy also has risks such as post-procedure bleeding (with blood in the urine, ejaculate, or per rectum), urinary retention, and infection (either a urine infection or septicaemia) [13,14]. Post-TRUS biopsy infection requiring hospitalisation has been of concern in recent years, with reported frequencies of up to 6.3% [13], and 2.15%–3.6% in the UK [15], despite prophylactic antibiotics. There is also concern regarding rising rates of antimicrobial antibiotic resistance [13]. Re-admission for infection following TRUS biopsy results in ~37 000 extra 'bed days' at a cost of £7.7–11.1 million/year to the NHS in the UK alone [15].

In recent years, the LA transperineal prostate (LATP) biopsy technique for prostate biopsy has been developed [16–19], primarily to reduce the risk of infection seen with TRUS biopsy and popularised by the campaign to move away from TRUS biopsy [20]. The infection rate from LATP biopsy in observational series is low at <1% [18,21]. The increased ability to sample the anterior prostate via the LATP biopsy route compared to TRUS biopsy may improve the sampling of the prostate gland and increase the detection rate of csPCa [17,18]. 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 [17]. Several large observational cohort series of LATP biopsy have been published [16–18], and the suggestion has been made that urology units should entirely switch from TRUS to LATP biopsy [20]. However, to date, there is no level-one evidence to support that change. LATP biopsy may be less tolerable than TRUS biopsy to patients [18], with a higher incidence of post-biopsy urinary retention, transient erectile dysfunction, and consequent impact on health-related quality of life (HRQoL) [17,18]. LATP biopsy may also take longer to perform compared to TRUS biopsy, with resultant cost implications. These factors could have important health economic implications given that ~70 000 men are biopsied annually in the UK alone. Conversely, if LATP biopsy improves sampling of the prostate gland compared with TRUS biopsy then it may achieve a more accurate result at initial biopsy, reducing the need for repeat hospital visits and further biopsy. The reduced risk of sepsis from LATP biopsy compared with TRUS biopsy could result in it being a more cost-effective technique with fewer post-procedure emergency hospital admissions.

No level-one evidence currently exists to justify LATP biopsy over TRUS biopsy. As a result, introduction of the LATP biopsy technique is being undertaken on an ad hoc basis, resulting in geographical variation in clinical practice. The UK-wide multicentre TRANSLATE randomised clinical trial aims to provide a robust evaluation of the performance characteristics of LATP biopsy vs TRUS biopsy in biopsy-naïve men being investigated for possible csPCa (ClinicalTrials.gov Identifier: NCT05179694), to inform policymakers, patients, and clinicians regarding the best approach to prostate biopsy.

Design and Methods: TRANSLATE Trial Protocol

Overview

The TRANSLATE study is a UK-wide, multicentre (10 centres, across England, Wales, and Scotland), randomised clinical trial that aims to assess the performance characteristics of LATP biopsy vs TRUS biopsy in the diagnosis of csPCa. The goal of the study is to provide

policymakers with the requisite high-quality evidence to establish whether LATP biopsy is 'superior' to TRUS biopsy, and thus should replace TRUS as the standard-of-care LA biopsy performed in the clinic in the evaluation of biopsy-naïve men referred with suspected csPCa. The primary and secondary objectives are listed in Table 1.

Trial Approvals

The TRANSLATE study (International Standard Randomised Controlled Trial Number [ISRCTN]98159689) is approved (Ethics Ref: 21/SC/0271) by the Oxford C Research Ethics Committee and is registered on the ClinTrials.gov (NCT05179694) clinical trials registry. The trial is funded by the UK National Institute for Health Research-Health Technology Assessment (NIHR-HTA; NIHR131233) and is being conducted according to local regulations using the principles in the Declaration of Helsinki and Good Clinical Practice.

