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Abstract

Transperineal biopsy devices in people with suspected prostate cancer - a systematic review and economic evaluation

Inês Souto-Ribeiro, Lois Woods, Emma Maund, David Alexander Scott, Joanne Lord, Joanna Picot and Jonathan Shepherd*

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Background: People with suspected prostate cancer are usually offered either a local anaesthetic transrectal ultrasound-guided prostate biopsy or a general anaesthetic transperineal prostate biopsy. Transperineal prostate biopsy is often carried out under general anaesthetic due to pain caused by the procedure. However, recent studies suggest that performing local anaesthetic transperineal prostate biopsy may better identify cancer in particular regions of the prostate and reduce infection rates, while being carried out in an outpatient setting. Devices to assist with freehand methods of local anaesthetic transperineal prostate may also help practitioners performing prostate biopsies.

Objectives: To evaluate the clinical effectiveness and cost-effectiveness of local anaesthetic transperineal prostate compared to local anaesthetic transrectal ultrasound-guided prostate and general anaesthetic transperineal prostate biopsy for people with suspected prostate cancer, and local anaesthetic transperineal prostate with specific freehand devices in comparison with local anaesthetic transrectal ultrasound-guided prostate and transperineal prostate biopsy conducted with a grid and stepping device conducted under local or general anaesthetic.

Data sources and methods: We conducted a systematic review of studies comparing the diagnostic yield and clinical effectiveness of different methods for performing prostate biopsies. We used pairwise and network meta-analyses to pool evidence on cancer detection rates and structured narrative synthesis for other outcomes. For the economic evaluation, we reviewed published and submitted evidence and developed a model to assess the cost-effectiveness of the different biopsy methods.

Results: We included 19 comparative studies (6 randomised controlled trials and 13 observational comparative studies) and 4 single-arm studies of freehand devices. There were no statistically significant differences in cancer detection rates for local anaesthetic transperineal prostate (any method) compared to local anaesthetic transrectal ultrasound-guided prostate (relative risk 1.00, 95% confidence interval 0.85 to 1.18) (n = 5 randomised controlled trials), as was the case for local anaesthetic transperineal prostate with a freehand device compared to local anaesthetic transrectal ultrasound-guided prostate (relative risk 1.40, 95% confidence interval 0.96 to 2.04) (n = 1 randomised controlled trial). Results of meta-analyses of observational studies were similar. The economic analysis indicated that local anaesthetic transperineal prostate is likely to be cost-effective compared with local anaesthetic transrectal ultrasound-guided prostate (incremental cost below £20,000 per quality-adjusted life-year gained) and less costly and no less effective than general anaesthetic transperineal prostate. local anaesthetic transperineal prostate with a freehand device is likely to be the most cost-effective strategy: incremental cost versus local anaesthetic transrectal ultrasound-guided prostate of £743 per quality-adjusted life-year for people with magnetic resonance imaging Likert score of 3 or more at first biopsy.

Limitations: There is limited evidence for efficacy in detecting clinically significant prostate cancer. There is comparative evidence for the PrecisionPoint™ Transperineal Access System (BXTAccelyon Ltd, Burnham, UK) but limited or no evidence for the other freehand devices. Evidence for other outcomes is sparse. The cost-effectiveness results are sensitive to uncertainty over cancer detection rates, complication rates and the numbers of core samples taken with the different biopsy methods and the costs of processing them.

Conclusions: Transperineal prostate biopsy under local anaesthetic is equally efficient at detecting prostate cancer as transrectal ultrasound-guided prostate biopsy under local anaesthetic but it may be better with a freehand device. Local anaesthetic transperineal prostate is associated with urinary retention type complications, whereas local anaesthetic transrectal ultrasound-guided prostate has a higher infection rate. Local anaesthetic transperineal prostate biopsy with a freehand device appears to meet conventional levels of costeffectiveness compared with local anaesthetic transrectal ultrasound-guided prostate.

Study registration: This study is registered as PROSPERO CRD42021266443.

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Contents

List of tables

List of figures

Glossary

Active surveillance Monitoring of a person following a diagnosis of prostate cancer with a view to the person having radical treatment if the cancer progresses. One of the aims of active surveillance is to avoid the risk of overtreatment by avoiding immediate radical intervention.

Adverse event Any undesirable experience associated with the use of a medical product or procedure in a patient.

Benign Not cancerous. Benign tumours do not spread to tissues around them or to other parts of the body.

Biopsy Sampling of tissue from a specific area of the body (e.g. the prostate) to check for abnormalities such as cancer.

Cancer Growth of abnormal cells in the body in an uncontrolled manner.

Digital rectal exam The doctor inserts a gloved, lubricated finger into the rectum and feels the rectum, anus and prostate to check for anything abnormal.

Erectile dysfunction The inability to get or maintain an erection.

Fusion biopsy A fusion biopsy combines the pre-biopsy magnetic resonance imaging image with the ultrasound image during the biopsy procedure in order to more accurately target any suspicious areas of the prostate. Cognitive fusion, or visual registration, is when the urologist views both sets of images and mentally translates the multiparametric magnetic resonance imaging target lesions onto the real-time ultrasound images during the biopsy procedure. Software-based fusion uses technology to fuse the images from the pre-biopsy multiparametric magnetic resonance imaging and the real-time ultrasound, creating a detailed three-dimentional image for the urologist to use.

General anaesthetic transperineal biopsy grid and stepping device For the purpose of this assessment report, 'general anaesthetic transperineal biopsy grid and stepping device' refers to general anaesthetic transperineal prostate biopsy done using a grid and stepping device

Gleason system A commonly used system used to grade prostate cancer cells to estimate how quickly they are likely to grow (the Gleason grade). The overall Gleason score is calculated by adding together the two most common Gleason grades. Grade Group 1 is the least aggressive, indicating that the cancer is likely to grow very slowly, if at all. Grade Group 5 is the most aggressive, indicating the cells look very abnormal and the cancer is likely to grow quickly.

Grade Describes the degree of severity of a cancer.

Haematuria The presence of blood in a person's urine.

Heterogeneous/heterogeneity Composed of a diverse mixture of different kinds or subgroups.

Local anaesthetic transperineal prostate-any (LATP-any) For the purpose of this assessment report, 'LATP-any' refers to local anaesthetic transperineal prostate biopsy done by any method with the National Institute for Health and Care Excellence scope [i.e. prostate biopsy using a grid and stepping device, a coaxial needle ('double freehand'), or a freehand device].

Local anaesthetic transperineal prostate-freehand (LATP-freehand) For the purpose of this assessment report, 'LATP-freehand' refers to local anaesthetic transperineal prostate biopsy done using one of the six freehand devices within the National Institute for Health and Care Excellence scope. This is a subcategory of the LATP-any grouping of biopsy methods.

Local anaesthetic transperineal prostate-other (LATP-other) For the purpose of this assessment report, 'LATP-other' refers to local anaesthetic transperineal prostate biopsy done without a freehand device. This includes LATP done with a coaxial needle or with a grid and stepping device.

Likert score A Likert score is reported using a five-point Likert scale. The Likert scale, when used in the diagnosis of prostate cancer, takes into account clinical factors and lesion size on multiparametric magnetic resonance imaging. A score of 1 indicates prostate cancer is very unlikely and a score of 5 indicates prostate cancer is very likely. Likert scores are used to help decide whether or not to have a prostate biopsy at the current time. The Likert score differs from the Prostate Imaging Reporting and Data System (PI-RADS) score in that it takes into account clinical factors and does not require specific sequential review of magnetic resonance imaging sequences.

Magnetic resonance imaging (MRI) MRIs use magnetic fields to create clear images of tissues, muscles, nerves and bones. MRIs makes better images of organs and soft tissue than other scanning techniques, such as computed tomography or X-ray.

Malignant Cancerous. Malignant tumours can invade and destroy nearby tissue and can spread to other parts of the body.

Multiparametric MRI-influenced prostate biopsy (mpMRI) The information from the mpMRI scan taken before prostate biopsy is used to determine the best needle placement. In rare cases, the biopsy may be MRI-guided (the needle is inserted within the MRI machine). In most cases, the biopsy that follows the mpMRI will be ultrasound-guided, but the specific area(s) targeted will be predetermined by the mpMRI data.

Prostate A walnut-sized gland surrounding the urethra, located immediately below the bladder in males. The prostate gland produces a thick, white fluid that gets mixed with sperm to create semen.

Prostate Imaging Reporting and Data System (PI-RADS) score The PI-RADS score is a system whereby each lesion identified by mpMRI is assigned a score from 1 to 5 to indicate the likelihood of clinically significant cancer (where 1 is very low and 5 is very high). PI-RADS v2 is the current validated version. It differs from the Likert score in that it does not take into account clinical factors and it requires specific sequential review of MRI sequences.

Prostate-specific antigen (PSA) PSA is a substance made by the prostate gland. A small amount of PSA in the blood is normal. If the prostate becomes enlarged, inflamed, infected or cancerous, larger amounts of PSA get into the blood.

Rectum The rectum, also known as the back passage, is the last 6 inches of the large bowel and connects the colon to the anus.

Scrotum A bag of skin near the penis that contains the testicles.

Sepsis Sepsis, also known as septicaemia or blood poisoning, is a life-threatening reaction to an infection. It happens when the body's immune system overreacts to an infection and starts to damage the body's own tissues and organs.

Transrectal ultrasound A small wand (probe) is put into the patient's rectum. It gives off sound waves and picks up the echoes as they bounce off the prostate gland. The echoes are made into a picture on a computer screen.

Urinary retention Difficulty in urinating fully or inability to completely empty the bladder.

Watchful waiting Monitoring of a person diagnosed with prostate cancer where any potential treatment offered is aimed at controlling rather than trying to cure the prostate cancer (palliative rather than curative).

List of abbreviations

ADT	androgen deprivation therapy
AE	adverse event
ASCO	American Society of Clinical Ontology
AUA	American Urologic Association
BAUS	British Association of Urological Surgeons
BNF	British National Formulary
BSA	body surface area
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CNS	clinically non-significant
CS	clinically significant
CSDR	Cochrane Database of Systematic Reviews
CT	computerised tomography
DAP	Diagnostics Assessment Programme
DARE	Database of Abstracts of Reviews of Effects
DRE	digital rectal examination
EAG	Evidence Assessment Group
EAU	European Association of Urology
EED	Economic Evaluations Database
eMIT	electronic market information tool
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
FN	false negative
GATP	general anaesthetic transperineal biopsy
GP	general practitioner
HR	high risk
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IIEF	International Index of Erectile Function
INAHTA	International Health Technology Assessment Database
IQR	interquartile range
IR	intermediate risk
ISPOR	The Professional Society for Health Economics and Outcomes Research
ISUP	International Society of Urological Pathology
JBI	Joanna Briggs Institute
LATP biopsy	local anaesthetic transperineal biopsy
LATRUS biopsy	local anaesthetic transrectal ultrasound biopsy
LHRH	luteinising hormone-releasing hormone
LR	low risk
LY	life-years
MD	metastatic disease
mpMRI	multiparametric magnetic resonance imaging
MRI	magnetic resonance imaging
NPCA	National Prostate Cancer Audit
NG131	NICE Guideline 131
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research

NMA	network meta-analysis
PC	prostate cancer
PI-RADS	prostate imaging – reporting and data system
PSA	prostate-specific antigen
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk/risk ratio
SCM	Specialist Committee Member
SD	standard deviation
SF-6D	short-form questionnaire – 6 items
SF-12	short-form questionnaire – 12 items
SF-36	short-form questionnaire – 36 items
TP	transperineal biopsy
TPM	template prostate mapping
TRUS	transrectal ultrasound
UTI	urinary-tract infection
VAS	visual analogue scale
YHEC	York Health Economics Consortium

Plain language summary

A prostate biopsy can help determine if a person has prostate cancer. The main ways of performing a prostate biopsy involve taking small samples of the prostate out through the rectum (back passage) or through the perineum – the skin area between the anus and the scrotum (testicles). Both methods use ultrasound images from a probe inserted into the rectum to help the clinician see what they are doing. Taking samples through the rectum is usually carried out under local anaesthetic, whereas taking samples through the perineum is usually carried out under general anaesthetic.

We wanted to find out if taking samples through the perineum under local anaesthetic (instead of general anaesthetic) would be equally effective at detecting prostate cancer as the other biopsy methods and whether there was any improvement or change in the sorts of side effects people may have. We also wanted to know if people found the biopsy painful or not. We carried out searches of computer research databases to find relevant clinical and cost-effectiveness studies and compared the effectiveness of the different biopsy methods they used. We read and summarised the results of the studies we found in our search.

Our findings showed that taking biopsy samples through the perineum under local anaesthetic had rates of detecting prostate cancer similar to those of the other biopsy methods. But if the clinician also used a freehand device that helps guide the biopsy needle as part of the procedure, then this may be a better method for detecting cancer. The studies we found agreed that performing this prostate biopsy under local anaesthetic was not too painful for most people. Our economic estimates suggest that using a freehand device for local anaesthetic perineal (through the skin of the perineum) biopsy may be a cost-effective use of National Health Service resources.

Scientific summary

Background

Prostate cancer accounts for 30% of all cancers diagnosed in men in the UK and the incidence is rising. It is more common in men over 45 years of age. Symptoms that cannot be attributed to other health conditions include lower back or bone pain, lethargy, erectile dysfunction, haematuria, weight loss and lower urinary tract symptoms.

National Institute for Health and Care Excellence (NICE) guideline NG12 advises on recognition and referral of people presenting with possible prostate cancer. A prostate-specific antigen (PSA) test and digital rectal examination should be performed. If PSA levels are raised above normal or if the prostate feels malignant, then the person should be referred for suspected cancer. NICE guideline NG131 advises on diagnosis and management. It recommends a multiparametric magnetic resonance imaging (mpMRI) test with the results reported using a five-point Likert scale to indicate how likely the presence of prostate cancer is.

The Likert scale score, or alternatively the Prostate Imaging Reporting and Data System (PI-RADS score, not mentioned in the NICE guideline), is used to assess whether the person is offered a prostate biopsy. People with a score of 3 or above should be offered a multiparametric magnetic resonance imaging (mpMRI)-influenced prostate biopsy. People with a score of 1 or 2 will discuss risks and benefits with a clinician and if a prostate biopsy goes ahead, it should be a systematic biopsy.

Two main options for biopsy are transrectal ultrasound prostate biopsy under local anaesthetic (LATRUS) and transperineal prostate biopsy under general anaesthetic (GATP). Biopsies can be either targeted (based on mpMRI findings) or systematic (samples are taken according to a predefined scheme) or both. Recent studies suggest that performing transperineal prostate biopsy under local anaesthetic (LATP) could better identify cancer in particular regions of the prostate and could have lower infection rates than transrectal biopsies while also being able to be carried out in an outpatient setting. Transperineal prostate biopsy is usually carried out under general anaesthetic due to pain caused by the procedure and tolerability is a key issue.

Various freehand devices to assist with LATP prostate biopsy are being introduced to the market. The six specific freehand devices specified in the NICE scope for this review are: Cambridge Prostate Biopsy Device (CamPROBE) (JEB Technologies Ltd, Suffolk, UK); EZU-PA3U (Hitachi Ltd, Tokyo, Japan); PrecisionPoint™ Transperineal Access System (BXTAccelyon Ltd, Burnham, UK); SureFire Guide (LeapMed, Jiangsu, China); Trinity® Perine Grid (KOELIS®, NJ, USA); UA1232 puncture attachment (BK Medical, MA, USA).

Objectives

The aim of this review is to evaluate the diagnostic yield, clinical effectiveness and cost-effectiveness of LATP prostate biopsies performed with or without available specialist devices and equipment, in people with suspected prostate cancer.

Two decision questions were prioritised by NICE for this assessment, with input from relevant stakeholders:

Decision question 1. Do LATP prostate biopsies in patients with suspected prostate cancer represent a clinically and cost-effective use of National Health Service (NHS) resources?

Decision question 2. Do freehand transperineal biopsy devices for LATP prostate biopsies in patients with suspected prostate cancer represent a clinically effective and cost-effective use of NHS resources?

There are five comparisons required to address the two decision questions in the NICE scope:

1. LATP-any (using coaxial needle or grid and stepping device or freehand device) versus LATRUS
2. LATP-any (using coaxial needle or grid and stepping device or freehand device) versus GATP
3. LATP-freehand (freehand device only) versus LATRUS
4. LATP-freehand (freehand device only) versus GATP
5. LATP-freehand (freehand device only) versus LATP-grid and stepping device.

Methods

Systematic review of diagnostic test evaluation and clinical effectiveness

A systematic review of diagnostic and clinical effectiveness evidence was conducted following a peer-reviewed protocol. Searches were based on a comprehensive search strategy. Bibliographic databases, including MEDLINE, EMBASE, Web of Science, The Cochrane Library and the International HTA database, were searched for English-language references in July 2021, and these searches were updated at the end of October 2021. Urology conferences and freehand-device company submissions were hand-searched, and reference lists of identified systematic reviews and meta-analyses were checked. Relevant studies were sought through contact with study authors and NICE Specialist Committee members.

Studies were eligible if they included people with suspected prostate cancer with an indication for prostate biopsy and reported diagnostic yield, for example, cancer detection rates, or other clinical or patient-reported outcomes. The eligible interventions were any LATP biopsy (of which LATP-freehand biopsy is a subset) and the eligible comparators were LATRUS and GATP; the LATP-grid and stepping device was an eligible comparator when compared with the LATP-freehand intervention.

The Cochrane risk of bias tool (version 1) was used to assess risk of bias for the included randomised controlled trials (RCTs) and The Joanna Briggs Institute critical appraisal checklists were used to assess the included observational studies. Two reviewers carried out study selection, data extraction and critical appraisal, with any disagreements resolved through discussion and referred to a third reviewer for resolution as necessary.

We conducted meta-analysis of the cancer detection rate outcomes for which sufficient comparative data were available. Pairwise meta-analysis was conducted for the above comparisons, with randomised and non-randomised studies analysed separately. Network meta-analysis was conducted for the two decision questions specified in the NICE scope. We synthesised the data for other outcomes narratively, as evidence was too sparse for meta-analysis.

Review of economic evaluations

We conducted a systematic review of the cost-effectiveness of the prostate biopsy methods in scope. The search strategies were based on an early version of the clinical effectiveness searches with the addition of an economics search filter. Included studies were full economic evaluations that assessed both costs and consequences for the different prostate biopsy methods. Outcomes included measures of resource use and costs and health outcomes: life-years or quality-adjusted life-years (QALYs) gained. Economic evaluations not meeting the inclusion criteria and studies that reported on resource use and costs, and health-related quality of life (utilities) were assessed as potential sources of information for the economic model.

External Assessment Group independent economic assessment

We developed a decision model to estimate the cost-effectiveness of alternative biopsy methods for people referred for biopsy with suspected prostate cancer. The model includes a decision tree to estimate diagnostic outcomes and biopsy-related complications, and a Markov model that predicts the long-term costs and consequences of false-negative biopsy results. We assessed cost-effectiveness for four subgroups at different prior levels of risk, based on previous mpMRI results (Likert 1 or 2; or Likert 3 or more) and history of prostate biopsy (none; previous negative biopsy).

The decision tree used published results from the economic evaluation of the Prostate MR imaging study (PROMIS) to estimate baseline prevalence in the subgroups of interest, and diagnostic yield of LATRUS biopsy. Cancer detection rates were adjusted for the other biopsy methods using relative risks (RRs) from our network meta-analyses, and evidence from the literature on biopsy complication rates and the probability of repeat biopsy. Costs of the biopsy methods were estimated in a microcosting analysis, as well as from submitted evidence and published sources. The Markov model was a replicated version of a model developed for the 2019 update of the NICE guideline (NG131). Model parameters were based on those in the NG131 model, with some adjustments to costs and utilities from more recent published sources.

Results

Systematic review of diagnostic test evaluation and clinical effectiveness

The literature searches identified a total of 1969 references of which 111 references were subjected to full-text screening. Twenty-seven publications reported 23 studies meeting the inclusion criteria for this review: 19 comparative studies of which 6 were RCTs and 13 were observational studies (1 of which is unpublished); and 4 single-arm studies for LATP-freehand devices where no comparative evidence was identified.

There were no statistically significant differences in cancer detection rates for LATP (any method) compared to LATRUS with RR = 1.00 [95% confidence interval (CI) 0.85 to 1.18] (n = 5 RCTs). A single randomised trial estimated a non-significant difference in cancer detection rates in favour of LATP using a freehand device (PrecisionPoint) compared to LATRUS RR = 1.40, 95% CI 0.96 to 2.04. This finding was supported by meta-analysis of observational comparative studies RR = 1.21 (95% CI 1.08 to 1.34) (n = 4 studies). There were no statistically significant differences in cancer detection rates in meta-analyses comparing other biopsy methods. Evidence from the systematic review for other clinical outcomes, biopsy-related complications and patient-reported outcomes was sparse.

Review of economic evaluations

One economic evaluation was eligible for inclusion in the economic review out of 725 results from the original and update searches. This study evaluated the CamPROBE (LATP-freehand) device versus LATRUS for use in diagnosing prostate cancer from the perspective of the UK NHS. It used a decision-tree model with a Markov model at the terminal nodes and was informed by a prospective case series for the CamPROBE device and data from the PROMIS study. The study suggested that compared with LATRUS, LATP using the CamPROBE freehand device would be cost saving at a device price below £41 per procedure, or more cost-effective at the £20,000 per QALY threshold with a price below £81 per procedure. These calculations assume a zero rate of infection for LATP and equal diagnostic accuracy for LATP using CamPROBE and LATRUS. We considered 13 excluded economic studies as sources to inform our model structure and inputs, including the cost-effectiveness analysis for the PROMIS study and the analysis for the update of the NICE guideline on prostate cancer published in May 2019 (NG131).

Evidence from the BXTAccelyon company submission included a cost minimisation study developed in 2020 by the York Health Consortium that compared the costs of LATP (with the PrecisionPoint freehand device) with different combinations of LATRUS and GATP for UK NHS Trusts. The study suggests that

LATP using the PrecisionPoint freehand device is cost saving, assuming equal diagnostic yield of the different biopsy methods.

Independent economic assessment

The base-case economic analysis comparing LATP (all methods) with LATRUS and GATP indicated that LATP is likely to be the most cost-effective option in all four subgroups, with incremental cost-effectiveness ratio (ICER) estimates for LATP compared with LATRUS below £20,000 per QALY gained, and GATP estimated as more expensive and less effective than LATP. These conclusions were supported by probabilistic sensitivity analysis and a wide range of scenario analyses, although the results for LATP compared with LATRUS were sensitive to some alternative sources of cancer detection rates, rates of biopsy-related hospital admissions, numbers of core samples and histopathology costs.

The economic analysis including LATP-freehand compared with other LATP methods, as well as LATRUS and GATP, indicated that LATP with a freehand device was the most cost-effective strategy, with an ICER of £743 per QALY for the highest-risk subgroup with MRI Likert score of 3 or more at first biopsy, and £4595 per QALY for the subgroup with a MRI Likert score 1 or 2 at first biopsy. For the subgroups with a previous negative biopsy, the ICER remained below £20,000 per QALY. Again, probabilistic sensitivity analysis supported these results, but scenario analysis highlighted uncertainty related to the cost of the devices, the number of core samples and costs of processing them, and the use of other sources of evidence for cancer detection and biopsy-related complication rates.

The more favourable cost-effectiveness estimates for LATP with a freehand device are mostly driven by the cancer detection rates, which rest on a single RCT for LATP with a freehand device (PrecisionPoint). In the scenario based on observational evidence of cancer detection rates, the ICERs for LATP with a freehand device were less favourable, although still well below £20,000 per QALY. Increasing the cost of LATP with a freehand device by assuming the cost of the most expensive device, the ICER remained below £20,000 per QALY for the highest-risk subgroup but not for the other subgroups.

Conclusions

Transperineal prostate biopsy under local anaesthetic is equally efficient at detecting prostate cancer as transrectal ultrasound-guided prostate biopsy under local anaesthetic but evidence from one RCT, supported by observational studies, suggests that it might be better when using a freehand device. Local anaesthetic transperineal prostate biopsy is associated with urinary retention-type complications, whereas local anaesthetic transrectal ultrasound-guided prostate biopsy has a higher infection rate. Economic evaluation suggests that LATP with a freehand device is likely to be cost-effective compared with LATP with other methods, LATRUS and GATP for patients with no previous biopsy at high risk of having prostate cancer indicated by previous MRI results. This result is sensitive to the estimated cost of the freehand device, the number of and cost of core samples taken, and the sources for biopsy complication rates.

Recommendations for research

- *Evidence for freehand devices*. There was no comparative evidence for several of the freehand devices in the NICE scope. The TRANSLATE study is expected to help address this question, as it is evaluating the PrecisionPoint, UA1232 and 'any ultrasound probe-mounted needle guidance device'.
- *Outcomes not covered in included available evidence*. We suggest that incidence of defined complications (standardised for grading of severity and length of follow-up), health-related quality of life and longer-term clinical outcomes could be defined in a core outcome set.
- *LATP versus GATP*. Evidence for this comparison is sparse (we identified one RCT reporting cancer detection rates).

- *Repeat biopsy population*. There is a need for separate reporting of results for this subgroup, or a separate prospective RCT.
- *UK NHS setting*. The three UK studies included in our review were single-centre observational studies with a limited set of outcomes. The TRANSLATE study is expected to remedy this; it is a multicentre randomised study across nine NHS Trusts in England.

Study registration

This study is registered as PROSPERO CRD42021266443.

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Chapter 1 Background

Description of the health problem

Prostate cancer is the most commonly diagnosed cancer in men in the UK[1] and for males born after 1960 in the UK the estimated lifetime risk of being diagnosed with prostate cancer is 1 in 6 (18%).[2] The risk of developing prostate cancer increases with age and it mainly affects people aged 50 years or more.[3] The risk of developing prostate cancer is also higher for people of African family origin and for people where there is a family history of prostate cancer.[4] Most people who are diagnosed when their prostate cancer is at its earliest stage will survive for 5 years or more. If any of the following symptoms cannot be attributed to other health conditions, prostate cancer might be suspected:

- lower back or bone pain
- lethargy
- erectile dysfunction
- haematuria
- weight loss
- lower urinary tract symptoms, such as frequency, urgency, hesitancy, terminal dribbling and/or overactive bladder.

Epidemiology

In 2018, there were 49,810 new diagnoses of prostate cancer in England, an increase of 7985 more registrations than the previous year.[5] The age-standardised incidence rate in England was 204.7 per 100,000 in 2018, which was an increase from 182.8 per 100,000 in 2009.[6] The incidence rate for prostate cancer in the UK is projected to rise to 233 cases per 100,000 males by 2035.[1]

Prostate cancer accounts for 30% of all male cancer diagnoses and is the most commonly diagnosed cancer in males over 45 years old. In 2018, 55% of prostate cancers were diagnosed at stages 1–2[5] and despite an increased incidence rate the age-standardised mortality rate decreased between 2009 and 2018 from 51 per 100,000 to 46 per 100,000.[6]

In England, the South East has the highest age–sex-standardised rate of prostate cancer (228 per 100,000 people), compared with the North West at 171 per 100,000 people.[5] Prostate cancer incidence rates in males in England are 17% lower in the most deprived quintile compared with the least deprived quintile (2013–7).[1] Cancer Research UK states that 'Prostate cancer is most common in black males, then white males and least common in Asian males'.[1]

Description of the diagnostic technologies under assessment

When a person presents to primary care with clinical signs and symptoms that may be indicative of prostate cancer (such as the above), the National Institute for Health and Care Excellence's (NICE) guideline on suspected cancer: recognition and referral (NG12[7]) advises the following:

- consider a prostate-specific antigen (PSA) test and digital rectal examination (DRE) to assess for prostate cancer in men with:
    - any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention; or
    - erectile dysfunction; or
    - visible haematuria.

- refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for prostate cancer if their:

    - PSA levels are above the age-specific reference range; or
    - prostate feels malignant on DRE.

The NICE guideline on prostate cancer: diagnosis and management (NG131[8]) recommends that a multiparametric magnetic resonance imaging (mpMRI) test should be offered to people referred with suspected clinically localised prostate cancer. The results of the mpMRI test should be reported using a five-point Likert scale. The Likert scale takes into account clinical factors and lesion size, where a score of 1 indicates prostate cancer is very unlikely and a score of 5 indicates prostate cancer is very likely.[9]

- People who have a Likert scale score of 3 or more should be offered a mpMRI-influenced prostate biopsy.
- For people with a Likert scale score of 1 or 2, the risks and benefits of having a biopsy are discussed and other factors, such as family history, are taken into account so that a shared decision about whether to have a biopsy or not can be made. If that decision is to have a biopsy, a systematic prostate biopsy should be offered.
- For people who are not able to have radical treatment (e.g. radical prostatectomy, radical radiotherapy, or docetaxel chemotherapy) NG131 states that mpMRI should not be routinely offered.

An alternative to Likert scale assessment of mpMRI results that is not mentioned in NG131 is the Prostate Imaging Reporting and Data System (PI-RADS). This system was developed in 2012[10] and updated in 2015[11] and 2019.[12] Each lesion is assigned a score from 1 to 5 indicating the likelihood of clinically significant (CS) cancer (where 1 is very low and 5 is very high). The 2018 National Health Service (NHS) England handbook on implementing a timed prostate cancer diagnostic pathway[13] indicates that people with a Likert or PI-RADS score of 1 or 2 and people with a Likert or PI-RADS score of 3 who also have a PSA density < 0.15 (or 0.12 in some centres) nanograms of PSA per ml of serum per ml of prostate volume can be discharged from the diagnostic pathway. This would only occur after a discussion of the risks and benefits of biopsy and consensus between the doctor and the person about the most appropriate course of action.

There are two main routes by which a prostate biopsy can be obtained, the transrectal route and the transperineal route. In addition to the route, there are also different approaches to sampling the prostate tissue. The site (or sites) for biopsy can be *targeted* based on the findings from mpMRI or the biopsies can be *systematic* (i.e. samples are taken in a systematic fashion from different regions of the prostate according to a predefined scheme). Sometimes, after targeting sites of interest for biopsy, additional biopsy cores are taken from the area around the target lesion, or a systematic biopsy may be done in addition to the targeted biopsy.

If a mpMRI is contraindicated, factors such as PSA density and family history of prostate cancer would influence a decision about whether a systematic biopsy would be appropriate.

Transrectal ultrasound prostate biopsy

During a transrectal ultrasound (TRUS) prostate biopsy a TRUS probe is inserted into the anus to image the prostate. Samples of prostate tissue are collected using a biopsy needle inserted via the anus, through the rectal wall, and into the prostate. This procedure is typically carried out under local anaesthetic in an outpatient setting but can also be carried out under general anaesthetic (e.g. if the patient is unlikely to be able to tolerate the procedure under local anaesthetic). However, because the biopsy needle is inserted through the rectal wall, biopsy-related infections can occur, including, in some cases, sepsis (estimated to be 0.8% in a 2016 systematic review).[14] Sepsis is a serious infection which requires a hospital admission and antibiotics.

Traditionally, most prostate biopsies in the NHS used the TRUS method. However, there has been an increase in the use of transperineal biopsy (TP), and this has been accelerated due to the COVID-19 pandemic. A strategy document issued by the British Association of Urological Surgeons (BAUS) Section of Oncology for the interim management of prostate cancer during the pandemic recommended that TRUS biopsies should be avoided if possible.[15]

Transperineal prostate biopsy

In common with TRUS, a transperineal prostate biopsy also uses a TRUS probe inserted into the anus to image the prostate, but the samples of prostate tissue are collected using a biopsy needle inserted through the perineum (the skin area between the anus and the scrotum) rather than through the rectal wall. Transperineal prostate biopsy can be conducted using any of the following methods:

- a grid and stepping unit
- a coaxial needle ('double freehand')
- a freehand device (using one of the six devices listed in the NICE scope for this assessment).

Transperineal prostate biopsy using a grid and stepping device

Traditionally, transperineal biopsies were performed (using a grid and stepping device). The biopsy needle is passed through the perineum multiple times, creating a new skin puncture for every biopsy taken, and a broad area of local anaesthetic coverage was needed, hence the procedure typically took place under general anaesthetic.

Stepping devices are used to cradle the ultrasound probe and the grid provides a guide for needle insertion. Grid and stepping units are also used to perform brachytherapy for prostate cancer, and therefore they are available in treatment centres for this purpose at least. Each biopsy of the prostate requires a separate skin puncture. Many steppers can be fitted to a variety of different ultrasound probes and the grids are typically disposable, consisting of rows and columns of holes spaced 5 mm apart. The stepping unit is usually fixed to a stabiliser that is either mounted onto a table or supported by a floor stand.

Transperineal prostate biopsy using a coaxial needle (double freehand)

More recent TP techniques use an access needle which acts as a cannula, through which the biopsy needle is passed, allowing multiple biopsy samples to be taken through one access point. The access needle can be separate from the ultrasound probe (e.g. a coaxial needle), in which case it is known as the 'double freehand' technique. However, it may be technically challenging to master because the needle and ultrasound probe have to be kept in line manually, and this procedure is not extensively used within the NHS.

Transperineal prostate biopsy using a freehand device

As an alternative to the double freehand approach, the access needle can also be inserted through a positioning guide which is attached to the ultrasound probe. When the access needle and the ultrasound probe are physically coupled together, the device may be referred to as a freehand TP device and the user can more easily track the location of the biopsy needle in relation to the ultrasound probe. The access needle is typically inserted only twice, once to the left of the anal verge and once to the right of the anal verge. This limited number of access points means the procedure can be routinely completed using local anaesthetic during an outpatient appointment. The NICE scope for this assessment identified six proprietary freehand devices which are available for use in clinical practice in the UK. We describe the key features of each device below.

PrecisionPoint™ Transperineal Access System (BXTAccelyon Ltd, Burnham, UK)

PrecisionPoint is a single-use transperineal access system distributed by the company BXTAccelyon in the UK (they are the sole distributor outside North America). The device consists of a rail/clamp assembly that is mounted onto a sliding carriage. The Perineologic 15-gauge, 7-cm access needle is

inserted through one of the five apertures on the sliding carriage (the aperture used depends on the height of the prostate). Local anaesthetic is used to enable the access needle to puncture the skin. Typically, only two punctures are required – one on the right and one on the left side of the anal verge. A biopsy needle is then inserted via the access needle and used to deliver local anaesthetic to the tract of tissues between the skin and the prostate so that the access needle can be advanced more deeply into the subcutaneous tissue. Multiple biopsies from different locations can be taken from each puncture of the skin. The PrecisionPoint transperineal access system can be used to perform targeted or systematic biopsies, with no limitation on the size of the prostate or the number of biopsies.

UA1232 puncture attachment (BK Medical, MA, USA)

The UA1232 puncture attachment is a reusable needle guide and mounting ring with lock screw that is designed for transperineal puncture and biopsy. The mounting ring and lock screw are used to attach the device to a BK medical ultrasound probe with the needle guide parallel to the centreline of the ultrasound transducer. The needle guide has nine parallel guide channels, spaced 5 mm apart vertically, each with an internal diameter of 2.1 mm, which is suitable for a 14-gauge coaxial/access needle. The coaxial/access needle can be inserted at different heights using the vertical guide channels and then localisation to the left and right is achieved by rotating the ultrasound probe (and so the attachment). If necessary, the position of the coaxial/access needle in the vertical guide can be changed (requiring an additional skin puncture) to access anterior, middle and posterior regions of the prostate. The 14-gauge needle is used for access and a separate biopsy needle is inserted through this to obtain the biopsy samples. After completion of the procedure, all parts of the puncture attachment are sterilised by either autoclave or immersion in a suitable disinfectant solution.

Cambridge Prostate Biopsy Device (JEB Technologies Ltd, Suffolk, UK)

The Cambridge Prostate Biopsy Device (CamPROBE) is a single-use transperineal access system designed to enable integrated local anaesthetic delivery. The device comprises a stainless-steel cannula housing an integrated needle. The integrated needle is used to deliver local anaesthetic under ultrasound guidance enabling the access needle to be placed in position. When the access needle is correctly located, the integrated needle is removed, and a standard 18-gauge core biopsy needle (not supplied as part of the device) is inserted via the access needle to take the prostate biopsies. The device is inserted on the left and right sides of the perineum mid-line: two punctures. A new device is used for each puncture; therefore, two devices are used per person. There is no physical connection between the access needle and the ultrasound probe and there is no needle guide, so the CamPROBE is therefore used with double freehand technique to manually keep the device in phase with the ultrasound probe. The CamPROBE device was initially for research use only while an application for CE marking was prepared. JEB Technologies launched the CE marked device in November 2022.

Trinity® Perine (KOELIS®, NJ, USA)

The Trinity Perine system, manufactured by KOELIS and distributed in the UK by Kebomed UK, includes reusable-guide Perine grids. The reusable-guide Perine grids come in two sizes, to accommodate either a 17–20-gauge or 14–16-gauge needle and they are designed to adapt on to a KOELIS K3DEL00 ultrasound probe. Each Perine grid has 20 marked needle positions spaced 3 mm apart. Grids can be reused up to 100 times.

SureFire Guide (LeapMed, Jiangsu, China)

The SureFire disposable transperineal needle guide biopsy kit includes a sterile needle guide, a latex-free cover and a sterile gel packet. The vertical needle guide has nine guide channels at different height settings allowing vertical access to 8 cm, and an ultrasound probe clamp. The needle guide is designed to adapt to BK Medical Biplane probes 8648, 8848, 9048 and E14C4b or Hitachi Healthcare Biplane probes U533, C41L47RP and UST-672. The vertical needle guide can be rotated to reach different areas of the left and right sides of the prostate. The device is used freehand (i.e. without the need for a stepper or stabilising device) and is available in two sizes, to accommodate either 15-/16-gauge needles or 17-/18-gauge needles.

EZU-PA3U (Hitachi Ltd, Tokyo, Japan)

The reusable EZU-PA3U puncture guide fixture is available for attachment to either the Hitachi CC41R or C41L47RP biplane transducers. The needle holder can slide vertically within the guide and the fixing screw is secured to keep it firmly in the intended position. The scale on the puncture guide fixture is marked with 0.5 cm divisions ranging from 1 to 5 cm. The puncture guide fixture is compatible with 14- and 18-gauge needles.

Care pathway

Figure 1 illustrates the current NICE pathway for people referred to specialist care for suspected prostate cancer.[16] Following referral [e.g. from a general practitioner (GP)], individuals follow different pathways based on key decision points, which can be summarised as follows:

- Pre-biopsy imaging to determine whether or not a biopsy is necessary at that time.
- Initial biopsy to detect the absence or presence of prostate cancer. This is where a transperineal or a TRUS approach to biopsy would be considered.
- If the biopsy is negative but there is ongoing suspicion of prostate cancer, a re-biopsy may be done after an appropriate interval.
- If the initial biopsy (or re-biopsy) is positive it may be termed CS/insignificant based on a risk classification incorporating biopsy core length and cancer grade. The level of significance reflects the predicted spread of the cancer over time and is informative when deciding to undergo active surveillance, or radical treatment.