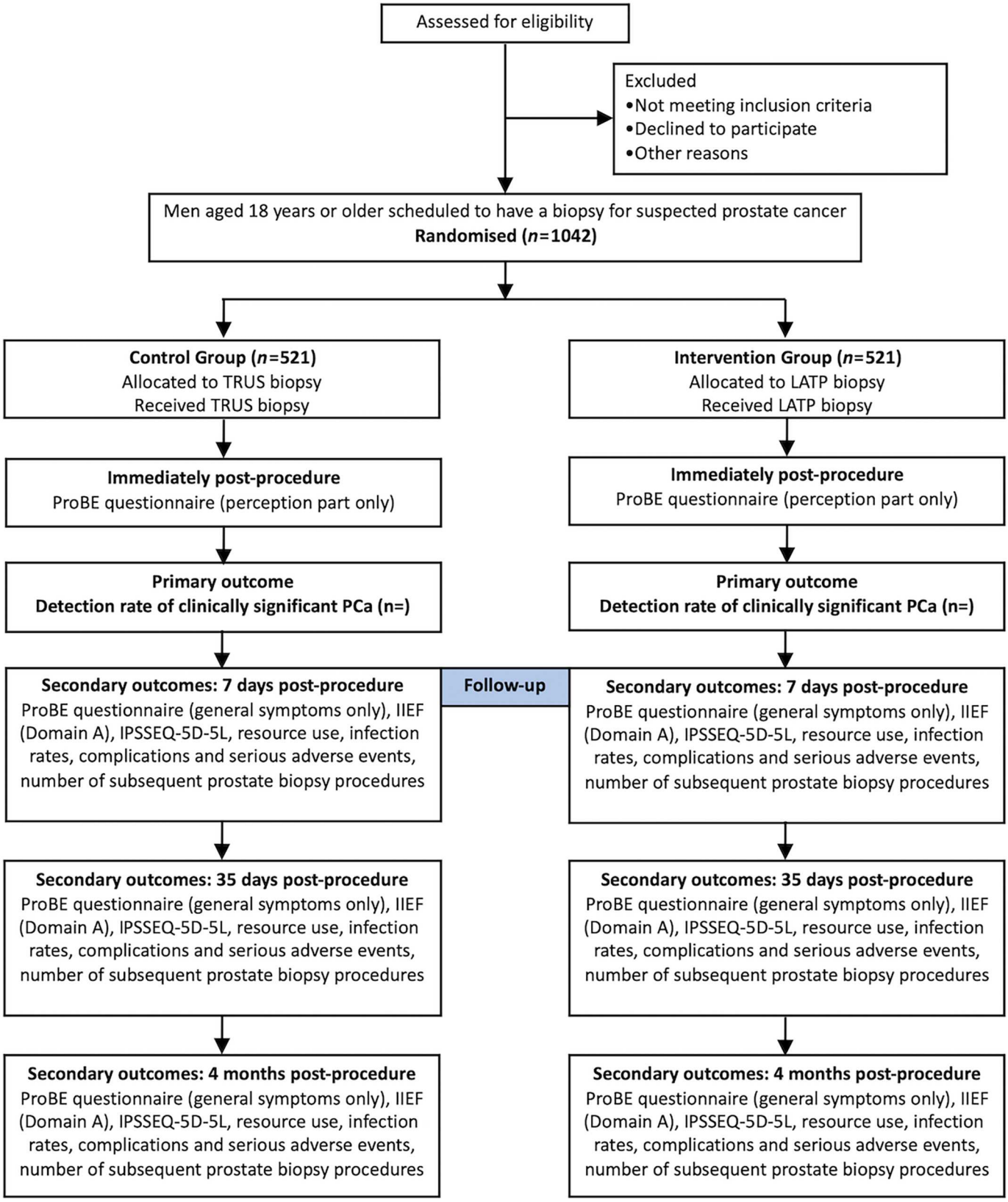
Study Population, and Inclusion/Exclusion Criteria