Clinically significant prostate cancer

When prostate cancer is diagnosed, it is often distinguished in terms of whether the cancer is CS or insignificant. The purpose is to assess how rapidly the cancer will progress and, hence, whether to recommend active surveillance or active treatment. Expert clinical opinion suggests there is no universally agreed definition of the term CS prostate cancer. There are varying definitions available in the literature. For example, clinicians at University College London (UCL) devised criteria for defining CS cancer, as localised cancer with a maximum total cancer core length of 10 mm, a maximum cancer core length of 6 mm and a Gleason score of at least 4 + 3 or 3 + 5 (UCL definition 1). A second set of criteria from this group defines CS cancer as a maximum total cancer core length of 6 mm, a maximum cancer core length of 4 mm and a Gleason score of at least 3 + 4 (UCL definition 2). These criteria have been used in clinical trials assessing different prostate biopsy modalities, including the PROMIS trial in the UK, which examined the diagnostic accuracy of mpMRI and TRUS biopsy in prostate cancer.[17]

The NICE clinical guideline prostate cancer diagnosis and management (NG131) defines CS prostate cancer as any prostate cancer of Gleason score 7 and above.[18]

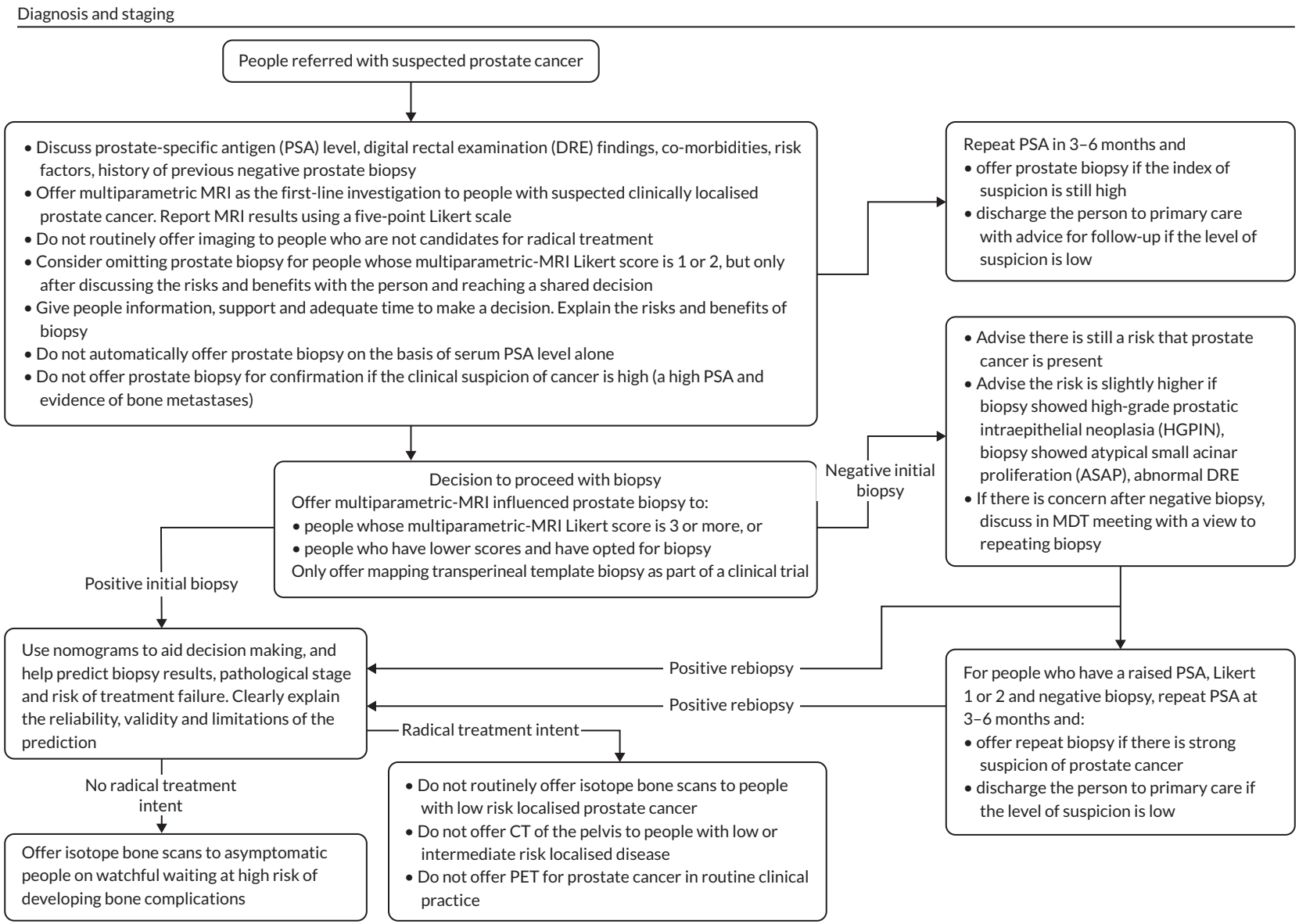

FIGURE 1 NICE pathway for diagnosing and staging prostate cancer.Reproduced from NICE guideline (NG131), Algorithm 1: diagnosis and staging.[16] CT, computed tomography; MDT, multidisciplinary team; MRI, magnetic resonance imaging; PET, positron emission technology.

Chapter 2 Definition of the decision problem

One of the potential benefits of more widespread use of local anaesthetic transperineal (LATP) biopsies in clinical practice would be fewer serious infections associated with puncture of the rectum by the biopsy needle during TRUS biopsy. Fewer infections will reduce the need for preventive antibiotics and the need for antibiotic treatment of infection-related hospital admissions. Another potential benefit of LATP compared to a TP approach conducted under general anaesthetic transperineal (GATP) biopsy is that the use of a limited number of access points in LATP biopsy could reduce pain during and after the biopsy and would release some operating-theatre time. The basis of this diagnostic assessment therefore is to evaluate the empirical evidence in support of these proposed benefits using an economic (cost-effectiveness) decision-making perspective, to inform guidance to the NHS.

The NICE scope for this assessment includes two decision questions, which have been developed and prioritised by NICE in consultation with relevant stakeholders.

Decision question 1. Do LATP prostate biopsies in patients with suspected prostate cancer represent a clinically and cost-effective use of NHS resources?

Decision question 2. Do freehand TP devices for LATP prostate biopsies in patients with suspected prostate cancer represent a clinically effective and cost-effective use of NHS resources?

These two questions comprise the decision problem for this assessment. The following subsections define the parameters relevant to the decision problem.

Population and relevant subgroups

The relevant population for this assessment is people with suspected prostate cancer where prostate biopsy is indicated. People who have already been diagnosed with prostate cancer are not included (e.g. those receiving treatment for prostate cancer and those whose cancer is being monitored by either active surveillance or watchful waiting). People presenting with metastatic prostate cancer are also not included.

The intervention

The intervention relevant to this assessment is LATP prostate biopsy conducted using any of the following methods:

- a grid and stepping device
- a coaxial needle ('double freehand')
- a freehand device within the NICE scope for this appraisal.

Details of these three types of biopsy are given above in *Description of the diagnostic technologies under assessment*. To recap, the six freehand devices within the NICE scope of this assessment are: PrecisionPoint, EZU-PA3U, CamPROBE, Trinity Perine, SureFire Guide and UA1232.

The comparator

There are three comparators relevant to this assessment:

- local anaesthetic transrectal ultrasound biopsy (LATRUS)
- LATP biopsy using a grid or template and stepping device
- GATP using a grid or template and stepping device.

Details of these three types of biopsy are given above in *Description of the diagnostic technologies under assessment*.

For each of these three comparators the biopsy could be 'targeted' (i.e. mpMRI is used to identify lesions from which a small number of tissue samples or cores are taken) or 'systematic' (multiple samples are taken from different regions of the left and right side of the prostate).

Two of the three comparators apply to decision question 1, and all three comparators apply to decision question 2 as detailed in *Table 1*. *Figure 2* depicts each of the five pairwise comparisons according to their relevant decision question.

Outcomes

The outcomes of relevance to the decision problem are grouped into three overarching categories reflecting the effects of the biopsy procedure itself and the interpretation of the biopsy result and its impact on subsequent healthcare decisions.

Intermediate outcomes can include measures of diagnostic accuracy (e.g. sensitivity and specificity), cancer detection rates (CS/insignificant); low-, medium-, high-risk cancer detection rates; biopsy sample suitability/quality; number of biopsy samples taken; procedure completion rates and re-biopsy events within 6 months.

Clinical outcomes evaluate unintended adverse effects associated with prostate biopsy. These include short-term (acute) events including hospitalisation events after biopsy, rates of biopsy-related complications (infection, sepsis and haematuria), and rates of urinary retention. Medium- to longer-term

TABLE 1 Interventions and comparators for each decision question

Decision question	Decision question
1. Do LATP prostate LATP biopsies in people with suspected prostate cancer represent a clinically and cost-effective use of NHS resources?	2. Do freehand TP devices for LATP prostate biopsies in people with suspected prostate cancer represent a clinically and cost-effective use of NHS resources?
Intervention LATP biopsy using a grid and stepping device, a coaxial needle ('double freehand') or a freehand device within the NICE scope	**Intervention** LATP biopsy using a freehand TP device within the NICE scope
Comparator LATRUS	**Comparator** LATRUS
Comparator GATP biopsy using a grid and stepping device	**Comparator** GATP biopsy using a grid and stepping device
	Comparator LATP biopsy using a grid and stepping device

Note
The shaded cell indicates that the comparator does not apply to this decision question.

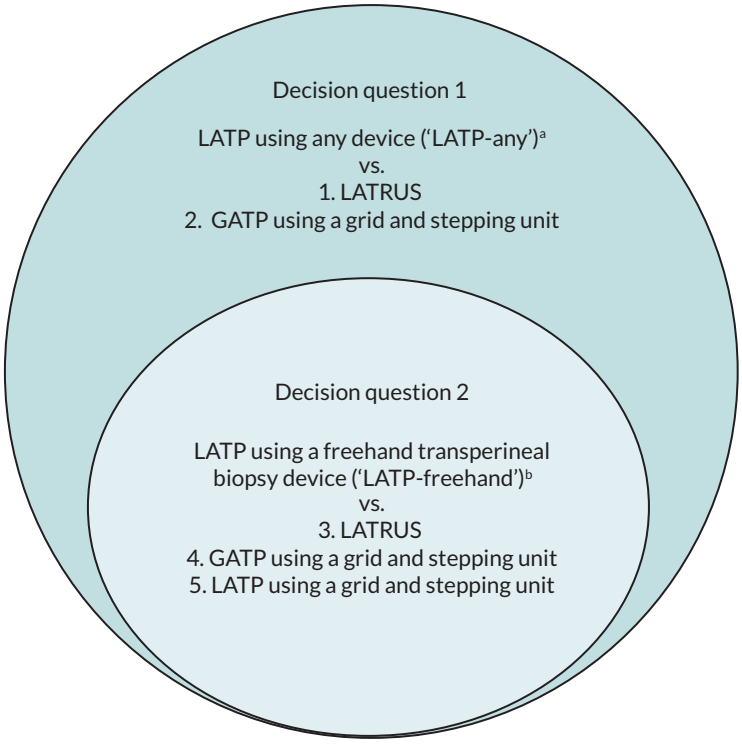

FIGURE 2 Visual summary of the decision problem for this assessment. GATP is general anaesthetic transperineal biopsy; LATP is local anaesthetic transperineal biopsy; LATRUS is local anaesthetic transurethral biopsy. a, A grid and stepping device; a coaxial needle ('double freehand') or a freehand device within the NICE scope (see b). b, Freehand devices: PrecisionPoint™ (BXTAccelyon) or UA1232 (BK Medical) or Trinity® Perine (KOELIS®) or CamPROBE (JEB) or SureFire Guide (LeapMed) or EZU-PA3U (Hitachi))

measures include rates of erectile dysfunction, survival (including progression-free survival) and adverse events from prostate cancer treatment (in patients the biopsy diagnosed as having prostate cancer).

Patient-reported outcomes evaluate aspects that have an impact on patients on a personal and/or functional level. These reflect the experience of the biopsy itself, including tolerability (taking into account pain and discomfort) and also the longer-term impacts on health-related quality of life (HRQoL).

Overall aims and objectives of the assessment

The aim of this diagnostic assessment is to estimate the clinical effectiveness and cost-effectiveness of LATP prostate biopsies performed with or without available specialist devices and equipment (e.g. a grid and stepping unit), in people with suspected prostate cancer. The results will inform NICE guidance to the NHS on use of this diagnostic technology.

The objectives of this diagnostic assessment are as follows:

1. To conduct a systematic review of diagnostic test evaluation and clinical effectiveness of LATP prostate biopsies compared to alternative biopsy modalities in people with suspected prostate cancer.
2. To conduct systematic reviews of evidence to inform a health economic evaluation of LATP prostate biopsies. We will conduct a systematic review of cost-effectiveness studies of LATP prostate biopsies in people with suspected prostate cancer and of HRQoL (utility) studies. We will take a systematic approach to identifying relevant resource use and cost data relating to the diagnosis, monitoring and treatment of prostate cancer.
3. To conduct a health economic evaluation using decision-analytic modelling to assess the incremental cost-effectiveness of LATP prostate biopsies compared to alternative biopsy modalities in people with suspected prostate cancer.

Chapter 3 Methods of clinical and diagnostic assessments

The proposed methods to produce the systematic review of diagnostic test evaluation and clinical effectiveness were reported a priori in a published research protocol (PROSPERO registration number 266443). The final protocol was published on the NICE website shortly after the final scope of this assessment was published in June 2021. The following subsections report further detail on the methods used, noting instances where changes to the protocol were necessary, with a suitable justification.

Identification of studies

Comprehensive, systematic literature search strategies were designed and tested by an experienced information specialist from the project team to inform searches for the systematic review of diagnostic test evaluation and clinical effectiveness, and systematic reviews of cost-effectiveness evidence and economic model input parameters (see *Chapter 5*). The draft strategy for diagnostic test evaluation and clinical effectiveness was piloted on MEDLINE. We examined the relevance of the references identified, and whether any relevant evidence was not identified. The search terms and combined sets of terms were revised iteratively until an acceptable balance of sensitivity (comprehensiveness) and specificity (precision) of search results was achieved, upon which the strategy was finalised and implemented.

Health and medical research database searches were performed on 9 July 2021 on the following databases: MEDLINE (including Epub Ahead of Print, In-process & Other Non-indexed Citations); EMBASE; the Cochrane Database of Systematic Reviews (CDSR); the Cochrane CENTRAL register of controlled trials; Web of Science; the International Health Technology Assessment Database (INAHTA); the Database of Abstracts of Reviews of Effects (DARE); the NHS Economic Evaluations Database (NHS EED); Epistemonikos; Open Grey; and PROSPERO.

Databases of research in progress were searched on 10 June 2021: ClinicalTrials.gov, National Institute for Health and Care Research (NIHR) Be Part of Research and the NIHR Clinical Research Network Portfolio. We re-ran all of the above database searches on 19 October 2021 to identify relevant references added in the 3 months since our first search.

The proceedings of four international urology conferences were hand-searched in June 2021 covering the period from January 2018 to June 2021: American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium; American Urologic Association (AUA) Annual Meeting; BAUS Annual Scientific Meeting; European Association of Urology (EAU) Annual Meeting.

We screened the reference lists of relevant systematic reviews identified by the database searches, to identify any additionally relevant primary studies we had not already found from the above searches. Likewise, we examined the evidence submissions to NICE from manufacturers and/or distributors of the freehand TP devices, to identify any additionally relevant primary studies. We also screened references brought to our attention by our clinical experts and NICE specialist committee members.

Further details on literature searching, including the full search strategy applied to each database, are reported in *Appendix 1*.

Inclusion and exclusion criteria

The predefined inclusion and exclusion criteria are based on the decision problem as outlined earlier in *Chapter 2*, and are described below. An extended PICO (population, intervention, comparator, outcome) tabulation of these criteria is included in *Table 50*, *Appendix 2*. This table is the basis of the worksheet we used to systematically apply the criteria to each study screened.

Population

The relevant population is people with suspected prostate cancer where prostate biopsy is indicated. People included in the review may have a clinical suspicion of prostate cancer (e.g. raised PSA level or abnormal DRE findings), or people may have had a previous prostate biopsy that was negative for prostate cancer but have a continued clinical suspicion. People are not included if they have already been diagnosed with prostate cancer and are receiving treatment or monitoring by active surveillance or by watchful waiting, and likewise people are not included if they are known to have metastatic prostate cancer.

Interventions and comparators

Local anaesthetic transperineal prostate biopsy is the diagnostic procedure relevant to this review, and for the purposes of this report is considered as the intervention. The relevant LATP procedures vary according to two separate (though related) decision questions.

- **Decision question 1** compares any LATP prostate biopsy procedure versus LATRUS prostate biopsy or versus GATP prostate biopsy. For example:
    - LATP using a grid and stepping unit
    - LATP using a coaxial needle ('double freehand')
    - LATP using a freehand TP device (see decision question 2).

The comparison of LATP versus LATRUS assess differences/similarities in diagnostic and clinical outcomes between the transperineal and transrectal prostate biopsy respectively, both using local anaesthetic. The comparison of LATP versus GATP assesses differences or similarities in diagnostic and clinical outcomes between different anaesthetic modalities used during the transperineal prostate biopsy.

- **Decision question 2** compares LATP using any of the six freehand devices listed below versus LATRUS, GATP or LATP using a grid and stepping unit (NB: name of the company making/distributing the device in parentheses):
    - PrecisionPoint (BXTAccelyon)
    - UA1232 (BK Medical)
    - Trinity Perine (KOELIS/Kebomed)
    - CamPROBE (JEB)
    - SureFire Guide (LeapMed)
    - EZU-PA3U (Hitachi).

As evident from the above, the intervention relevant to decision question 2 (LATP using any of the six freehand devices) is nested within the broader range of biopsy interventions relevant to decision question 1 (any LATP prostate biopsy procedure). The comparators relevant to decision question 2 overlap with those relevant to decision question 1, but additionally, include LATP using a grid and stepping device (see *Table 1* for a summary of the above).

No restriction was placed on the inclusion of specific biopsy protocols and procedures, such as number of biopsy cores taken, or whether prostate biopsy sampling was systematic and/or targeted, and

whether mpMRI was used to determine whether a prostate biopsy is needed, and, if so, which prostate lesions should be targeted for core sampling. Cognitive fusion biopsies, also known as visual registration biopsies, were eligible, whereas software-based fusion biopsies were not. Biopsy techniques using sedation in place of local or general anaesthetic were not included.

Outcomes

We categorised relevant outcome measures according to which aspect of the prostate biopsy they evaluate, following the same approach used in the NICE scope for this diagnostic assessment. Our synthesis of the results of the studies is structured according to these categories for consistency and ease of report navigation (see *Intermediate outcomes*, *Clinical outcomes* and *Patient-reported outcomes*).

Intermediate and diagnostic outcomes of relevance were: measures of diagnostic accuracy (e.g. sensitivity/specificity); cancer detection rates; CS cancer detection rates; clinically insignificant cancer detection rates; low-, medium-, high-risk cancer detection rates; biopsy sample suitability/quality; number of biopsy samples taken; procedure completion rates; re-biopsy events within 6 months and length of time to perform the biopsy procedure (we added the latter outcome to inform biopsy cost estimates for potential inclusion in our economic model to assess cost-effectiveness; see *Economic analysis*).

Clinical effectiveness outcomes of relevance were hospitalisation events after biopsy; rates of biopsy-related complications, including infection, sepsis and haematuria; rates of urinary retention; rates of erectile dysfunction; survival; progression-free survival; adverse events from treatment.

Patient-reported outcome**s** of relevance were HRQoL and patient-reported tolerability. We added biopsy procedure time to the inclusion criteria for outcomes because it impacts on the cost of the procedure.

Study design

Any primary comparative research study evaluating the biopsy methods outlined in the 'Interventions and comparators' subheading above is included. We noted single-arm evaluations of LATP biopsy during screening so that we could potentially include them if there was insufficient available comparative evidence.

Inclusion screening process

At the first stage of screening, two reviewers independently applied the above criteria to the titles and abstracts using an inclusion/exclusion worksheet (see *Table 50*, *Appendix 2*). Any disagreements between reviewers in judgements about study eligibility were resolved through discussion or with the opinion of a third reviewer where necessary.

At the second stage of screening one reviewer screened the full texts of references judged potentially relevant on title and abstract screening. A second reviewer checked the first reviewer's judgement on eligibility based on the full text. The reviewers discussed any discrepancies in judgement and before agreeing a final decision to include or exclude the reference. Where study eligibility remained unclear due to missing information to inform reviewers' judgement, we contacted the authors of the study and requested the required information.

To ensure consistency between reviewers in the application of the inclusion/exclusion criteria, the Evidence Assessment Group (EAG) developed decision rules to be followed when screening studies with complex characteristics or ambiguously reported procedures.