The study aims to recruit 1042 biopsy-naïve men referred with suspected csPCa based on an elevated age-specific PSA or abnormal DRE, and suitable for investigation with pre-biopsy MRI and prostate biopsy (Fig. 1). Inclusion criteria include biopsy-naïve men aged ≥18 years with an elevated age-specific PSA as defined at each institution (e.g., current National Institute for Health and Care Excellence [NICE] guidelines define elevated age-specific PSA as >2.5 ng/mL at age 40–49 years, >3.5 ng/mL at age 50–59, >4.5 ng/mL at age 60–69, and >6.5 ng/mL at age 70–79, and recommend use of clinical judgement if aged >79 years) regardless of MRI result, an abnormal DRE regardless of PSA or MRI result, or an abnormal pre-biopsy MRI (Pristate Imaging Reporting And Data System [PI-RADS] score 3–5) on a ≥1.5 Tesla MRI scanner. Participants must be suitable for both LATP biopsy and TRUS biopsy, able to give informed consent, and able to understand written English to enable completion of validated

Table 1 Summary of primary and secondary objectives of TRANSLATE.

Objectives	Outcome measures	Time-point of evaluation of this outcome measure
Primary objective		
To compare TRUS biopsy vs LATP biopsy evaluation in detecting csPCa (defined as GGG ≥2, i.e., any Gleason pattern ≥4 disease)	Detection rate of csPCa, defined as GGG ≥2, i.e., any Gleason pattern ≥4 disease	This is a pathology-based end-point (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, re-admissions to hospital for infection, and microbiologically confirmed infection	7 days post-procedure, 35 days post-procedure, 4 months post-procedure
HRQoL	IIEF (Domain A), IPSS, 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	Patient questionnaire	7 days post-procedure, 35 days 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 PCa (GGG1 disease).	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

Fig. 1 Trial schema.



study forms. Exclusion criteria include any previous prostate biopsy, features suggestive of extensive local disease easily detectable by any biopsy method (e.g., PSA level of >50 ng/mL or entire gland replaced by tumour on MRI), symptoms suggestive of concurrent or recent infection, history of immunocompromise, any need for enhanced antibiotic prophylaxis (e.g., indwelling catheter), absent rectum (e.g., due to previous abdomino-perineal resection), inability to position in lithotomy, and inability to undergo MRI (e.g., due to pacemaker or claustrophobia) (Table 2).

End-points

The primary outcome is detection of csPCa as defined by any Gleason pattern 4 disease detected on prostate biopsy. The secondary outcomes include: rates of infection; patient-reported tolerability (using the Prostate Biopsy Effects [ProBE] questionnaire); HRQoL using the EuroQoL five Dimensions five Levels (EQ-5D-5L); histological parameters; need for further intervention including repeat biopsy; cost effectiveness; and patient-reported outcome measures (PROMs) including the International Index of Erectile Function (IIEF), IPSS, and ProBE questionnaires (Table 1).

Study Stages

TRANSLATE has an internal pilot phase, the aim of this being to evaluate the willingness of men to consent to recruitment and randomisation in this clinical trial. This will be assessed as a 'stop/go' criterion after 6 months of recruitment, with at least four centres being open and recruiting, and at least 140 men recruited, by the end of the internal pilot study. Contingent upon successful internal pilot phase recruitment, the full trial will continue and will include results of men recruited in the pilot stage.

Screening

Centres will identify potential study participants through suspected PCa referral pathways, and the research team will screen patients for eligibility for study enrolment (Table 2). Informed consent for TRANSLATE participation can be obtained either electronically via e-mail and a telephone call or, if necessary, in person in clinic. Men will also be invited to consent to use of surplus biopsy material for research; however, no additional biopsies will be taken specifically for research, to avoid the risk of additional complications related to increased biopsies being taken. Consented men will be randomised to either TRUS biopsy or LATP biopsy using a 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 Research Electronic Data Capture (REDCap) instance. A minimisation algorithm will be used to ensure balanced allocation across treatment groups, stratified in a 1:1 ratio to either LATP biopsy or TRUS 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 will be randomised by simple randomisation. Stratification by centre will help 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. In addition, due to the preliminary evidence that mpMRI lesion

Table 2 Inclusion and exclusion criteria for TRANSLATE.