- **Mixed populations:** for example, a study population comprising people with clinical suspicion of prostate cancer and people on active surveillance following a previous diagnosis of prostate cancer. Such studies were eligible if:
    - the outcomes of relevance to this review were reported separately by participant subgroup, allowing us to extract only outcome data for the relevant subgroup, or
    - the proportion of the study population relevant to this review was at least 70%, based on a pragmatic threshold for inclusion agreed by the EAG.
- **Mixed types of anaesthesia:** for example, a study in which some participants chose local anaesthesia for their biopsy and others chose general anaesthesia. We used the same decision rule as for mixed populations above. That is, we included if relevant outcomes were reported separately for participants having local and general anaesthesia, or if the proportion of participants in the study who received the anaesthesia relevant to the comparison of relevance to this review was at least 70%.
- **Definitions of local anaesthesia:** described variously in the literature as local anaesthetic, spinal anaesthetic, periprostatic anaesthetic, periprostatic nerve block, caudal nerve block, etc. Consultation with our clinical experts confirmed that pain relief given in the region around the prostate could be described as a local anaesthetic procedure. We therefore used this as a decision rule for local anaesthesia when applying inclusion criteria. We did not include studies describing use of sedation rather than local anaesthesia.
- Of note, NICE subsequently queried whether it is clinically appropriate to consider spinal anaesthesia and caudal block (used in two included trials) as local anaesthetic. We therefore excluded these two trials from our economic base case and retained them in scenario analyses, as will be discussed in *Cancer detection rates*.
- **Intraparticipant biopsy comparison:** if a study performed transperineal and transrectal biopsies simultaneously (i.e. in the same session) on the same participant, the study was eligible for inclusion if relevant outcomes for each biopsy approach were reported separately.

Data-extraction strategy

Relevant data were extracted from each included study, including study design and methods, the socio-demographic characteristics and health and disease status of the study population, the intervention (i.e. the biopsy), and comparator(s) evaluated and the study outcomes. Each study underwent data extraction by a single reviewer, using a structured and piloted data-extraction form (see *Appendix 3* for the data-extraction template). The extracted data were checked for accuracy and interpretation by a second reviewer, and any discrepancies between them were resolved through discussion. The finalised data-extraction form for each study comprised information identified from one or more publications describing that study, as applicable (NB: these can be made available on request).

Critical appraisal of study methodology

As stated in the research protocol, we planned to use the quality assessment of diagnostic accuracy studies (QUADAS) 2 tool to appraise the risk of bias of diagnostic test evaluation studies.[19] The tool assesses risk of bias and applicability across four key study domains relating to diagnostic evaluation: patient selection, index test, reference standard, and flow of patients through the study and timing of the index test(s) and reference standard. We began piloting QUADAS 2 on a sample of included studies but found that many of the questions were not applicable. For example, the reference standard domain features questions relating to the standard's accuracy in correctly classifying disease, biases arising in the interpretation of reference standard results and the applicability of the reference standard to the condition under evaluation. As we report later (see *Results of clinical and diagnostic assessments*), studies meeting our inclusion criteria did not evaluate prostate biopsy in terms of diagnostic/prognostic

accuracy and the use of a reference standard was rarely mentioned. Instead, the studies compared LATP prostate biopsy against comparators across a range of intermediate, clinical and patient-reported outcomes, reflecting a broader focus of investigation beyond diagnostic accuracy. It is for these reasons we decided not to use QUADAS 2 as a critical appraisal instrument in the review.

We assessed the internal validity of randomised controlled trials (RCTs) using the Cochrane risk of bias tool, version 1.[20] This is a validated and widely used tool designed for use in systematic reviews to assess the potential risk of bias in RCTs of health interventions. The tool covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias (as relevant).

Non-randomised (observational) studies were appraised using The Joanna Briggs Institute (JBI) critical appraisal checklist for cohort studies/case series studies (as applicable).[21] These checklists are comprehensive in their consideration of potential risks of bias that affect observational studies. They cover factors such as similarity of study groups, measures to identify and address confounding variables, validity and reliability of data collection and analysis, loss to follow-up and addressing incomplete follow-up/missing data, and appropriateness of statistical analyses. We edited questions two and three in the checklist for cohort studies to replace 'exposures' with relevant biopsy details.

We consider the aforementioned tools for random and non-randomised evidence are relevant and comprehensive for an informed critical appraisal of the studies included in this diagnostic assessment. Omission of a diagnostic test-specific critical appraisal instrument from this review does not imply that relevant aspects of diagnostic evaluation validity have been overlooked. The results of our critical appraisal are summarised in *Results of critical appraisal of study methodology* and reported in full in *Appendix 9*.

Method of data synthesis

We summarised the characteristics of the included studies and study outcomes through a structured narrative synthesis. Numerical and statistical data were tabulated and summarised in the text. We assessed the appropriateness and feasibility of meta-analysis, taking into account factors including the availability of necessary study data and the degree of clinical and statistical heterogeneity across the included studies. We performed pairwise meta-analysis for the prostate biopsy comparisons relevant to the decision problem for the outcome of cancer detection rates, expressed as relative risk (RR). This outcome was selected because it directly informs estimates of biopsy clinical effectiveness in our economic model (see *Economic analysis*). Furthermore, cancer detection rates were the most consistently reported of the outcomes across the included studies, thus providing sufficient data for a meaningful meta-analysis.

We used Stata 17 (College Station, TX, USA) software to conduct pairwise meta-analysis of cancer detection rates, expressing effects as RRs with 95% confidence intervals (CIs). We conducted pairwise meta-analyses for each biopsy comparison relevant to the decision problem (e.g. LATP vs. LATRUS), where data were available. We analysed randomised and non-randomised studies separately, as recommended by methodological guidance,[22] but we pooled both types of evidence for exploratory analysis purposes. This exploratory analysis assumed equal study weights regardless of design, which is clearly a limitation.

Where a connected study network was present, we performed indirect comparisons of the biopsy modalities via network meta-analysis (NMA). The purpose was to provide relative treatment effect estimates (cancer detection rates) to inform an incremental assessment of the biopsy modalities in our economic analysis (see *Model parameters*). The NMA was restricted to RCTs and was conducted using MetaInsight software using the frequentist *netmeta* package.[23] Effect estimates were presented as RRs, with LATRUS as the reference treatment. We used random effects (random-effects maximum likelihood REML) in preference to fixed-effect models due to apparent clinical heterogeneity between studies.

Chapter 4 Results of clinical and diagnostic assessments

Quantity and validity of research available

Initial literature searches (reported in *Identification of studies* and *Appendix 1*) identified a total of 1969 potentially relevant references after duplicate references were removed. Independent screening of titles and (where provided) abstracts by two reviewers determined that 1858 of these references did not meet the inclusion criteria, while the full texts of the remaining 111 references were obtained for further screening. Of the 111 full texts, it was unclear whether 36 met our inclusion criteria. Of the 36 unclear full texts, we were able to contact the authors of 32 for clarification. We received author clarification responses for 15 of the 32 full texts; two authors provided us with an additional full text each, and two confirmed they did not have access to the data to answer our clarification questions. The authors of the remaining 17 full texts did not respond.

Comparative studies were identified for one of the six freehand biopsy devices within the scope of this review (PrecisionPoint). We therefore modified our inclusion criteria to include single-arm (i.e. non-comparative) studies for the remaining five freehand devices, when reported. We considered that these studies may be informative to the NICE diagnostics advisory committee's consideration when the only alternative would be no evidence at all for these devices.

Update searches (reported in *Identification of studies* and *Appendix 1*) identified a further 37 unique references that were independently screened by two reviewers, of which 31 did not meet our inclusion criteria and 6 (all conference abstracts, none reporting RCTs) reported insufficient information to determine eligibility. Authors of all six abstracts were contacted for clarification, of whom two responded.

In summary, the combined July 2021 and October 2021 searches of literature and other sources identified a total of 2008 references of which 1889 were excluded after screening titles and abstracts. Of 119 references subjected to full-text screening, 65 were excluded, the majority for reporting an intervention not relevant to the scope (reasons for exclusion are given in *Appendix 3*). A further 27 references did not report sufficient information to fully inform a screening decision to include or exclude. The remaining 27 publications reported a total 23 studies meeting the inclusion criteria for this systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow chart in *Figure 3* shows the flow of records through the stages of inclusion/exclusion screening.

Table 2 lists the 23 included studies according to their relevant decision question(s), organised by pairwise comparisons, and stratified by study design. The comparison with the largest number of studies was 'LATP-any' [i.e. prostate biopsy using a grid and stepping device, a coaxial needle ('double freehand') or a freehand device within the NICE scope] versus LATRUS (n = 15 studies). Far fewer studies compared LATP-any versus GATP using a grid and stepping device (n = 4 studies). Nested within the LATP-any group is a subset of studies comparing LATP prostate biopsy using a freehand transperineal device (LATP-freehand) versus LATRUS (n = 7 studies). This comparison is the focus of decision question 2; hence these seven studies appear twice in *Table 2* (bold type is used to highlight this). Of the six freehand TP devices in the NICE scope, relevant comparative evidence was identified for just one device, PrecisionPoint. Single-arm non-comparative studies were included for the remaining devices where available.

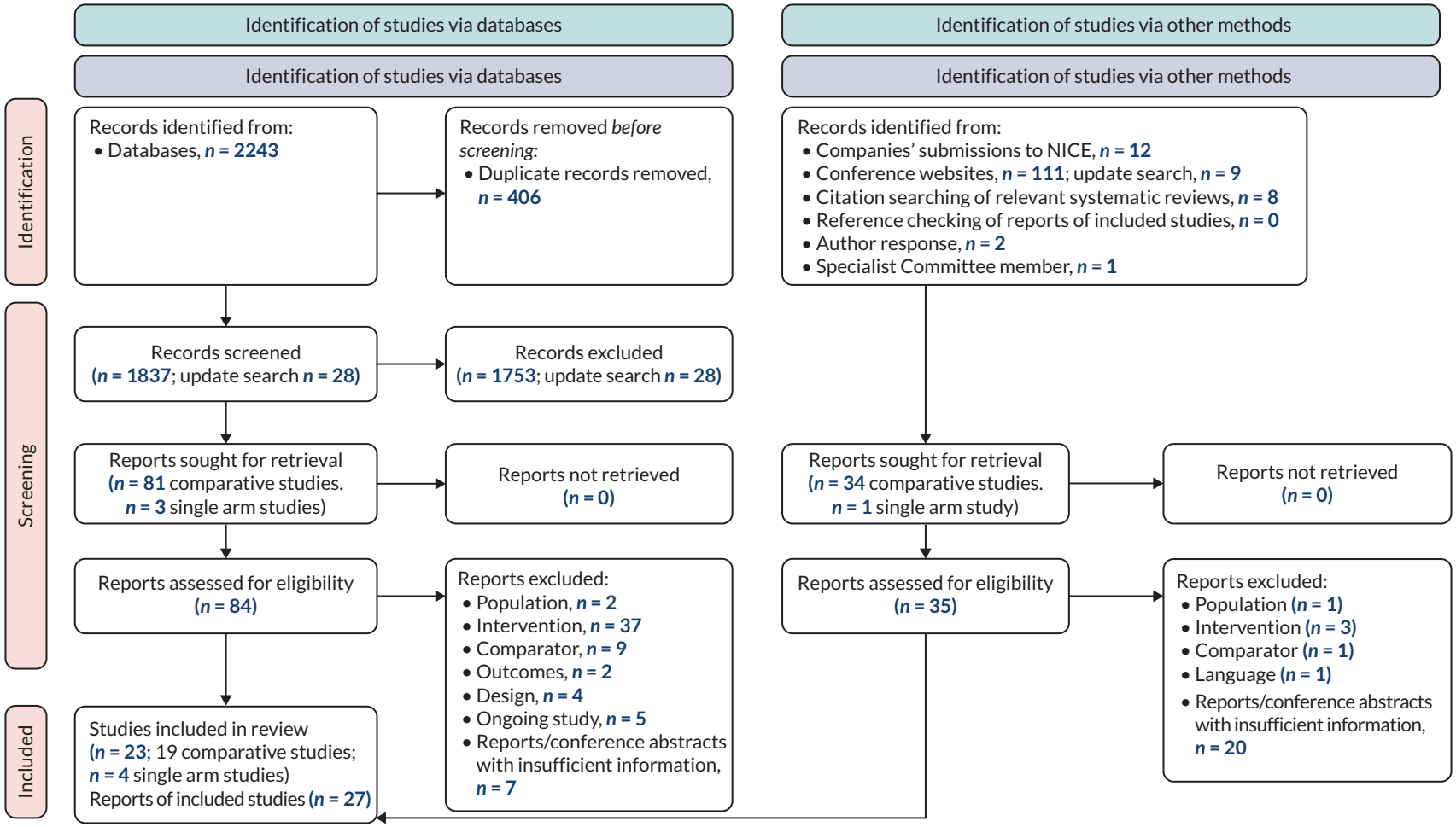

FIGURE 3 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow chart.

TABLE 2 Overview of included studies by decision question and comparison

Decision question 1	**Decision question 2**
Intervention: LATP biopsy using a grid and stepping device, a coaxial needle ('double freehand'), or a freehand device within the NICE scope. ('LATP-any')	**Intervention: LATP biopsy using a freehand TP device within the NICE scope. ('LATP-freehand')**
Comparator: LATRUS (*n* = 15 studies) • 5 RCTs ◦ Cerruto 2014[24] ◦ Guo 2015[25] ◦ Hara 2008[26] ◦ **Lam 2021 (AB)[27]** ◦ Takenaka 2008[28] • 7 non-randomised prospective studies ◦ **Bojin 2019 (unpublished slide set)[29]** ◦ **Chen 2021**[30,31] ◦ Emiliozzi 2003[32] ◦ **Hung 2020 (AB)[33]** ◦ **Kum 2018 (AB)**[34,35] ◦ **Starmer 2021**[36,37] ◦ Watanabe 2005[38] • 3 retrospective studies ◦ Abdollah 2011[39] ◦ Jiang 2019[40] ◦ **Szabo 2021**[a,41]	**Comparator: LATRUS** (*n* = 7 studies) • 1 RCT ◦ **Lam 2021 (AB)[27]** (PrecisionPoint) • 5 non-randomised prospective studies ◦ **Bojin 2019 (unpublished slide set)[29]** (PrecisionPoint) ◦ **Chen 2021**[30,31] (PrecisionPoint) ◦ **Hung 2020 (AB)[33]** (PrecisionPoint) ◦ **Kum 2018 (AB)**[34,35] (PrecisionPoint) ◦ **Starmer 2021**[36,37] (PrecisionPoint) • 1 retrospective study ◦ **Szabo 2021**[a,41] (PrecisionPoint)
Comparator: GATP using a grid and stepping device (*n* = 4 studies) • 1 RCT ◦ Lv 2020[42] • 2 non-randomised prospective studies ◦ Takuma 2012 (AB)[43] ◦ Walters 2021 (AB)[44] • 1 retrospective study ◦ **Rij 2020 (AB)[45]**	**Comparator: GATP using a grid and stepping device** (*n* = 1 study) • 1 retrospective study ◦ **Rij 2020 (AB)[45]** (PrecisionPoint)
	Comparator: LATP using a grid and stepping device No studies met inclusion criteria
	Comparator: None[b] • 4 prospective single-arm studies: ◦ Gnanapragasam 2020[46] (CamPROBE) ◦ Lau 2020 (AB)[47] (UA1232) ◦ Yamamoto 2019 (AB)[48] (UA1232) ◦ Yamamoto 2020 (AB)[49] (UA1232)

a The Szabo *et al.* study comprised three intervention cohorts with two relevant pairwise comparisons: LATP using PrecisionPoint vs. LATRUS, and LATP using a coaxial needle sheath vs. LATRUS.
b Single-arm studies of freehand biopsy devices within the NICE scope are included only for those devices where no comparative evidence was identified.

Notes
(AB) denotes study only available as a conference abstract at the time of writing.
NB: shaded cells indicate that the comparator does not apply to this decision question; bold font indicates the same study is relevant to both decision questions.

Characteristics of studies comparing local anaesthetic transperineal biopsy by any method versus local anaesthetic transrectal ultrasound prostate biopsy (decision question 1)

Overview of general study characteristics

Table 3 gives an overview of the LATP prostate biopsy versus LATRUS biopsy studies included in the review.

Of the 15 included studies comparing LATP-any versus LATRUS biopsies, 5 are RCTs, 7 prospective cohort studies and 3 retrospective cohort studies.

The RCTs were conducted in Japan,[26,28] China,[25] Hong Kong[27] and Italy,[24] and all were single-centre studies. The participants in all RCTs were prostate biopsy naïve with suspected prostate cancer, and no study reported any pre-biopsy mpMRI. The LATP techniques varied: one study used a coaxial needle,[24] another used an unnamed attachment for needle guidance,[28] another used PrecisionPoint[27] and two studies did not specify a device.[25,26]

The seven prospective cohort studies are all single-centre studies, set in England,[29,34–36] Hong Kong,[33] Japan,[38] Singapore[30,31] and Italy.[32] They comprise two studies which carried out both transperineal and transrectal biopsies in the same participants in the same session,[32,38] three studies where the LATRUS arm is a historical comparison group,[29–31,34,35] one study that assigned participants to study arms according to pre-biopsy MRI findings and other criteria,[36,37] and one study that does not report how it assigned participants to study arms.[33]

The participants in the three English prospective cohort studies are a mixed population of those who were biopsy naïve, those who were undergoing repeat biopsy and a small proportion of participants on active surveillance. In all the other studies participants were exclusively prostate biopsy naïve. All English studies used the PrecisionPoint device to perform LATP,[29,34–37] as did the Hong Kong study,[33] and the earlier studies do not report any device.[32,38]

One of the studies[33] is reported only in a conference abstract and another is an unpublished slide-set presentation[29] and so they have limited information. The other studies are reported in full publications.

The retrospective studies were set in Italy,[39] China[40] and the USA.[41] The Italian and Chinese studies were multicentre (two-centre) studies where LATP was performed at one centre and LATRUS was performed at the other. The USA study is a single-centre study. One study population consists entirely of repeat biopsy participants[39] one study consists entirely of biopsy naïve participants,[40] and one study included a mixed population of biopsy naïve, repeat biopsy and active surveillance participants.[41] Two studies performed propensity score matching of the participants: one study reports propensity score matched results only[39] and the other reports both the unmatched and propensity score matched results.[40] The LATP techniques varied according to device used: one study used a coaxial needle,[39] one study used the PrecisionPoint freehand device[41] and one study did not report using a device.[40]

Details of local anaesthetic transperineal prostate-any biopsy procedures

Table 53 in *Appendix 4* gives details of the LATP-any biopsy procedures. Most studies used systematic biopsy sampling, with the number of cores taken (where reported) ranging from 6 to 24 across studies. Two studies based the number of cores taken on the size of the prostate, one by whether or not the prostate volume was above or below 50 ml,[25] and another study reports that the samples were spaced 1 cm apart.[41]

Where targeted biopsy sampling was performed this could be in addition to systematic sampling biopsies, or targeted sampling alone.[34,35] Reasons to prompt additional targeted sampling were:

TABLE 3 Overview of studies comparing LATP-any vs. LATRUS biopsy (decision question 1) (*n* = 15)

Study	Country; no. centres	Design	Intervention	Comparator	Study population
RCTs					
Cerruto *et al.* 2014[24]	Italy; single centre	RCT; *n* = 108 randomised	TRUS-guided LATP biopsy using coaxial needle; *n* = 54	LATRUS biopsy; *n* = 54	Prostate biopsy naïve participants with suspected prostate cancer
Guo *et al.* 2015[25]	China; single centre	RCT; *n* = 339 randomised	TRUS-guided LATP biopsy (device not reported); *n* = 173	LATRUS biopsy; *n* = 166	Prostate biopsy naïve participants with suspected prostate cancer
Hara *et al.* 2008[26]	Japan; single centre	RCT; *n* = 246 randomised	TRUS-guided LATP biopsy (device not reported); *n* = 126	LATRUS biopsy; *n* = 120	Prostate biopsy naïve participants with suspected prostate cancer
Lam *et al.* 2021 (AB)[27]	Hong Kong; single centre	RCT; *n* = 266 randomised	LATP biopsy using the PrecisionPoint freehand device (imaging guidance not reported); *n* = 134	LATRUS biopsy; *n* = 132	Prostate biopsy naïve participants with suspected prostate cancer
Takenaka *et al.* 2008[28]	Japan; single centre	RCT; *n* = 200 randomised	TRUS-guided LATP biopsy using an attachment for needle guidance; *n* = 100	LATRUS biopsy using an attachment for needle guidance; *n* = 100	Prostate biopsy naïve participants with suspected prostate cancer
Other prospective studies					
Bojin 2019[29]	England; single centre	Case series with historical comparison group; *n* = 292	TRUS-guided LATP biopsy using the PrecisionPoint device; *n* = 103	LATRUS biopsy; *n* = 189	Prostate biopsy naïve participants with suspected prostate cancer; participants who underwent repeat biopsy; participants on active surveillance
Chen *et al.* 2021[30,31]	Singapore; single centre	Prospective cohort with historical comparison group; *n* = 390	TRUS-guided LATP biopsy using the PrecisionPoint freehand device; *n* = 212	LATRUS biopsy; *n* = 178	Prostate biopsy naïve participants (> 90%)
Emiliozzi *et al.* 2003[32]	Italy; single centre	Prospective single cohort study; transperineal and transrectal biopsies obtained in all patients in the same session; *n* = 107	TRUS-guided LATP biopsy (device not reported); *n* = 107	LATRUS biopsy; *n* = 107	Prostate biopsy naïve participants with suspected prostate cancer
Hung *et al.* 2020 (AB)[33]	Hong Kong; single centre	Prospective comparative study. How participants were assigned to each arm is not reported; *n* = 120	LATP biopsy using the PrecisionPoint freehand device (imaging guidance not reported); *n* = 63	LATRUS biopsy; *n* = 57	Prostate biopsy naïve participants with suspected prostate cancer

continued

TABLE 3 Overview of studies comparing LATP-any vs. LATRUS biopsy (decision question 1) (*n* = 15) (*continued*)

Study	Country; no. centres	Design	Intervention	Comparator	Study population
Kum *et al.* 2018 (AB)[34,35]	England; single centre	Cohort study with historical comparison group	TRUS-guided LATP biopsy using the PrecisionPoint freehand device; *n* = 176	LATRUS biopsy; *n* = 77	Prostate biopsy naïve participants with suspected prostate cancer; participants who underwent repeat biopsy; participants on active surveillance
Starmer *et al.* 2021[36,37]	England; single centre	Prospective cohort study; participants assigned to intervention or comparator for different reasons; *n* = 108	LATP biopsy using the PrecisionPoint freehand device (imaging guidance not reported); *n* = 56	LATRUS biopsy; *n* = 52	Prostate biopsy naïve participants with suspected prostate cancer; participants who underwent repeat biopsy; participants on active surveillance
Watanabe *et al.* 2005[38]	Japan; single centre	Prospective cohort study; transperineal and transrectal biopsies obtained in all patients in the same session; *n* = 402	Ultrasound-guided LATP biopsy (device not reported); *n* = 402	LATRUS biopsy; *n* = 402	Prostate biopsy naïve participants with suspected prostate cancer
Retrospective studies					
Abdollah *et al.* 2011[39]	Italy; two centres	Retrospective cohort study; *n* = 280 propensity score matched	TRUS-guided LATP biopsy using a coaxial needle; *n* = 140	LATRUS biopsy; *n* = 140	Participants with continued suspicion of prostate cancer who underwent a saturation repeat biopsy
Jiang *et al.* 2019[40]	China; two centres	Retrospective cohort study; *n* = 2962 (*n* = 752 propensity score matched)	TRUS-guided LATP biopsy (device not reported); *n* = 1746 (*n* = 376 propensity score matched)	LATRUS biopsy; *n* = 1216 (376 propensity score matched)	Prostate biopsy naïve participants with suspected prostate cancer
Szabo *et al.* 2021[41]	USA; single centre	Retrospective case series; *n* = 375	(1) Ultrasound-guided LATP biopsy using the PrecisionPoint freehand device *n* = 242; (2) LATP using coaxial needle *n* = 62;	LATRUS biopsy; *n* = 133	Prostate biopsy naïve participants with suspected prostate cancer; participants who underwent repeat biopsy; participants on active surveillance

Note
(AB) denotes study only available as a conference abstract at the time of writing.

suspicious areas detected by TRUS or DRE,[25] any hypoechoic areas noted,[32] PI-RADS score > 2 on pre-biopsy mpMRI,[36,37] hypoechoic lesions or palpable nodules on DRE,[38] or participants with pre-biopsy mpMRI PI-RADS score of 4 or 5.[36]

Additional variations to the biopsy procedures that are not reported above are: any other medications administered or ceased (e.g. anticoagulation medication), whether antibiotic prophylaxis was given (and

how much), what position the participant was in (e.g. lithotomy or dorsal lateral) and where they were performed (e.g. in outpatient clinics or day theatres), thus further illustrating the heterogeneous nature of the biopsy procedures and the studies.

Participant characteristics

Most of the included studies reported age, PSA level, prostate volume and the proportion of participants with abnormal DRE or pre-biopsy imaging findings (see *Table 54*, *Appendix 4*).

Age is reported in various combinations of mean or median with interquartile range (IQR), range or standard deviation (SD), with a mean age of 63–72 years across the studies. PSA level is also reported in various combinations of mean or median with IQR, range or SD. It can be seen that mean PSA levels varied from around 7–8 to 12–19 ml, with one of the retrospective studies having participants with PSA levels 38–40 (Jiang *et al.*).[40] Only five studies reported PSA density.[28–31,34,35,41]

The PI-RADS score, based on pre-biopsy imaging, is only reported in two studies neither of which correspond exactly with the NICE subgroups of interest (people with a Likert or PI-RADS score of 2 or less, or a score of 3, 4 or 5). One study reports the proportion of participants with PI-RADS 2/3, 3/4 and 5 separately, but only for the LATP arm.[34,35] The other reports the proportion of participants with PI-RADS 4 or 5.[41] None reported the location of lesions identified in pre-biopsy imaging.

Two studies reported body mass index,[24,25] one study reported ethnicity.[41] None reported any family history of prostate cancer.

There is not enough evidence to review the efficacy of the biopsy procedures for several of the NICE subgroups (people with anterior lesions; people with posterior lesions; people with apical lesions; people with basal lesions; people with a Likert or PI-RADS score of 2 or less; people with a Likert or PI-RADS score of 3, 4 or 5).

Summary

The comparison of LATP-any versus LATRUS biopsy (decision question 1) is the largest in terms of number of included studies, comprising five RCTs, seven non-randomised prospective studies and three retrospective studies. This is not unsurprising given the broad scope of the LATP-any intervention grouping in this assessment, which encapsulates the spectrum of transperineal prostate biopsy techniques in use. Three studies (non-randomised) were set in England, but many were done in East Asian countries. The vast majority of study participants were prostate biopsy naïve with suspected prostate cancer, with just one study assessing the effects of repeat biopsies in people with suspected prostate cancer who had a previous negative biopsy. The TP biopsy protocols (e.g. device used/sampling method/number of cores taken) varied between studies, which may partly reflect local clinical practice guidelines in study host institutions, but also the evolution of transperineal prostate biopsy practices over time (e.g. increases in the number of cores sampled). Some of the more recently published studies used pre-biopsy mpMRI to inform biopsy sampling, but this constitutes a small proportion of the evidence base as a whole.

Characteristics of studies comparing local anaesthetic transperineal prostate biopsy by any method versus general anaesthetic transperineal prostate biopsy using a grid and stepping device (decision question 1)

Overview of general study characteristics

Table 4 gives an overview of the four studies comparing LATP-any biopsy versus GATP biopsy with grid and stepping device. Three of the studies are available only as conference abstracts currently; thus some of the necessary detail in the following subsections is limited.[43–45]

TABLE 4 Overview of studies comparing LATP-any biopsy vs. GATP with grid and stepping device biopsy (decision question 1)

Study	Country; no. centres	Design	Intervention	Comparator	Study population
RCTs					
Lv *et al.* 2020[42]	China; single centre	RCT; *n* = 216 randomised	TRUS-guided LATP biopsy using a stepper and grid; *n* = 108	TRUS-guided GATP biopsy using a stepper and grid; *n* = 108	All participants were suspected of prostate cancer. Prior biopsy experience is not reported
Other prospective studies					
Takuma *et al.* 2012 (AB)[43]	Japan; single centre	Prospective comparative cohort study; *n* = 66	LATP biopsy (imaging guidance not reported); *n* = 37	GATP biopsy using a template (imaging guidance not reported); *n* = 29	All participants had one or more previous negative biopsies
Walters *et al.* 2021 (AB)[44]	England; single centre	Case series; *n* = 407	LATP biopsy (imaging guidance not reported); *n* = 339	GATP biopsy (imaging guidance not reported); *n* = 68	All participants undergoing TP biopsy identified from a prospective prostate cancer diagnostic registry
Retrospective studies					
Rij and Chapman 2020 (AB)[45]	New Zealand; single centre	Retrospective cohort study; *n* = 143	LATP biopsy using the PrecisionPoint device (imaging guidance not reported); *n* = 72	GATP biopsy using a brachytherapy grid (image guidance not reported); *n* = 71	All participants undergoing TP biopsy. Prior biopsy experience and reasons for suspected prostate cancer are not reported

Note
(AB) denotes study only available as a conference abstract at the time of writing.

Of the four studies, one was a RCT set in China,[42] two were prospective non-randomised studies set in England[44] and Japan[43] respectively, while the fourth was a retrospective study set in New Zealand.[45]

One study[42] used a grid and stepping device to perform LATP biopsy; another performed LATP using the PrecisionPoint freehand device[45] and two studies did not specify use of a device.[43,44]

Details of prior biopsy history were not clearly reported, but in one study it is stated that all participants had previously had one or more negative biopsies.[43]

Details of local anaesthetic transperineal-any biopsy procedures

Table 55 in *Appendix 4* gives details of LATP-any biopsy procedures used. Reporting of details by the studies was limited, but the available information shows that systematic sampling was commonly performed, with additional targeting of cores based on pre-biopsy imaging. Details of image guidance and anaesthesia are limited.

Participant characteristics

Available information on the characteristics of study participants (e.g. age, PSA level, prostate volume) is extremely limited, and only one study gave adequate detail (see *Table 56*, *Appendix 4*).[42]

Summary

This comparison (LATP vs. GATP, decision question 1) is based on a smaller evidence base: one RCT, two prospective observational studies and one retrospective observational study. The location of the studies

is mixed, including two studies done in Asia, and one each from New Zealand and England, respectively. LATP was performed using a grid and stepping device in at least one study, and using a freehand device (PrecisionPoint) in another. Sampling was systematic with additional targeting of cores in some cases. With the exception of the RCT, the other three studies are reported in conference abstracts only, thus limited information is available.

Characteristics of studies comparing local anaesthetic transperineal prostate biopsy using a freehand device versus local anaesthetic transrectal ultrasound prostate biopsy (decision question 2)

Overview of general study characteristics

Seven studies were identified that compare LATP biopsy using a freehand device with LATRUS biopsy. All freehand devices are the PrecisionPoint device; see *Table 10*. In contrast, only one study compares LATP biopsy using a specific freehand device with GATP (n = 1, PrecisionPoint device); see *Table 12*. No studies were identified that compare LATP-freehand with LATP using a grid and stepping device.

As no comparative studies were identified for any devices other than PrecisionPoint, we included single-arm studies for devices where no comparative evidence was available. One study reports a single-cohort study (i.e. with no comparative biopsy group) reporting 'the first in man' evaluation of the CamPROBE device.[46] Three conference abstracts report three separate single-cohort studies that used the UA1232 device.[47–49] See *Table 13*.

Of the seven studies comparing LATP-PrecisionPoint to LATRUS, one is a RCT,[27] five were prospective cohorts[29–31,33–37] and one was a retrospective case series.[41] All studies were single-centre studies, with three conducted in the England, two in Hong Kong, one in Singapore and one in the USA. The English and American studies were of mixed populations, whereas the others were prostate biopsy naïve participants with suspected prostate cancer only, and only two studies reported the number of cores taken during biopsy: 12 cores[30] and 24 cores.[29]

Participant characteristics

Participant characteristics are reported for the LATP freehand device PrecisionPoint versus LATRUS studies and are summarised in *Table 57* in *Appendix 4*.

Summary

The evidence for this comparison (LATP-freehand vs. LATRUS, decision question 2) is a subset of the evidence for the LATP-any versus LATRUS, decision question 1 comparison. All the evidence is for the PrecisionPoint freehand device as the intervention. Included within this set of seven studies is one RCT and the three non-randomised studies set in England.

Characteristics of studies comparing local anaesthetic transperineal prostate biopsy using a freehand device versus general anaesthetic transperineal prostate biopsy by grid and stepping device (decision question 2)

Overview of general study characteristics

Table 6 gives an overview of the single study comparing LATP-PrecisionPoint versus GATP biopsy.[45]

Rij and Chapman report a retrospective cohort study conducted in a single centre in New Zealand.[45] At the current time (November 2021) the study is available publicly only as a conference abstract. The precise details of the study methods and outcomes are therefore limited. This study did not report the indications for biopsy, nor the number of cores taken during the biopsies, nor any participant characteristics.

TABLE 5 Overview of included studies for decision question 2 (LATP using a freehand device vs. LATRUS biopsy)

Study	Country; no. centres	Design	Intervention	Comparator	Study population
RCTs					
Lam *et al.* 2021 (AB)[27]	Hong Kong; single centre	RCT; *n* = 266 randomised	LATP biopsy using the PrecisionPoint device (imaging guidance not reported); *n* = 134	LATRUS biopsy; *n* = 132	Prostate biopsy naïve participants with suspected prostate cancer
Other prospective studies					
Bojin 2019[29]	England; single centre	Case series with historical comparison group; *n* = 292	TRUS-guided LATP biopsy using the PrecisionPoint device; *n* = 103	LATRUS biopsy; *n* = 189	Prostate biopsy naïve participants with suspected prostate cancer; participants who underwent repeat biopsy; participants on active surveillance
Chen *et al.* 2021[30,31]	Singapore; single centre	Prospective cohort with historical comparison group; *n* = 390	TRUS-guided LATP biopsy using the PrecisionPointdevice; *n* = 212	LATRUS biopsy; *n* = 178	Prostate biopsy naïve participants (> 90%)
Hung *et al.* 2020 (AB)[33]	Hong Kong; single centre	Prospective comparative study. How participants were assigned to each arm is not reported; *n* = 120	LATP biopsy using the PrecisionPoint device (imaging guidance not reported); *n* = 63	LATRUS biopsy; *n* = 57	Prostate biopsy naïve participants with suspected prostate cancer
Kum *et al.* 2018 (AB)[34,35]	England; single centre	Cohort study with historical comparison group	TRUS-guided LATP biopsy using the PrecisionPoint device; *n* = 176	LATRUS biopsy; *n* = 77	Prostate biopsy naïve participants with suspected prostate cancer; participants who underwent repeat biopsy; participants on active surveillance
Starmer *et al.* 2021[36,37]	England; single centre	Prospective cohort study; participants assigned to intervention or comparator for different reasons; *n* = 108	LATP biopsy using the PrecisionPoint device (imaging guidance not reported); *n* = 56	LATRUS biopsy; *n* = 52	Prostate biopsy naïve participants with suspected prostate cancer; participants who underwent repeat biopsy; participants on active surveillance
Retrospective studies					
Szabo *et al.* 2021[41]	USA; single centre	Retrospective case series; *n* = 375	Ultrasound-guided LATP biopsy using the PrecisionPoint device and LATP prior to using the PrecisionPoint device; *n* = 242	LATRUS biopsy; *n* = 133	Prostate biopsy naïve participants with suspected prostate cancer; participants who underwent repeat biopsy; participants on active surveillance

Note
(AB) denotes study only available as a conference abstract at the time of writing.

Characteristics of single-arm studies evaluating local anaesthetic transperineal biopsy using a freehand device where no comparative evidence was identified

Overview of general study characteristics

No comparative evidence was identified for the LATP freehand devices CamPROBE, UA1232, SureFire, EZU-PA3U and Trinity Perine Grid. We therefore looked for any relevant single-arm (non-comparative)

TABLE 6 Overview of included studies for decision question 2 (LATP using a freehand device vs. GATP)

Study	Country; no. centres	Design	Intervention	Comparator	Study population
Retrospective					
Rij and Chapman 2020 (AB)[45]	New Zealand; single centre	Retrospective cohort study; *n* = 143	LATP biopsy using the PrecisionPoint device (imaging guidance not reported); *n* = 72	GATP biopsy using a brachytherapy grid (image guidance not reported); *n* = 71	All participants undergoing TP biopsy. Prior biopsy experience and reasons for suspected prostate cancer are not reported

Note
(AB) denotes study only available as a conference abstract at the time of writing.

studies of these freehand devices. We did not identify any relevant single-arm studies with SureFire, the Trinity Perine Grid (for which all the studies we found used software-based fusion techniques outside the scope of this review) or EZU-PA3U. *Table 7* gives an overview of the CamPROBE and UA1232 studies.

The one study evaluating CamPROBE was a prospective single-cohort study (i.e. with no comparative biopsy group) conducted in six centres in England.[46] It has a small (*n* = 40) study population. The

TABLE 7 Overview of included studies for decision question 2 (LATP using freehand device with no comparator group)

Study	Country; no. centres	Design	Intervention	Study population
Prospective studies for CamPROBE				
Gnanapragasam *et al.* 2020[46]	England; multicentre (a lead centre provided training to the five other centres)	Prospective cohort study	LATP using the disposable single-use CamPROBE device	56 men were screened over an 8-month period, and 40 were recruited. No further information reported; *n* = 40 (*n* = 80 biopsies, study counts right and left prostate biopsies separately, i.e. two CamPROBE devices per patient per biopsy)
Prospective studies for UA1232				
Lau *et al.* 2020 (AB)[47]	England; single centre	Prospective cohort study	LATP using a coaxial needle and a transducer-mounted needle guide (BK Medical). Use of UA1232 device as the mounted needle guide is implied by inclusion in the company submission	Prostate biopsy naïve participants with suspected prostate cancer; *n* = 482
Yamamoto *et al.* 2019 (AB)[48]	England; single centre	Prospective cohort study	LATP using a transducer-mounted needle guide and a perineal coaxial needle. Use of UA1232 device is implied by inclusion in the company submission	Prostate biopsy naïve participants with suspected prostate cancer; *n* = 200
Yamamoto *et al.* 2020 (AB)[49]	England. Single centre	Prospective cohort study	LATP using a co-axial needle and transperineal needle guide (BK Medical). Use of UA1232 device as the needle guide is implied by inclusion in the company submission	Prostate biopsy naïve participants with suspected prostate cancer; *n* = 219

Note
(AB) denotes study only available as a conference abstract at the time of writing.

indications for prostate biopsy were not reported and two devices were used per patient per biopsy, for the right and left sides of the prostate, respectively.

The three studies evaluating the UA1232 device are all single-centre prospective single-cohort studies conducted in England.[47–49] The study populations are larger (n = 482, n = 200, n = 219) and all the participants are biopsy naïve. All three studies were identified via the company submission as none of the abstracts explicitly report using the UA1232 device. All are conference abstracts and as such contain limited information.

Participant characteristics

The reporting of participant characteristics for the single-arm studies for CamPROBE and UA1232 is minimal: the CamPROBE study[46] reports participants' median and range for age, and one of the UA1232 studies[47] reports median age and median PSA level.

Summary

The evidence available for LATP-freehand devices specified in the NICE scope, other than the PrecisionPoint device, is limited to single-arm studies: CamPROBE[46] with a small population and UA1232 with limited information from three conference abstracts.[47–49] There is no evidence for the other devices in the NICE scope. Details of study characteristics and participant characteristics are limited.

Results of critical appraisal of study methodology

In this section, we the report results of our critical appraisal of the RCTs included in this systematic review, followed by our critical appraisal of the included observational studies.

Critical appraisal of randomised controlled trials

As mentioned earlier (see *Critical appraisal of study methodology*), we used the Cochrane risk of bias tool (version 1)[20] to critically appraise the six RCTs in our review.[24–28,42] A key finding from this exercise is that we are unable to fully judge the studies' overall risk of bias due to inadequate reporting of study methodological details in the available publications. Commonly, therefore, we recorded 'unclear' risk of bias for studies across the domains, notably those concerning reporting bias (due to selective outcome reporting), detection bias (due to lack of blinding of outcome assessors to type of prostate biopsy performed) and selection bias (due to inadequate randomisation of participants to trial arms, and/or inadequate concealment of the randomisation sequence). However, sufficient detail was available to inform judgements relating to other bias domains, including attrition bias. Overall, we advise caution in the interpretation of these study findings due to uncertainty regarding potential risks to their internal validity. Below is a brief summary of our findings; full details are reported in *Table 59* in *Appendix 5*.