Inclusion criteria	
All biopsy-naïve men aged ≥18 years 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)
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 UTI • Immunocompromised (due to history of prior immunocompromising medical condition, or medication, 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, estimated GFR <50 mL/min/1.73 m^2, claustrophobia) • - PSA level >50 ng/mL (i.e., locally advanced/metastatic PCa easily detectable by TRUS biopsy)

location can affect csPCa detection, TRANSLATE will stratify by presence of anterior lesions.

MRI

All TRANSLATE patients will have had a mp/bp-MRI prior to biopsy. The mp/bp-MRI will be performed on a 1.5-Tesla or higher MRI scanner, with a radiology report provided by a suitably qualified radiologist, according to PI-RADS version 2.1 guidelines or using a Likert scale according to local protocol. The location of radiologically suspicious lesions will guide targeted biopsy at either LATP biopsy or TRUS biopsy. Allowing for the fact that some men may opt to not receive a prostate biopsy in the context of a 'normal' pre-biopsy MRI (e.g., a PSA density of <0.15 ng/mL^2 and a PI-RADS score of 1–2 for their MRI), we estimate that ~75% of patients will meet the eligibility criteria for the trial, and that about 30%–40% of eligible patients will consent to participate.

Biopsy

The TRANSLATE recruitment centres will have the capability to undertake either a LATP biopsy or TRUS biopsy according to randomisation, and will recruit men with equipoise. A key overarching principle of TRANSLATE is to achieve equivalent mean number of systematic biopsy cores taken with either LATP or TRUS biopsy, and the same mean number of target biopsy cores if a lesion is present, to avoid bias in detection of csPCa and in secondary outcomes from either type of prostate biopsy approach. Either a clinician or a specialist nurse, depending on local practice at each recruiting centre, may perform the LATP and TRUS biopsies. All participating centres will have performed several 100 TRUS biopsies and will be undertaking LATP with audit of local results ensuring local quality assurance. Clinician and/or specialist nurse participation in performing a biopsy will be determined on a competency basis.

LATP Biopsy

The LATP biopsy will be performed with an average of 12 systematic biopsy cores in six sectors, i.e., a modified Ginsburg protocol [22] with two 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. An additional three to five (average four) target biopsy cores will be taken for each significant target lesion seen on the pre-biopsy MRI. Clinicians will use judgement regarding whether same sector systematic biopsies are required or not depending on the size of the lesion and size of the 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. LATP biopsy will 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 will be performed without antibiotics [23]. Each centre will use its existing LATP biopsy technique and ultrasound probe-mounted LATP needle-guide devices (either the 'Precision-Point' or BK UA1232 access system, or similar probe-mounted device), 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).

TRUS Biopsy

Depending on prostate size, this will be performed with an average of 12 systematic biopsy cores (six per side, i.e., two biopsy cores per base, mid, and apical regions of the prostate, left and right sided) using a TRUS probe. An additional three to five (average four) target biopsy cores will be taken for each significant target lesion seen on the pre-biopsy MRI. Identical to LATP, clinicians will use their judgement as to how many additional systematic biopsies are required on the side of a target lesion. Centres will follow their own local procedures regarding sending the biopsy cores to pathology in pots, but the target biopsies, at least, will be in a separate pot. The TRUS biopsy will be performed in the outpatient setting with the patient in the left lateral position, using LA infiltration, with pre- and post-procedure antibiotics (typically for 48 h, but may vary according to local guidelines and/or clinician preference). Each centre will use its existing TRUS biopsy technique in order to reflect real-world clinical practice (given the minor variations in TRUS biopsy technique across the UK).

Histology Reporting

Prostate biopsies will be reported at local recruitment sites according to standards set in the Royal College of Pathologists' 'dataset for histopathology reports for prostatic carcinoma' (current version – June 2016). Each recruitment site has specialist uropathology teams as per standard NHS practice, and this may include the use of digital pathology. Grading will be based on the International Society of Urological Pathology (ISUP) guidance issued in 2005 and 2014, which is the 'gold standard' in the UK and internationally. Each recruitment site will generate a separate report for each pot (specimen) received in the pathology report, with separate data for each specimen on Gleason Grade Group (GGG) and tumour burden. After the allocated biopsy, the results of the MRI and biopsy of all trial participants will be reviewed as standard of care as part of the 'Suspected PCa Pathway' at the regional Uro-Oncology Multidisciplinary Team (MDT) meeting of the recruitment centre. Core members of the MDT at the local recruiting centre will decide whether to recommend a repeat prostate