There was a lack of detail given on the methods used for random sequence generation in four of the trials,[24,26–28] leading to uncertainty about whether or not 'true' randomisation had been achieved and selection bias avoided. Likewise, little or no information was given on whether adequate procedures were in place to conceal the random allocation sequence from study personnel, particularly those involved in enrolling participants to the study.

We judged all six trials to be at high risk of performance bias on the reasonable assumption that study participants and investigators knew which type of biopsy procedure participants had been randomly allocated to. This is an unavoidable consequence of this type of intervention, whereby the clinician performing the biopsy cannot be blinded to the type of biopsy the participant has been allocated to.

Likewise, it is unlikely that the study participant would not be informed of their surgical procedure. It is also unclear whether any protocols were in place to reduce the risk of differential behaviours by participants and healthcare providers associated with knowledge of the type of biopsy performed. All six trials were judged at low risk of attrition bias, due to no or minimal reported participant loss to follow-up or study withdrawal.

Our judgements of the risk of bias across the five domains were identical for four of the six RCTs.[24,26–28] The trial by Guo *et al.* was at low risk of bias for the greatest number of domains:[25] specifically, low risk of detection bias due to blinding of the outcome assessor (pathologist), low risk of selection bias due to adequate (computer-generated) randomisation (though we cannot rule out selection bias completely because details of allocation concealment were not reported) and low risk of reporting bias.

Critical appraisal of observational studies

As stated earlier (see *Critical appraisal of study methodology*) we used the checklists from the JBI suite of critical appraisal tools to critically appraise observational studies.[21] Eleven of the 13 observational studies were assessed using the JBI checklist for cohort studies[50] and the remaining 2 studies were assessed using the JBI checklist for case series.[51]

Most of the cohort studies recruited biopsy comparison groups from the same or a similar population. Likewise, the case series reported consecutive/complete inclusion of participants. However, limited reporting of study inclusion criteria and participants' demographic and clinical information means it is unclear how comparable the biopsy groups within the studies are. Confounding factors were identified and handled in only about half of all the studies (both cohort studies and case series); the remainder are mostly unclear. Therefore, we judge the studies to have unclear risk of selection bias.

Follow-up times and methods to deal with loss to follow-up were mostly unclear, raising the potential for attrition bias. However, some key outcomes relevant to this diagnostic assessment are unlikely to be affected by loss to follow-up as they are measured/taken during the biopsy procedure itself (e.g. cancer detection rate based on biopsy samples) or immediately afterwards (e.g. pain questionnaires). Therefore, we judge the risk of attrition bias as low for cancer detection rate and pain/tolerability outcomes, but unclear for other outcomes.

The risk of detection bias was judged as generally low because in almost all the studies the biopsy methods are clearly reported and over half of the studies reported using a protocol or schema for the biopsy procedure. In addition, the cancer detection rate outcome was measured in a valid and reliable way in most of the studies, usually referring to a specific grade group or score. However, there may be a risk of detection bias when considering the validity and reliability of measurement of the other outcomes in several of the studies, for example complications, where for some studies only complications that occurred were reported and no time frame was stated for reporting any complications. Therefore, when considering different outcomes in the studies, detection bias is either low or unclear depending on the outcome in question (as for attrition bias).

There is a high risk of reporting bias (and several other bias domains) in studies available, at the time of writing, only as conference abstracts. Commonly, abstracts are restricted in word limits, prohibiting authors from reporting all intended outcome data. Clarity on reporting bias may improve if full text reports of studies are published (personal communication with study authors indicates that some are in the process of preparing manuscripts for publication). There is lack of clarity around several domains of bias due to the limited amount of information that can be conveyed in a conference abstract.

Our critical appraisal judgements for each cohort study and each case series are presented in *Table 60* in *Appendix 5*.

Intermediate outcomes

Below we present a synthesis of studies measuring the diagnostic yield of LATP prostate biopsy in suspected prostate cancer. We regard the term diagnostic yield as synonymous with cancer detection rates, the most commonly reported outcome measure in the included studies. We take each pairwise biopsy comparison in the decision problem in turn (*Figure 2*) and present cancer detection rates for individual studies and for studies combined in meta-analyses (where meta-analysis was possible).

Prostate cancer detection (local anaesthetic transperineal-any biopsy vs. local anaesthetic transrectal ultrasound, decision question 1)

Prostate cancer detection was the most commonly reported of all the outcome measures relevant to this assessment (*n* = 14 of 15 studies). Only the study by Starmer *et al.* did not report this outcome.[36,37] In marked contrast, CS prostate cancer detection, informative for assessing the risk of rapid cancer progression, was reported in just five studies.[27,29,33–35,41] *Table 8* reports study cancer detection rates, including CS cancer rates, where available.

TABLE 8 Prostate cancer detection rates (LATP-any vs. LATRUS, decision question 1)

Study	Outcome measure	Intervention LATP-any	Comparator LATRUS	Statistical significance (*p*-value)
RCTs				
Cerruto *et al.* 2014[24]	Cancer detection rate, *n*/*N* (%)	24/54 (44.4)	25/54 (46.3)	0.846
Guo *et al.* 2015[25]	Cancer detection rate: positive rate, *n*/*N* (%)	61/173 (35.3)	53/166 (31.9)	0.566
Hara *et al.* 2008[26]	Cancer detection rate, *n*/*N* (%)	53/126 (42.1)	58/120 (48.3)	0.323
Lam *et al.* 2021 (AB)[27]	Cancer detection rate, *n*/*N* (%)	47/134 (35.1)	33/132 (25.0)	< 0.05
	CS cancer detection rate[a]	22/134 (16.4)	19/132(14.4)	*p* = 0.74
Takenaka *et al.* 2008[28]	Cancer detection rates overall, *n*/*N* (%)	47/100 (47.0)	53/100 (53.0)	0.333
Other prospective studies				
Bojin 2019[29]	Cancer detection rates malignant, *n*/*N* (%)	76/103 (73.7)	117/189 (61.9)	Not reported
	Cancer detection rates benign, *n*/*N* (%)	27/103 (26.2)	72/189 (38.1)	Not reported
	CS cancer pick up, *n*/*N* (%)[b]	51/76 (67.1)	48/117 (41.2)	Not reported
Chen *et al.* 2021[30,31]	Cancer detection rate in biopsy naïve patients, *n*/*N* (%)	127/200 (63.5)	86/172 (50.0)	0.0115
Emiliozzi *et al.* 2003[32]	Cancer detection rate, *n*/*N* (%)[c]	43/107 (40.0)	34/107 (32.0)	0.012
Hung *et al.* 2020 (AB)[33]	Cancer detection rate (%)	20/63 (31.7)	14/57 (24.6)	0.851
	CS prostate cancer, (%)	57.1	45.0	0.501
Kum *et al.* 2018 (AB)[34,35]	Cancer detection rate, overall *n*/*N* (%)	139/176 (79.0)	Not reported	Not reported
	CS cancer detection *n*/*N* (%)[d,e] Systematic	28/46 (60.9)	25/43 (58.1)	*p* = 0.80
	Targeted and systematic	29/35 (82.9)	Not reported	Not reported
	Targeted	33/38 (86.8)	Not reported	Not reported

TABLE 8 Prostate cancer detection rates (LATP-any vs. LATRUS, decision question 1) (*continued*)

Study	Outcome measure	Intervention LATP-any	Comparator LATRUS	Statistical significance (*p*-value)
Watanabe *et al.* 2005[38]	Positive biopsy, *n*/*N* (%)	166/402 (41.3)	161/402 (40.0)	Not reported
Retrospective studies				
Abdollah *et al.* 2011[39]	Prostate cancer diagnosis rate, *n*/*N* (%)	36/140 (25.7)	44/140 (31.4)	0.3
Jiang *et al.* 2019[40]	Cancer detection rates Unmatched group	785/1746 (45.0)	524/1216 (43.1)	0.314
	Propensity score matched group	182/376 (48.4)	184/376 (48.9)	0.884
Szabo *et al.* 2021 I[41]	Overall cancer detection rate, *n*/*N* (%)	105/242 (43.4)	52/133 (39.0)	0.4451
Szabo *et al.* 2021 II[41]	Overall cancer detection rate, *n*/*N* (%)	20/62 (32.0)	52/133 (39.0)	Not reported
Szabo *et al.* 2021 I and II[41]	CS cancer detection rate, *n*/*N* (%)[f]	35/242 (14.0)	Not reported	Not reported

a Definition of clinical significance not reported in study publication.
b Clinical significance defined as Gleason > 3 + 4;
c Patients underwent both LATP and LATRUS biopsies, thus denominator is the same for both study arms.
d Gleason ≥ 3 + 4.
e Participants in both study arms were biopsy naïve.
f Clinical significance defined as Gleason grade group 2.

Notes
(AB) denotes study only available as a conference abstract at the time of writing.
Szabo I refers to the comparison of LATP using the PrecisionPoint Transperineal Access System vs. LATRUS from this study; Szabo II refers to the comparison of LATP using a coaxial needle sheath vs. LATRUS from this study.

There was variation between the studies in overall cancer detection rates, which highlights the heterogeneous nature of this evidence base. In terms of differences in detection rates between LATP and LATRUS, the results are mixed. Some studies reported similar rates for the two biopsy methods, while others reported differences in rates. There is not a clear pattern to these differences – in some cases LATP biopsy detects a greater proportion of cancers than LATRUS, but the opposite is also evident. We urge caution when interpreting these results given the predominance of observational study methods. The similarities and differences in cancer detection rates between the two biopsy methods may be driven, in part, by selection bias from lack of random allocation of participants to LATP biopsy or LATRUS biopsy study arms.

Figure 9 in *Appendix 4* shows pooled study estimates from a random-effects meta-analysis of LATP-any versus LATRUS for detection of prostate cancer. There is no statistically significant difference between LATP-any biopsy and LATRUS biopsy in detection of prostate cancer based on RCTs (RR = 1, 95% CI 0.85 to 1.18) (*n* = 5 RCTs) and based on observational comparative studies (RR = 1.10, 95% CI 1.01 to 1.21) (*n* = 8 studies). Caution is advised in the interpretation of these results given that the overall risk of bias in the RCTs is unclear due to limited available study details (see *Results of critical appraisal of study methodology*). Furthermore, although heterogeneity was low and not statistically significant, we note the presence of clinical heterogeneity across the studies.

Figure 10 in *Appendix 4* reports pooled study estimates from a random-effects meta-analysis of LATP-any versus LATRUS for detection of CS prostate cancer. There is no statistically significant difference between LATP-any biopsy and LATRUS biopsy in detection of CS prostate cancer, based on a single RCT

(RR = 1.14, 95% CI 0.65 to 2.01) and based on observational comparative studies (RR 1.20, 95% CI 0.98 to 1.47) (*n* = 4 studies).

Prostate cancer detection (local anaesthetic transperineal-any vs. general anaesthetic transperineal grid and stepping device, decision question 1)

Table 9 reports study cancer detection rates from the four studies which compared LATP-any biopsy versus GATP biopsy using grid and stepping device, and *Figure 11* in *Appendix 4* shows a meta-analysis forest plot containing three of the four studies (NB: the study publication by Walters *et al.* did not provide numerical cancer detection rates and was therefore not included in the meta-analysis).[44] There was some inconsistency between the studies in the direction of effects, with two studies marginally favouring LATP-any[42,45] and another (smaller) study showing a large effect in favour of GATP.[43] Overall, there is no statistically significant difference between the two biopsy modalities in detection of prostate cancer, as estimated by a single RCT (RR = 1.05, 95% CI 0.76 to 1.44) and observational comparative evidence (RR = 0.76, 95% CI 0.34 to 1.72) (*n* = 2 studies).

Prostate cancer detection (network meta-analysis of local anaesthetic transperineal-any vs. local anaesthetic transrectal ultrasound vs. general anaesthetic transperineal grid and stepping device, decision question 1)

We used MetaInsight software[23] to conduct a frequentist random-effects NMA of cancer detection rates for the biopsy modalities relevant to decision question 1 (see *Figure 12*, *Appendix 4*). The NMA provides an indirect comparison between LATP-any, LATRUS and GATP grid and stepping device to provide clinical effect estimates used in our economic analysis (see *Model parameters*). We restricted the NMA to RCTs because, in principle, randomised study designs have greater internal validity than observational studies (notwithstanding the uncertain risk of bias in RCTs we discussed earlier– see *Results of critical appraisal of study methodology*).

Consistent with the results of the pairwise meta-analyses above, the results of the NMA show RRs just below or just above RR = 1 for the respective biopsy modalities. Confidence intervals cross 1, indicating no statistically significant differences in cancer detection rates between the three biopsy modalities (see *Figure 13*, *Appendix 4*).

Our original economic base case included these NMA cancer detection rates in the economic model; however, at the request of NICE the base case was subsequently revised to exclude the Hara *et al.*[26] and Takenaka *et al.*[28] trials from the NMA. This was due to uncertainties raised by NICE Specialist Committee

TABLE 9 Prostate cancer detection rates (LATP-any vs. GATP grid and stepping device, decision question 1)

Study	Outcome measure	Intervention LATP-any	Comparator GATP	Statistical significance (*p*-value)
RCTs				
Lv *et al.* 2020[42]	Cancer positive detectable rate, *n* (%)	45 (41.7)	43 (39.8)	0.782
Other prospective studies				
Takuma *et al.* 2012 (AB)[43]	Cancer detection rate, *n*/*N* (%)	9/37 (24.0)	15/29 (51.0)	0.041
Walters *et al.* 2021 (AB)[44]	Histology outcomes	'No significant differences in histology outcome' between the different anaesthetic methods (LATP vs. LATRUS)		Not reported
Retrospective studies				
Rij and Chapman 2020 (AB)[45]	Cancers detected, *n*/*N* (%)	65/72 (90.0)	59/71 (83.0)	Not reported

Note
(AB) denotes study only available as a conference abstract at the time of writing.

Members about the most appropriate anaesthesia classification for these studies (i.e. LATP or GATP) arising from the clinically atypical approach to anaesthesia administration taken (spinal injection in the transperineal trial arm and caudal block in the transrectal trial arm). The revised economic base case was accompanied by two economic scenario analyses: scenario 1 in which Hara *et al.*[26] and Takenaka *et al.*[28] were retained in the NMA as originally classified (i.e. LATP, as *Figure 13*, *Appendix 4*); and scenario 2 in which Hara *et al.*[26] and Takenaka *et al.*[28] were reclassified as GATP. The results for all three NMAs are given in *Table 31*.

Prostate cancer detection (local anaesthetic transperineal-freehand vs. local anaesthetic transrectal ultrasound, decision question 2)

Cancer detection rates, including CS cancer rates (where available), for six of the seven studies comparing LATP-freehand versus LATRUS are reported in *Table 10* (NB: the remaining study[36,37] did not report cancer detection as an outcome). The PrecisionPoint freehand device was evaluated in all six studies, and collectively the studies comprise a subset of LATP-any studies for decision question 1 presented earlier.

TABLE 10 Prostate cancer detection rates (LATP-freehand vs. LATRUS, decision question 2)

Study	Outcome measure	Intervention LATP-freehand	Comparator LATRUS	Statistical significance (*p*-value)
RCTs				
Lam *et al.* 2021 (AB)[27]	Cancer detection rate, *n*/*N* (%)	47/134 (35.1)	33/132 (25.0)	< 0.05
	CS cancer detection rate[a]	22/134 (16.4)	19/132 (14.4)	0.74
Prospective studies				
Bojin 2019[29]	Cancer detection rates malignant, *n*/*N* (%)	76/103 (73.7)	117/189 (61.9)	Not reported
	Cancer detection rates benign, *n*/*N* (%)	27/103 (26.2)	72/189 (38.1)	Not reported
	CS cancer pick up, *n*/*N* (%)[b]	51/76 (67.1)	48/117 (41.2)	Not reported
Chen *et al.* 2021[30,31]	Cancer detection rate in biopsy naïve patients, *n*/*N* (%)	127/200 (63.5)	86/172 (50.0)	0.0115
Hung *et al.* 2020 (AB)[33]	Cancer detection rate (%)	20/63 (31.7)	14/57 (24.6)	0.851
	CS prostate cancer, (%)	57.1	45.0	0.501
Kum *et al.* 2018[34,35]	Cancer detection rate, overall, *n*/*N* (%)	139/176 (79.0)	Not reported	Not reported
	Malignant primary biopsy, *n*/*N* (%)[c]			
	Systematic	46/75 (61.3)	43/77[d] (55.8)	0.50
	Targeted and systematic	35/40 (88.6)	Not reported	Not reported
	Targeted	38/41 (92.7)	Not reported	Not reported
	CS cancer detection *n*/*N* (%)[e,f]			
	Systematic	28/46 (60.9)	25/43 (58.1)	0.80
	Targeted and systematic	29/35 (82.9)	Not reported	Not reported
	Targeted	33/38 (86.8)	Not reported	Not reported

continued

TABLE 10 Prostate cancer detection rates (LATP-freehand vs. LATRUS, decision question 2) (*continued*)

Study	Outcome measure	Intervention LATP-freehand	Comparator LATRUS	Statistical significance (*p*-value)
Retrospective studies				
Szabo *et al.* 2021 I[41]	Overall cancer detection rate, *n*/*N* (%)	105/242 (43.4)[g]	52/133 (39.0)	0.4451
	CS cancer detection rate, *n*/*N* (%)[h]	35/242 (14.0)	Not reported	Not reported

a Definition of clinical significance not reported in study publication.
b Clinical significance defined as Gleason > 3 + 4.
c One hundred and fifty-six of 176 LATP-freehand group study participants who were biopsy naïve.
d All 77 were biopsy naïve LATRUS participants.
e Clinically significant cancer defined as Gleason ≥ 3 + 4.
f Participants in both study arms were biopsy naïve.
g LATP using PrecisionPoint Transperineal Access System vs. LATRUS.
h Clinical significance defined as Gleason grade group 2.

Notes
(AB) denotes study only available as a conference abstract at the time of writing.
Szabo I refers to the comparison of LATP using PrecisionPoint Transperineal Access System vs. LATRUS from this study.

Figure 14 in *Appendix 4* reports results of the random-effects meta-analysis of cancer detection rates for LATP-freehand versus LATRUS. A borderline non-statistically significant difference favouring LATP-freehand was estimated by the single relevant RCT (RR = 1.40, 95% CI 0.96 to 2.04). A statistically significant difference favouring LATP-freehand was estimated by the pooled observational comparative studies (RR = 1.21, 95% CI 1.08 to 1.34) (*n* = 4 studies).

To permit an incremental assessment of biopsy modality effects in our economic model we considered splitting the 'LAPT-any' study category into its constituent biopsy subtypes, that is LATP-freehand, LATP grid and stepping device and LATP coaxial needle (double freehand). However, details of biopsy procedures were limited in some study publications and it was unclear whether studies of LATP grid and stepping device or LATP coaxial needle (double freehand) could be reliably classified as such. Hence, as a pragmatic adjustment to allow an assessment of incremental cost-effectiveness, we combined these two biopsy modalities into a general category we refer to as 'LATP-other'. It should be acknowledged, however, that a potential limitation is the underlying assumption that LATP using a grid and stepping device and LATP with a coaxial needle are necessarily equivalent in effects.

When RCT and observational evidence are pooled in our exploratory meta-analysis there is a statistically significant effect in favour of LATP-freehand compared to LATRUS (RR 1.22, 95% CI 1.10 to 1.35) (see *Figure 13*, *Appendix 4*). In contrast, there is no statistically significant difference between LATP-other and LATRUS for RCT evidence or observational comparative evidence or the two combined (see *Figure 15*, *Appendix 4*).

In the random-effects meta-analysis of LATP-freehand compared to LATRUS for CS prostate cancer detection, RRs non-significantly favoured LATP-freehand, as based on a single RCT (RR = 1.14, 95% CI 0.65 to 2.01) (see *Figure 16*, *Appendix 4*). There was a borderline statistically significant difference favouring LATP-freehand based on the observational comparative studies (RR = 1.31, 95% CI 1.00 to 1.72) (*n* = 3 studies). When observational and RCT studies are pooled in our exploratory analysis, a statistically significant difference is estimated (see *Figure 16*, *Appendix 4*).