biopsy, e.g., following benign TRUS biopsies in the context of a radiologically significant anterior lesion (PI-RADS score 4–5 lesions), on a case-by-case basis. Clinical teams will know that an individual is in the TRANSLATE study and will not be blinded to the method of biopsy. Where a repeat biopsy is recommended, these will be performed as an LATP biopsy procedure within 12 weeks of the original randomised biopsy, unless a newly-arising clinical condition precludes this, or the repeat biopsy requires a general anaesthetic.

Subsequent Visits after Biopsy

The study protocol does not require additional research-related visits by participants. Participants will receive their biopsy result according to local practice and follow their local pathway for both benign and malignant findings.

Health Economic Analysis

We will conduct a within-trial cost-effectiveness analysis of LATP biopsy compared to TRUS biopsy as a diagnostic test for csPCa. Resource utilisation, cost, and cost-effectiveness of implementing LATP biopsy, compared against the current practice of TRUS biopsy, will be assessed, adhering to good economic evaluation practice with a NHS and Personal Social Services perspective [24] and based on experience from previous PCa trials [25]. Self-completed resource use questionnaires 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. These will be administered at baseline, 7 days post-procedure, 35 days post-procedure, and 4 months post-procedure, to indicate healthcare resource use from baseline to 7 days, from 7 days to 35 days, and from 35 days to 4 months (Table 3). 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. Case report forms will be completed at each recruitment site to capture the time taken for each procedure, and the 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, 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), the EQ-5D-5L [26] questionnaire will be used to measure HRQoL at baseline, and at 7 days, 35 days, and 4 months after the procedure.

Incremental cost-effectiveness ratios (ICERs) will be estimated by dividing the difference in costs between LATP biopsy and TRUS biopsy 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

Table 3 Summary of follow-up evaluations in TRANSLATE.

Time point	Data	Data collection method
Baseline	• Patient demographics • IIEF questionnaire (Domain A) • IPSS questionnaire • EQ-5D-5L questionnaire	Research nurse administers baseline data collection – completing baseline case report form 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) • IPSS 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 serious adverse events; 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 24 h before the 7-day time-point and will be due 48 h after the 7-day time-point.
35 days post-procedure	As for 7 days post-procedure	Patient completes information/ questionnaires either electronically or via a telephone call or a posted pack. This will be sent to the participant 48 h before 35-day time-point and will be due 7 days after the 35-day time-point
4 months post-procedure	As for 7 days post-procedure	Patient completes information/ questionnaires either electronically or via a telephone call or a posted pack. This will be sent to the participant 7 days before the 4-month time-point and will be due 14 days after the 4-month time-point

£30 000 per QALY). Uncertainty around the ICER will be explored using non-parametric bootstrapping. Cost-effectiveness results will be presented on planes, and as acceptability curves, indicating where the results fall in relation to given thresholds. The impact of each of the two available devices to conduct LATP biopsy 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 LATP biopsy proves to be more effective in identifying csPCa, without an excess morbidity or poorer tolerability compared with TRUS biopsy, 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 [27,28].

Patient Impact

We are not assessing long-term HRQoL as part of this trial. Specifically, we are not assessing the impact of a missed csPCa 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 LATP biopsy or TRUS 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 related to LATP biopsy or TRUS biopsy, and the tolerability of the procedure. Analysis of the patients' experience and tolerability of the LATP or TRUS biopsy, including effects on urinary and sexual function, and HRQoL, will be compared through use of standardised questionnaires at baseline and at multiple time-points after biopsy.