Prostate cancer detection (local anaesthetic transperineal-freehand vs. general anaesthetic transperineal grid and stepping device decision question 2)

A single study compared cancer detection rates between LATP-freehand (PrecisionPoint) versus GATP grid and stepping device.[45] The study is a retrospective review of people who underwent transperineal prostate biopsy under local anaesthetic or under general anaesthetic, performed by a single surgeon. There was a small difference of seven percentage points in cancer detection rates, favouring PrecisionPoint [cancers detected: 65/72 (90.0%) PrecisionPoint versus 59/71 (83.0%) GATP]. [NB; this is one of the studies included in the comparison of LATP-any vs. GATP grid and stepping device presented earlier: see *Prostate cancer detection (LATP-any vs. GATP grid and stepping device, decision question 1)*].

Prostate cancer detection (network meta-analysis of local anaesthetic transperineal-freehand vs. local anaesthetic transperineal-other vs. local anaesthetic transrectal ultrasound vs. general anaesthetic transperineal grid and stepping device, decision question 2)

We used MetaInsight software (Owen *et al.*)[23] to conduct a frequentist random-effects NMA of cancer detection rates from RCTs for decision question 2 (see *Figure 17*, *Appendix 4*). This provided an indirect comparison between LATP-freehand versus LATP-other versus LATRUS versus GATP grid and stepping device, to inform an incremental assessment of cost-effectiveness in our economic analysis (see *Model parameters*).

Consistent with the pairwise meta-analyses described above, the NMA shows no statistically significant differences in cancer detection rates from RCTs between biopsy modalities (see *Figure 18*, *Appendix 4*).

Prostate cancer detection risk classification

Table 11 compares risk classification scores for people with detected prostate cancer biopsy for LATP-any versus LATRUS. The risk of the prostate cancer progressing aggressively was commonly assessed using Gleason scores (higher scores indicate greater progression risk), though other classification systems appear to have been used.[34] Not all studies provided risk classification for the comparator biopsy arm, but where comparative data were given Gleason scores were similar. Two of the studies[34,41] are also relevant to the comparison of LATP-freehand versus LATRUS (decision question 2).[34,35,41]

A single (retrospective observational) study reported cancer risk classification for the comparison of LATP-any versus GATP grid and stepping device.[45] The study used the International Society of Urological Pathology (ISUP) grade group classification as 'low risk' to 'Intermediate Favourable risk'. The LATP biopsy was done using the PrecisionPoint freehand device, thus this study is also relevant

TABLE 11 Prostate cancer detection risk classification (LATP-any vs. LATRUS, decision question 1)

Study	Risk classification of prostate cancer detected	Intervention LATP-any	Comparator LATRUS	Statistical significance (*p*-value)
RCTs				
Guo *et al.* 2015[25]	Gleason score, *n*/*N* (%)			
	≤ 6	18/173 (10.4)	18/166 (10.8)	0.547
	= 7	18/173 (10.4)	15/166 (9.0)	1.000
	≥ 8	25/173 (14.5)	18/166 (10.8)	0.564
	Very LR prostate cancer, *n*/*N* (%)	6/173 (3.5)	5/166 (3.0)	1.000

continued

TABLE 11 Prostate cancer detection risk classification (LATP-any vs. LATRUS, decision question 1) (*continued*)

Study	Risk classification of prostate cancer detected	Intervention LATP-any	Comparator LATRUS	Statistical significance (*p*-value)
Other prospective studies				
Emiliozzi *et al.* 2003[32]	Gleason score, *n*/*N* (%)			
	Gleason 5	2/41 (5.0)	0 (0)	Not reported
	Gleason 6	20/41 (49.0)	19/34 (56.0)	
	Gleason 7	17/41 (41.0)	14/34 (41.0)	
	Gleason 8–9	2/41 (5.0)	1/34 (3.0)	
Kum *et al.* 2018 (AB)[34,35]	LR[a], *n*/*N* (%)			
	Systematic	36/91[b] (39.0)	Not reported	Not reported
	Targeted and systematic	7/40[b] (17.0)		
	Targeted	6/45[b] (13.0)		
	IR[c], *n*/*N* (%)			
	Systematic	52/91[b] (57.0)	Not reported	Not reported
	Targeted and systematic	28/40[b] (69.0)		
	Targeted	26/45[b] (58.0)		
	HR[a], *n*/*N* (%)			
	Systematic	4/91[b] (4.0)	Not reported	Not reported
	Targeted and systematic	6/40[b] (14.0)		
	Targeted	13/45[b] (29.0)		
Watanabe *et al.* 2005[38]	Clinical stage[d], *n*/*N* (%)			
	T1c	29/39 (74.4)	25/39 (64.1)	Not reported
	T2	71/86 (82.6)	70/86 (81.4)	
	T3-T4	66/70 (94.3)	66/70 (94.3)	
	Gleason score, *n*/*N* (%)			
	Gleason 2–4	25/37 (67.6)	26/37 (70.3)	Not reported
	Gleason 5–6	59/70 (84.3)	55/70 (78.6)	
	Gleason 7	47/52 (90.4)	45/52 (86.5)	
	Gleason 8–9	35/36 (97.2)	35/36 (97.2)	
Retrospective studies				
Jiang *et al.* 2019[40]	Gleason score, *n*/*N* (%)[b]			
	≤ 6	32/182 (17.6)	58/184 (31.5)	Not reported
	7	73/182 (40.1)	90/184 (48.9)	< 0.001
	≥ 8	77/182 (42.3)	36/184 (19.6)	Not reported

TABLE 11 Prostate cancer detection risk classification (LATP-any vs. LATRUS, decision question 1) (*continued*)

Study	Risk classification of prostate cancer detected	Intervention LATP-any	Comparator LATRUS	Statistical significance (*p*-value)
Szabo *et al.* I[41]	Gleason grade, *n*/*N* (%)			
	Grade group 1	70/105 (66.7)	Not reported	Not reported
	Grade group 2	20/105 (19.0)		
	Grade group 3	4/105 (3.8)		
	Grade group 4	2/105 (1.9)		
	Grade group 5	9/105 (8.6)		

a Risk level not defined.
b Propensity score matched subgroup.
c Intermediate risk was defined as Gleason score 3 + 4 or > 4 mm cancer length.
d According to the TNM 1997 classification.

Notes
(AB) denotes study only available as a conference abstract at the time of writing.
Szabo I refers to LATP using PrecisionPoint vs. LATRUS.

to 'LATP-freehand versus GATP grid and stepping device (decision question 2)'. A higher percentage of participants were classified as ISUP > 2 by the LATP biopsy than GATP, but this was not statistically significant [*n* = 35/65 (53.8%) vs. *n* = 28/59 (47.5%), respectively, *p* = 0.48].

Diagnostic accuracy of prostate biopsy

None of the included studies fully reported the diagnostic or prognostic accuracy of LATP biopsy. Rather, as mentioned earlier, studies tended to report cancer detection rates without necessarily verifying the accuracy of cancer detected against a reference standard in terms of measures such as sensitivity and specificity.

One study reported the proportion of all cancers detected under LATP and under GATP (clinical sensitivity), but did not provide information on proportion of cancers not detected (clinical specificity).[45] A reference standard was not reported either. This study is currently available only as a conference abstract, hence limited information.

Another study reported the pathological accordance of Gleason scores based on biopsy with histological analysis of prostatectomy specimens (i.e. a reference standard).[43] This resulted in a small proportion of participants having their Gleason scores upgraded and upstaged.

Clinical outcomes

Hospitalisation events after biopsy

Hospitalisation following prostate biopsy was reported by a total of 10 studies, for 4 of the 5 biopsy comparisons relevant to the decision problem (see *Tables 12–14*). Studies tended to report the number of participants admitted to hospital at various time points after the biopsy (e.g. up to 30 days post biopsy), while others reported hospitalisation in response to serious complications such as fever and pneumonia. Less commonly reported was the duration of hospital stay. Overall, rates of hospitalisation were numerically higher for comparator biopsy approaches compared to LATP across the four biopsy comparisons. However, hospitalisation rates were very low in general, and it is therefore difficult to make definitive conclusions on the currently available evidence.

TABLE 12 Hospitalisation events after biopsy (LATP-any biopsy vs. LATRUS biopsy, decision question 1)

Study	Hospitalisation outcome	LATP-any biopsy	LATRUS biopsy
RCTs			
Takenaka *et al.* 2008[28]	Major complications, *n*/*N* (%)[a]		
	Total	1/100 (1.0)	4/100 (4.0)
	Macrohematuria	0/100 (0)	1/100 (1.0)
	Fever > 38.5 °C	0/100 (0)	2/100 (2.0)
	Urinary retention	0/100 (0)	1/100 (1.0)
Other prospective studies			
Chen *et al.* 2021[30,31]	Hospitalised for monitoring and discharged after 1 day, *n*/*N* (%)	1/212 (0.5)	0/178 (0)
Emiliozzi *et al.* 2003[32]	Post-biopsy hospitalisation, *n*/*N* (%)	0/107 (0)	0/107 (0)
Kum *et al.* 2018 (AB)[34,35]	Hospitalisation overnight, *n*/*N*	1/176	Not reported
Starmer *et al.* 2021[36,37]	Readmission within 30 days, *n*/*N* (%)	0/56 (0)	1/52 (1.9)[b]
	Pneumonia requiring readmission, *n*/*N* (%)	0/56 (0)	1/52 (1.9)[b]
Watanabe *et al.* 2005[38]	Prolonged hospital stay, *n*/*N* (%)	0/402 (0)	0/402 (0)
Retrospective studies			
Szabo *et al.* 2021 I[41]	Hospital admission, *n*/*N* (%)	Not reported	1/133 (0.75)
Szabo *et al.* 2021 II[41]	Hospital admission, *n*/*N* (%)	Not reported	1/133 (0.75)

a Defined as those requiring additional in-patient treatment.
b This is the same patient. Szabo *et al.* I compares LATP using PrecisionPoint vs. LATRUS; Szabo *et al.* II compares LATP coaxial needle sheath vs. LATRUS.

Note
(AB) denotes study only available as a conference abstract at the time of writing.

TABLE 13 Hospitalisation events after biopsy (LATP-any biopsy vs. GATP biopsy using a grid and stepping device, decision question 1)

Study	Hospitalisation outcome	LATP-any biopsy	GATP biopsy grid and stepping device
RCTs			
Lv *et al.* 2020[42]	Duration of hospital stay, hours, mean (SD)	23.50 (± 3.48)	23.12 (± 2.85)
Retrospective studies			
Rij and Chapman 2020 (AB)[45]	Readmission to hospital post biopsy, *n*/*N* (%)	0/72 (0)[a]	0/71 (0)[a]

a Percentage value calculated by reviewer.

The cost of hospital stays can be influential in the assessment of cost-effectiveness of health care. We discuss the hospitalisation estimates which inform our economic analysis of prostate biopsy in *Biopsy-related complications*.

Overall biopsy-related complications

Six studies reported overall rates of complications following prostate biopsy. Some, but not all, of the studies reported overall rates in addition to rates of the constituent complications. We report

TABLE 14 Hospitalisation events after biopsy (LATP-freehand biopsy vs. LATRUS biopsy/GATP biopsy using a grid and stepping device, decision question 2)

Study	Hospitalisation outcome	LATP-freehand biopsy	LATRUS biopsy
Other prospective studies			
Chen *et al.* 2021[30,31]	Hospitalised for monitoring and discharged after 1 day, *n*/*N* (%)	1/212 (0.5)	0/178 (0)
Kum *et al.* 2018 (AB)[34,35]	Hospitalisation overnight	1/176	Not reported
Starmer *et al.* 2021[36,37]	Readmission within 30 days, *n*/*N* (%)	0/56 (0)	1/52 (1.9)[a]
	Pneumonia requiring readmission, *n*/*N* (%)	0/56 (0)	1/52 (1.9)[a]
Retrospective studies			
Szabo *et al.* 2021 I[41]	Hospital admission, *n*/*N* (%)	Not reported	1/133a (0.8)
Rij and Chapman 2020 (AB)[45]	Readmission to hospital post biopsy, *n*/*N* (%)	0/72 (0)[b]	0/71 (0)[b]

a This is the same patient. Szabo *et al.* I compares LATP using PrecisionPoint vs. LATRUS.
b Defined as those requiring additional inpatient treatment.

Note
(AB) denotes study only available as a conference abstract at the time of writing.

here only studies which presented an overall complication rate; we did not sum rates of specific named complications to create an overall total complication rate for each study. All six studies were comparisons of LATP-any biopsy versus LATRUS biopsy and are relevant to decision question 1 (*Table 15*). Two of the six studies compared freehand transperineal devices versus LATRUS and therefore are also relevant to decision question 2.[30,31,34,35]

Specific biopsy-related complications

Bleeding and haematuria

Various types of bleeding events were reported as biopsy-related complications, including rectal and urethral bleeding and haematuria (the presence of blood in urine). In some cases, the severity of these events was defined, ranging from mild symptoms to severe symptoms such as retention of blood clots in the bladder requiring urgent medical attention. In other cases there was little or no elaboration beyond stating the location of the bleed.

For the comparison of LATP-any versus LATRUS (decision question 1), 9 of the 15 included studies reported a relevant bleeding and/or haematuria outcome (*Table 16*). Generally, bleeding/haematuria rates were low (e.g. < 30% of participants), and in relative terms rates were higher with LATRUS than LATP-any. Conversely, urethral bleeding was more common with LATP-any in the study by Cerruto *et al.*,[24] but the sample size for this analysis was very small (< 20 participants) and is unlikely to be sufficient to ensure a definitive effect.

For the comparison between LATP-any biopsy and GATP biopsy with grid and stepping device, two of the four included studies reported bleeding-related outcomes (*Table 17*). Observation of the data gives a faint suggestion that bleeding is potentially worse for GATP biopsy grid and stepping device than

TABLE 15 Overall complication rates after biopsy (LATP-any biopsy vs. LATRUS biopsy, decision question 1)

Study	Complication	LATP-any biopsy	LATRUS biopsy	Statistical significance
RCTs				
Cerruto *et al.* 2014[24]	Overall complication rate, *n*/*N* (%)[a]	7/54 (13.0)	*n* = 7/54 (13.0)	Not significant
Guo *et al.* 2015[25]	All complications, *n*/*N* (%)	76/167 (45.5)	73 (45.3)	0.912
	All minor complications, *n*/*N* (%)	75/167 (44.9)	66 (41.0)	0.504
	All major complications, *n*/*N* (%)	1 (0.6)	7 (4.3)	0.034
Takenaka *et al.* 2008[28]	Total complications (inclusive of major complications), *n*/*N* (%)	19/100 (19.0)	20/100 (20.0)	
Other prospective studies				
Chen *et al.* 2021[b,30,31]	Overall complication rate, *n*/*N* (%)	13/212 (6.1)	20/178 (11.2)	0.0993
Kum *et al.* 2018 (AB)[b,34,35]	Complications (Clavien–Dindo I/II), *n*/*N* (%)	5/176 (2.8)	Not reported	Not reported
Watanabe *et al.* 2005[38]	Adverse event, *n*/*N* (%)	5/402 (1.2)	5/402 (1.2)	Not reported

a All patients were clinically evaluated 30 days after the biopsy to record eventual complications related to procedures.
b Study compares LATP-freehand vs. LATRUS biopsy, and therefore is also relevant to decision question 2. As these are the only two such studies, we have not repeated them in a separate table; rather, we refer readers to this current table with respect to outcomes for decision questions 1 and 2.

Note
(AB) denotes study only available as a conference abstract at the time of writing.

TABLE 16 Bleeding and haematuria (LATP-any vs. LATRUS, decision question 1)

Study	Outcome	LATP-any	LATRUS	Statistical significance
RCTs				
Cerruto *et al.* 2014[24]	Rectal bleeding, *n*/*N* (%)[a]	0/7 (0)	4/7 (57.2)	0.04
	Urethral bleeding, *n*/*N* (%)[a]	5/7 (71.4)	0/7 (0)	0.022
Guo *et al.* 2015[25]	Mild rectal bleeding, *n*/*N* (%)	0/167 (0)	14/161 (8.7)	< 0.001
	Severe rectal bleeding, *n*/*N* (%)	0/167 (0)	2/161 (1.2)	Not reported
	Mild haematuria, *n*/*N* (%)	33/167 (19.8)	37/161 (23.0)	0.502
	Severe haematuria, *n*/*N* (%)	0/167 (0)	0/161 (0)	Not reported
Hara *et al.* 2008[26]	Major rectal bleeding, *n*/*N* (%)	0 (0)	0 (0)	N/A
	Haematuria > 1 day, *n*/*N* (%)	2 (1.6)	0 (0)	0.166
Takenaka *et al.* 2008[28]	Rectal bleeding, *n*/*N* (%)	0/100 (0)	1/100 (1.0)	Not reported
	Macrohaematuria, *n*/*N* (%)	11/100 (11.0)	12/100 (12.0)	Not reported
Other prospective studies				
Chen *et al.* 2021[30,31]	Haematuria, *n*/*N* (%)	2/212 (0.9)	3/178 (1.7)	0.6640
Emiliozzi *et al.* 2003[32]	Temporary haematuria, *n*/*N* (%)	33/107 (31.0)[b]		Not reported

TABLE 16 Bleeding and haematuria (LATP-any vs. LATRUS, decision question 1) (*continued*)

Study	Outcome	LATP-any	LATRUS	Statistical significance
Kum *et al.* 2018 (AB)[34,35]	Clot retention (Clavien–Dindo Grade II), *n*/*N* (%)	1/176 (0.6)	Not reported	Not reported
Watanabe *et al.* 2005[38]	Significant haematuria requiring transurethral coagulation of prostatic bleeding, *n*/*N* (%)	1/402 (0.2)		Not reported
Retrospective studies				
Szabo *et al.* 2021 I[41]	Gross haematuria with clot retention, *n*/*N* (%)	3/242 (1.2)	Not reported	Not reported
Szabo *et al.* 2021 II[41]	Gross haematuria with clot retention, *n*/*N* (%)	1/62 (1.6)	Not reported	Not reported

a All patients were clinically evaluated 30 days after the biopsy to record eventual complications related to procedures.
b Participant underwent LATP and LATRUS biopsy in the same session.

Notes
(AB) denotes study only available as a conference abstract at the time of writing.
Szabo I refers to the comparison of LATP using PrecisionPoint Transperineal Access System vs. LATRUS from this study; Szabo II refers to the comparison of LATP using a coaxial needle sheath vs. LATRUS from this study.

TABLE 17 Bleeding and haematuria (LATP-any vs. GATP grid and stepping device, decision question 1)

Study	Outcome	LATP-any biopsy	GATP biopsy grid and stepping device	Statistical significance
RCTs				
Lv *et al.* 2020[42]	Blood loss, ml, mean (SD)	3.35 (± 1.04)	3.60 (± 1.13)	0.092
	Perineal haematoma, *n*/*N* (%)	0/108 (0)	1/108 (0.93)	0.996
	Urethral bleeding, *n*/*N* (%)	19/108 (17.59)	25/108 (23.15)	0.311
Retrospective studies				
Rij and Chapman 2020 (AB)[45]	Prolonged haematuria, *n*/*N* (%)	2/72 (3.0)	Not reported	Not reported
	Perineal haematomas, *n*/*N* (%)	Not reported	3/71 (4.0)	Not reported

Note
(AB) denotes study only available as a conference abstract at the time of writing.

for LATP-any biopsy. However, this is based on a small number of events from a single RCT.[42] Rates of urethral bleeding were generally between the two biopsies, in stark contrast to the aforementioned comparison between LATP-any and LATRUS by Cerruto *et al.*[24]

Moving on to decision question 2, four of the seven LATP-freehand (PrecisionPoint) device studies (all observational studies) assessed bleeding as a biopsy complication (*Table 18*). Rates of bleeding were very low overall, and it is difficult to draw any definitive conclusions regarding whether they are more common with LATP-freehand versus LATRUS. Likewise, for the single-study comparison of LATP-freehand biopsy versus GATP biopsy grid and stepping device,[45] data are very sparse and, thus, inconclusive at present.