Statistical Methods

Data collected from 792 patients in Oxford over a 12-month period suggests that the detection rate of csPCa in previously biopsy-naïve men through TRUS biopsy following pre-biopsy mpMRI is 45% [29], in line with the reported literature, whilst our observational cohort study with data from 1218 patients in 10 centres suggests a detection rate of 59% for csPCa in biopsy-naïve men [18]. We therefore consider a 10% improvement (from 45% to 55%) in the rate of detection of csPCa (defined as GGG ≥2, i.e., any Gleason pattern ≥4 disease) through LATP biopsy vs TRUS biopsy to be clinically meaningful. To detect this primary outcome difference with 90% power and 5% significance, we need to recruit 1042 men over a 15-month period across the multiple participating recruitment centres.

The primary outcome of the TRANSLATE study is the proportion of patients with a prostate biopsy positive for csPCa (defined as GGG ≥2, i.e., any Gleason pattern ≥4 disease), and this will be compared across the two randomised groups (LATP biopsy and TRUS biopsy) using a logistic regression model adjusted for the stratification factors (recruitment centre, and site of prostatic lesion on pre-biopsy MRI). A supporting unadjusted analysis will be conducted, and a further analysis adjusting for important prognostic factors (such as PSA level 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% CIs. 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.

All analyses will be carried out on the intention-to-treat population (i.e., all patients will be analysed in the group to which they were randomised, regardless of actual intervention received). It is not anticipated that there will be any significant protocol deviations, but in the event that any occur we will repeat the primary analysis for the per protocol population (patients excluded from this population are pre-specified in the Statistical Analysis Plan). Stata (StataCorp LP, College Station, TX, USA) or other appropriate validated statistical software such as R (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) will be used for analysis.

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% CIs, and all tests will be carried out at a 5% two-sided significance level. A detailed statistical analysis plan will be agreed early in the trial and will receive review and input from the Trial Steering Committee (TSC) and Data and Safety Monitoring Committee (DSMC). No formal interim analyses with stopping guidelines are planned.

Results

The TRANSLATE trial commenced recruitment 1 December 2021, and successfully transitioned through its internal pilot phase on 1 May 2022. The main trial is now in progress.

Discussion

There is interest among Urology Departments to shift from TRUS biopsy to LATP biopsy in the diagnostic pathway for detection of csPCa, driven by the desire to reduce infection risk from TRUS biopsy, coupled with enthusiasm from

urologists to modernise aspects of clinical practice, in the absence of level-one evidence to make this change. The campaign and publicity to move away from TRUS biopsy has been a key voice in this; however, whilst there are several observational cohort series for LATP biopsy outcomes [16–18], to date no level-one evidence exists comparing LATP biopsy vs TRUS biopsy. Several randomised clinical trials of general anaesthetic transperineal biopsy vs TRUS biopsy have been performed [30–33], and a recent systematic review and meta-analysis [34] showed no difference in diagnostic accuracy (relative risk 0.94, 95% CI 0.81–1.1) between these approaches to prostate biopsy. However, to date no randomised clinical trial of LATP biopsy vs TRUS biopsy has been conducted or reported. Whilst LATP biopsy may have a lower associated infection risk compared to TRUS biopsy, TRUS biopsy may be more tolerable for patients, and may be more cost-effective. Moreover, all long-term PCa outcomes data are based on TRUS biopsy. An important feature of TRANSLATE is that this study uniquely compares csPCa detection rates using the same number of biopsy cores in each of the TRUS biopsy and LATP biopsy arms in an adequately powered randomised clinical trial. Conducting a pragmatic large multicentre randomised clinical trial such as this is necessary to provide the essential data on the diagnostic accuracy of LATP biopsy vs TRUS biopsy, along with robust data regarding the relative tolerability, costs and side-effects of these procedures, which can then be assessed by policymakers such as NICE ahead of clinical guidelines statements.

In addition to TRANSLATE, there are several other ongoing clinical trials in this clinical space. The ProBE-C trial (NCT04081636) from Albany, New York commenced in 2019 and is randomising 568 men being investigated for suspected PCa to TRUS biopsy or MRI-guided LATP biopsy, with the primary outcome being infection and bleeding within 30 days, and cancer detection, tolerability, PROMs and cost as secondary outcomes. The PCORI trial (NCT04815876) led by a team from Weill Cornell commenced in 2021 and will randomise 400 men to LATP biopsy or TRUS biopsy and primarily assess infection rates, with cancer detection, patient-reported comfort and anxiety, and other adverse events as secondary outcomes. A second study (NCT04843566) from this same group commenced in 2021 and is randomising 1302 men already on active surveillance for GGG1 PCa, to LATP biopsy or TRUS biopsy with the same outcomes. A further smaller study in Hong Kong (NCT04108871) started in 2018 and is randomising 180 participants between LATP biopsy and TRUS biopsy with primary outcome being cancer detection, and secondary outcomes tolerability, HRQoL, erectile function, sepsis, and pathology-specific outcomes.

We hypothesise that the increased sampling of the prostate gland available via LATP biopsy will increase the rate of detection of csPCa compared to TRUS biopsy. Our previous observational cohort series for TRUS biopsy reported a detection rate for csPCa, defined as GGG2 disease, of 45% in the pre-biopsy mpMRI era [29], whilst our multicentre cohort of LATP biopsies report a detection rate of csPCa in biopsy-naïve men of 59%. Based on these previous observations, TRANSLATE will require 1042 men to be randomised to TRUS biopsy or LATP biopsy in order to detect a conservatively estimated 10% increase in detection of csPCa, which we would consider to be a clinically meaningful uplift in the performance characteristics of prostate biopsy.

We note the steady decline in numbers of men undergoing prostate biopsy in the context of a 'negative' MRI since the publication of reports detailing the negative predictive value of PI-RADS score 1–2 on pre-biopsy MRI [35]. This is being reflected in current guidelines such that men without a radiologically significant lesion on pre-biopsy mpMRI (PI-RADS score 1–2), and with a low PSA density and without a significant risk factor such as a family history of PCa, may defer biopsy and instead undergo PSA observation. It is possible that by enriching the TRANSLATE cohort with patients with radiologically significant lesions on pre-biopsy mpMRI we may observe higher than previously reported rates of csPCa for both TRUS biopsy and LATP biopsy. We eagerly await completion of recruitment and reporting of our data.

The secondary outcomes of TRANSLATE are similarly important, given the interest in infection and sepsis rates after TRUS biopsy, and urinary retention, erectile dysfunction, patient tolerability, and the potential cost-effectiveness of LATP biopsy compared to TRUS biopsy.

The TRANSLATE study commenced recruitment in December 2021, and aims to complete recruitment within 18 months, and report mid-2024. The study has a pragmatic design and aims to provide real-world level-one evidence of the relative performance characteristics of TRUS biopsy and LATP biopsy in order to inform patients, the urological community, and policymakers, ahead of potential guidelines statements from NICE and other stakeholders. It will contribute significantly to the clinical guidance in this common area of urological practice and has the potential to be one of the practice-defining trials regarding modern-day prostate biopsy technique.

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Disclosure of Interests

Richard J. Bryant, Alastair D. Lamb and Tom Leslie received support from BXT Accelyon to attend LATP biopsy training provided by Rick Popert at Guys Hospital. Alastair D. Lamb is a co-author of a paper campaigning to move away from TRUS biopsy [20]. Hide Yamamoto is an expert panel member of NICE panel DAP57 and has previously received support from BK Medical to provide LATP biopsy training to other UK centres. Matthew Liew is a consultant for Teleflex.

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Abbreviations: bpMRI, bi-parametric MRI; csPCa, clinically significant prostate cancer; EQ-5D-5L, EuroQoL five Dimensions five Levels; GGG, Gleason Grade Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IIEF, International Index of Erectile Function; ISUP, International Society of Urological Pathology; LA, local anaesthetic; LATP, local anaesthetic transperineal prostate biopsy; MDT, multidisciplinary team; mpMRI, multiparametric MRI; NICE, National Institute for Health and Care Excellence; NIHR-HTA, National Institute for Health and Care Research Health Technology Assessment; PCa, prostate cancer; PI-RADS, Prostate Image-Reporting and Data System; ProBE, Prostate Biopsy Effects (questionnaire); PROMs, patient-reported outcome measures; QALYs, quality-adjusted life-years.