TABLE 18 Bleeding and haematuria (LATP-freehand vs. LATRUS/GATP biopsy grid and stepping device, decision question 2)

Study	Outcome	LATP-freehand	LATRUS	Statistical significance
Other prospective studies				
Chen *et al.* 2021[30,31]	Haematuria, *n*/*N* (%)	2/212 (0.9)	3/178 (1.7)	0.6640
Kum *et al.* 2018 (AB)[34,35]	Clot retention (Clavien–Dindo Grade II), *n*/*N* (%)	1/176 (0.6)	Not reported	Not reported
Retrospective studies				
Szabo *et al.* 2021 I[41]	Gross haematuria with clot retention, *n*/*N* (%)	3/242 (1.2)	1/62 (1.6)	Not reported
Rij and Chapman 2020 (AB)[45]	Prolonged haematuria, *n*/*N* (%)	2/72 (3.0)	Not reported	Not reported
	Perineal haematomas, *n*/*N* (%)	Not reported	3/71 (4.0)	Not reported

Notes
(AB) denotes study only available as a conference abstract at the time of writing.
Szabo I refers to the comparison of LATP using PrecisionPoint Transperineal Access System vs. LATRUS from this study.

Sepsis

Relatively few studies reported post-biopsy sepsis as an outcome. Where reported, rates of sepsis were generally low (< 10%) and exclusively to LATRUS biopsy participants; no LATP biopsy participants are recorded as having post-biopsy sepsis (see *Tables 19* and *20*).

None of the LATP-any versus GATP grid and stepping device studies (decision question 1) and none of the LATP-freehand biopsy versus GATP biopsy grid and stepping device studies (decision question 2) included sepsis as an outcome measure.

Fever

Post-biopsy fever was reported by four studies (all RCTs) all of which compared LATP-any versus LATRUS (decision question 1). None of the LATP biopsy procedures involved use of a freehand device (*Table 21*). Rates of high fever were numerically higher for LATRUS though the event rates are low overall, and it is difficult to make definitive conclusions on small numbers of participants.

Rates of urinary retention

Post-biopsy urinary retention is reported by nine studies in total across three biopsy comparisons (see *Tables 22–24*). Some studies reported retention data for the LATP biopsy but not the comparator. Where comparative evidence was available, retention rates were similar between biopsy modalities, though it is difficult to make definitive conclusions based on small event rates.

No studies reported post-biopsy urinary retention for the comparison of LATP-freehand versus GATP/LATP using a grid and stepping device (decision question 2).

Rates of erectile dysfunction

Only two studies in this systematic review reported assessing post-biopsy erectile dysfunction.[27,33] Both used the International Index of Erectile Function (IIEF-5) instrument, in which lower scores indicate greater severity of erectile dysfunction. The observational study by Hung *et al.* reports that mean IIEF-5 change post biopsy was 2.74 in LATRUS and 6.03 in LATP, and was statistically significant (p = 0.023).[33]

TABLE 19 Sepsis rates (LATP-any vs. LATRUS, decision question 1)

Study	Outcome	LATP-any	LATRUS	Statistical significance
RCTs				
Guo *et al.* 2015[25]	Major complications: sepsis, *n* (%)	0 (0)	1 (0.6)	Not reported
Hara *et al.* 2008[26]	Major complications: sepsis/mortality, *n* (%)	0 (0)	0 (0)	Not reported
Lam *et al.* 2021 (AB)[27]	Post-biopsy sepsis	0/0 (0)	11/132 (8.3)	Not reported
Other prospective studies				
Chen *et al.* 2021[30,31]	Urosepsis, *n*/*N* (%)[a]	0/212 (0)	4/178 (2.2)	0.0431
Hung *et al.* 2020 (AB)[33]	Sepsis, *n*/*N* (%)	0/63 (0)	3/57 (5.3)	0.045
Retrospective studies				
Szabo *et al.* 2021 I[41]	Sepsis, *n*/*N* (%), Clavien grade	0/242 (0) Not applicable	1/133a (0.8) Clavien IVb	Not reported
Szabo *et al.* 2021 II[41]	Sepsis, *n*/*N* (%), Clavien grade	0/62 (0) Not applicable	1/133a (0.8) Clavien IVb	Not reported

a Defined as at least two out of four systemic inflammatory response syndrome (SIRS) criteria with a proven infection.

Notes
(AB) denotes study only available as a conference abstract at the time of writing.
Szabo I refers to the comparison of LATP using PrecisionPoint Transperineal Access System vs. LATRUS from this study;
Szabo II refers to the comparison of LATP using a coaxial needle sheath vs. LATRUS from this study.

TABLE 20 Sepsis rates (LATP-freehand vs. LATRUS, decision question 2)

Study	Outcome	LATP-any	LATRUS	Statistical significance
RCTs				
Lam *et al.* 2021 (AB)[27]	Post-biopsy sepsis	0/0 (0)	11/132 (8.3)	Not reported
Other prospective studies				
Chen *et al.* 2021[30,31]	Urosepsis, *n*/*N* (%)[a]	0/212 (0)	4/178 (2.2)	0.0431
Hung *et al.* 2020 (AB)[33]	Sepsis, *n*/*N* (%)	0/63 (0)	3/57 (5.3)	0.045
Retrospective studies				
Szabo *et al.* I[41]	Sepsis, *n*/*N* (%), Clavien grade	0/242 (0) Not applicable	1/133a (0.75) Clavien IVb	Not reported
Szabo *et al.* II[41]	Sepsis, *n*/*N* (%), Clavien grade	0/62 (0) Not applicable	1/133a (0.75) Clavien IVb	Not reported

a Defined as at least two out of four systemic inflammatory response syndrome (SIRS) criteria with a proven infection.

Notes
(AB) denotes study only available as a conference abstract at the time of writing.
Szabo I refers to the comparison of LATP using PrecisionPoint Transperineal Access System vs. LATRUS from this study;
Szabo II refers to the comparison of LATP using a coaxial needle sheath vs. LATRUS from this study.

TABLE 21 Fever rates (LATP-any vs. LATRUS, decision question 1)

Study	Outcome	LATP-any	LATRUS	Statistical significance
RCTs				
Cerruto *et al.* 2014[24]	Fever > 38.5 °C, *n*/*N* (%)	0/7 (0)	1/7 (14.3)	0.315
Guo *et al.* 2015[25]	Low fever < 38.5 °C, *n*/*N* (%)	2/167 (1.2)	2/167 (1.2)	0.099
	High fever > 38.5 °C, *n* (%)	0 (0)	2 (1.2)	Not reported
Hara *et al.* 2008[26]	Fever > 38.5 °C, *n* (%)	0 (0)	2 (1.7)	0.136
Takenaka *et al.* 2008[28]	Fever > 38.5 °C, *n*/*N* (%)	1/100 (1.0)	2/100 (2.0)	Not reported

TABLE 22 Urinary retention rates (LATP-any vs. LATRUS, decision question 1)

Study	Outcome	LATP-any	LATRUS	Statistical significance
RCTs				
Lam *et al.* 2021 (AB)[27]	Post-biopsy urinary retention	'No statistically significant difference between both arms' $p = 0.107$		$p = 0.107$
Hara *et al.* 2008[26]	Urinary retention, *n* (%)	2 (1.6)	3 (2.5)	0.612
Takenaka *et al.* 2008[28]	Urinary retention, *n* (%)	2/100 (2.0)	3/100 (3.0)	Not reported
Other prospective studies				
Chen *et al.* 2021[30,31]	Acute urinary retention, *n*/*N* (%)	8/212 (3.8)	8/178 (4.5)	0.8008
Hung *et al.* 2020 (AB)[33]	Urinary retention rate	'No statistically significant difference'		Not reported
Kum *et al.* 2018 (AB)[34,35]	Urinary retention (Clavien-–Dindo Grade II), *n*/*N* (%)	1/176 (0.6)	Not reported	Not reported
Watanabe *et al.* 2005[38]	Urinary retention requiring urethral catheterisation, *n*/*N* (%)	2/402 (0.5)		Not reported
Retrospective studies				
Szabo *et al.* 2021a[41]	Acute urinary retention, *n*/*N* (%), Clavien grade	1/242 (0.4) Clavien I	Not reported	Not reported

Note
(AB) denotes study only available as a conference abstract at the time of writing.

TABLE 23 Urinary retention rates (LATP-any vs. GATP grid and stepping device, decision question 1)

Study	Outcome	LATP-any	GATP biopsy grid and stepping device	Statistical significance
RCT				
Lv *et al.* 2020[42]	Retention of urine, *n* (%)	3 (2.8)	2 (1.9)	0.997

TABLE 24 Urinary retention rates (LATP-freehand vs. LATRUS, decision question 2)

Study	Outcome	LATP-any	LATRUS	Statistical significance
Other prospective studies				
Chen *et al.* 2021[30,31]	Acute urinary retention, *n*/*N* (%)	8/212 (3.8)	8/178 (4.5)	0.8008
Hung *et al.* 2020 (AB)[33]	Urinary retention rate	'No statistically significant difference'		Not reported
Kum *et al.* 2018 (AB)[34,35]	Urinary retention (Clavien–Dindo Grade II), *n*/*N* (%)	1/176 (0.6)	Not reported	Not reported
Retrospective studies				
Szabo *et al.* 2021[41]	Acute urinary retention, *n*/*N* (%), Clavien grade	1/242 (0.4) Clavien I	Not reported	Not reported

Note
(AB) denotes study only available as a conference abstract at the time of writing.

The RCT by Lam *et al.* reports a reduction in the IIEF-5 score that was 'more significant in LATP arm' $p < 0.05$.[27] No further detail is given to quantify this statement. Details of these two studies are publicly available only as a conference abstract at the time of writing. The EAG has been told, via personal communication with the lead investigator,[27] that a manuscript is being prepared for submission to a journal.

Survival

None of the included studies reported survival outcomes for participants receiving biopsy.

Progression-free survival

None of the included studies reported progression-free survival for participants treated for prostate cancer detected on biopsy.

Adverse events from treatment

None of the included studies reported adverse events in participants treated for prostate cancer detected on biopsy.

Patient-reported outcomes

Patient-reported tolerability

A total of 12 studies reported data on the degree of pain and discomfort during prostate biopsy as rated by patients (see *Tables 25* and *26*). Tolerability was measured in a variety of ways across the studies, but often data are only presented for the LATP biopsy group, thus limiting comparisons to be drawn between types of biopsy.

Ongoing studies

The EAG identified five ongoing studies relevant to this review, all of which are RCTs. Four studies are investigating LATP biopsy compared with LATRUS biopsy and one will investigate LATP biopsy compared with GATP biopsy. Below is a brief narrative summary of the five studies, with a tabular summary available in *Table 58* in *Appendix 4*.

TABLE 25 Patient-reported tolerability (LATP-any vs. LATRUS, decision question 1)

Study	Patient-reported tolerability	Intervention LATP-any	Comparator LATRUS	Statistical significance (*p*-value)
RCTs				
Cerruto *et al.* 2014[24]	VAS pain level, mean (SD)	1.42 (1.37)	1.56 (1.73)	0.591
Guo *et al.* 2015[25]	Pain, VAS score, median (IQR)	4.0 (1.0–6.0)	2.0 (0.0–4.0)	< 0.001
	Most painful procedure, *n* (%)			
	None	3 (1.7)	37 (22.3)	< 0.001
	Probe insertion	30 (14.5)	67 (42.2)	< 0.001
	Anaesthesia	110 (63.6)	29 (17.5)	< 0.001
	Sampling	26 (15.0)	25 (15.1)	1.000
	Others	9 (5.2)	5 (3.0)	0.415
	Additional anaesthesia, number of times, *n* (%)	26 (15.0)	2 (1.2)	< 0.001
Lam *et al.* 2021 (AB)[27]	Patient tolerability comparison measured by VAS	'No statistically significant difference between both arms'		$p = 0.14$
Other prospective studies				
Bojin 2019[29]	Tolerability, VAS pain score 0–6, median	1.9	Not reported	Not reported
Chen *et al.* 2021[30,31]	VAS pain score for the entire procedure, mean (SD, range)	3.67 (2.57, 0–9)	Not reported	Not reported
Emiliozzi *et al.* 2003[32]	Mild post-biopsy perineal discomfort, *n*/*N* (%)	7/107 (6.0)		Not reported
Hung *et al.* 2020 (AB)[33]	Overall pain scores	'No statistically significant difference'		0.527
Kum *et al.* 2018 (AB)[34,35]	Procedure tolerability (100 mm VAS score) during three stages of procedure: ultrasound (US) probe insertion, local anaesthesia (LA) administration, biopsies, and an overall rating	Pain scores of the LATP group were not significantly different to TRUS at any procedural stage		Not reported
	Overall VAS rating of tolerability, median (IQR)	27.5 (15, 49.25)	45 (40–50)	$p = 0.004$
Starmer *et al.* 2021[36,37]	VAS scores, rated 0–9, for discomfort, median			
	At probe insertion	3	4	0.66
	Probe presence	3	3	0.91
	Local anaesthetic injection	3	2	0.15
	Taking biopsy	3	3	0.18
	VAS scores, rated 0–3, median			
	Overall pain	1	1	0.17
	Embarrassment	0	0	0.34
	Describe to a friend	1	1	0.2

TABLE 25 Patient-reported tolerability (LATP-any vs. LATRUS, decision question 1) (*continued*)

Study	Patient-reported tolerability	Intervention LATP-any	Comparator LATRUS	Statistical significance (*p*-value)
Retrospective studies				
Szabo *et al.* 2021 I[41]	VAS pain ratings, 0–10, average, median (range and SD)	3.9, 4 (0–10, 1.9)[a]	Not reported	Not reported

VAS, visual analogue scale.
a One hundred and sixty-nine of the last 172/242 LATP using PrecisionPoint cases were assessed for pain at the end of the procedure

Notes
(AB) denotes study only available as a conference abstract at the time of writing.
Szabo I refers to the comparison of LATP using PrecisionPoint Transperineal Access System vs. LATRUS from this study.

TABLE 26 Patient-reported tolerability (LATP-any vs. GATP grid and stepping device, decision question 1)

Study	Patient-reported tolerability	Intervention LATP-any	Comparator GATP	Statistical significance (*p*-value)
RCTs				
Lv *et al.* 2020[42]	Degree of pain VAS scores during the perioperative period (0 = no pain, 10 = unbearable pain) mean (SD)			
	VAS1 (during anaesthesia)	2.92 (± 0.96)	0.00 (± 0.00)	Not calculated
	VAS2 (during biopsy)	2.91 (± 1.09)	0.00 (± 0.00)	Not calculated
	VAS3 (6 hours after biopsy)	1.03 (± 0.76)	1.06 (± 0.76)	0.810
	VAS4 (1 day after biopsy)	1.04 (± 0.82)	0.91 (± 0.78)	0.238
Retrospective studies				
Rij and Chapman 2020 (AB)[45]	Participants tolerating the procedure, *n* (%)	72/72 (100.0)	Not reported	Not reported

VAS, visual analogue scale.

Note
(AB) denotes study only available as a conference abstract at the time of writing.

LATP versus LATRUS. The multicentre UK study (TRANSLATE) will provide evidence for freehand LATP using any ultrasound probe-mounted needle guidance device, including the PrecisionPoint and UA1232 devices.[52–54] As the study uses freehand devices to perform the biopsies it will assist with both decision question 1 (LATP-any vs. LATRUS) and decision question 2 (LATP-freehand vs. LATRUS). This will be the first comparative evidence to become available for the UA1232 device. As well as CS prostate cancer [Gleason grade (GG) > 2] detection rates and infection rates, this study will report on outcomes for which there is limited evidence in this review: erectile function and the number of subsequent biopsies within 4 months. It will also report cost outcomes. It is expected to have a larger study population (n = 1042) than any of the prospective studies included in this review.

The other three LATP versus LATRUS studies are based in the USA. ProBE-PC is a single-centre study and will report on sexual function, for which there is limited evidence in this review.[55] It will also report

cost outcomes. Two multicentre studies (unnamed) run by the same institution differ in terms of the population: one study population is men with elevated PSA or abnormal DRE, and the other is men on active surveillance, or with prior negative prostate biopsy and a clinical concern for the presence of prostate cancer, which is partially relevant to this review.[56,57]

All four LATP versus LATRUS studies incorporate using a pre-biopsy MRI to inform additional targeted biopsies that are performed during the procedure and will be relevant to the UK diagnostic pathway (not all included studies in this review reported the use of a pre-biopsy MRI).

LATP versus GATP. One Australian study (LATProBE), yet to start recruiting, will provide evidence for freehand LATP compared with GATP using a grid template.[58] It will report similar outcomes to studies already included in this review: cancer detection rates, costs, patient experience, pain, 30-day complications and HRQoL.

The earliest study completion date is December 2022 (ProBE-PC),[55] the UK study is expected to complete the following year in October 2023 (TRANSLATE),[52,53] and one study has not yet started recruiting (LATProBE).[58]

Chapter 5 Economic analysis

The aim of this chapter is to assess the cost-effectiveness of LATP prostate biopsies in people with suspected prostate cancer. It comprises:

1. A systematic review of economic evidence comprising (1) a systematic review of cost-effectiveness studies of LATP prostate biopsies in people with suspected prostate cancer and (2) a systematic review of HRQoL (utility) for people with suspected or diagnosed prostate cancer.
2. An overview of evidence from company submissions to NICE.
3. An independent economic model developed by the EAG.

The EAG health economic base case originally submitted to NICE went through several changes to accommodate corrections and updated assumptions proposed by NICE and stakeholders. We report the results of a revised EAG base case in this monograph. The original EAG base case and the EAG addenda submitted to NICE can be accessed from the NICE website.[59]

Systematic review of existing cost-effectiveness evidence

Methods for review of economic studies

The database searches for cost-effectiveness were carried out on 17 June 2021 and updated on 2 November 2021. The search strategies were based on an early version of the clinical-effectiveness searches with the addition of the Canadian Agency for Drugs and Technologies in Health (CADTH) filter for Economic Evaluations/Cost/Economic Models applied to the MEDLINE and EMBASE strategies and amended versions of the filter applied to the Cochrane Library and Web of Science strategies.[60] The INAHTA, DARE and NHS EED strategies were the same as for the clinical-effectiveness searches. In addition, the EconLit database was searched. An English-language limit was applied. The full search strategies are shown in *Appendix 1* (*Table 47*).

The relevant population, interventions and comparators are the same as for the systematic review of test yield and clinical effectiveness (see *Inclusion and exclusion criteria*) but differed in terms of the relevant study design and outcomes. Studies were included if they were full economic evaluations, assessing both costs and consequences, for the specified diagnostic strategies. Outcomes included are those consistent with full economic evaluations, including measures of resource use and costs, and health outcomes: life-years (LYs) or quality-adjusted life-years (QALYs) gained. Each step of the review was completed by two health economists and any disagreements were resolved by discussion. Studies that reported resource use, costs or HRQoL in the area of prostate cancer were excluded if they did not meet the inclusion criteria above, but considered separately as possible sources of evidence to inform model structure and inputs.

The EAG planned to extract data related to the study design, methods, parameter sources, relevant model inputs and results of the included cost-effectiveness studies. The credibility of the included cost-effectiveness studies and their relevance to current UK practice were assessed using a pre-defined checklist, shown in *Appendix 6*, *Table 64*. This checklist was based on the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[61] and Philips *et al.*'[62] checklists.

Results of the review of economic studies

Starting with 724 potentially relevant references identified in the original (704) and updated (20) searches, 10 studies were retrieved for full-text screening (see flowchart in *Appendix 6*, *Figure 19*). After inspection, nine references were excluded (see *Appendix 6*, *Table 62* for the reasons for exclusion).

Summary of included cost-effectiveness study: Wilson *et al.*

We identified one economic evaluation for inclusion within the scope of this assessment: Wilson *et al.*[63] Wilson *et al.* reported the cost-effectiveness of LATP (with the CamPROBE transperineal prostate biopsy device) versus LATRUS for use in the diagnosis of prostate cancer in men with suspected localised prostate cancer from the perspective of the UK NHS. The relevance and credibility checklist for this study and further details including a list of the model inputs are shown in *Appendix 6*, *Tables 63* and *64*.

Wilson *et al.* built a lifetime model comprising a decision tree with a Markov model at the terminal nodes. The model was informed by a prospective case series on the safety and acceptability of the CamPROBE device[46] and published studies including an economic analysis of diagnostic strategies including mpMRI and TRUS biopsy based on data from the PROMIS study, reported by Faria *et al.*[64,65] The diagnostic pathway was based on NICE guidance[8] and strategy 'M7' of the Faria study. The risks of biopsy complications were derived from a Cochrane review of antibiotic prophylaxis for transrectal prostate biopsy,[66] with a base-case assumption of zero risk of infection with LATP. The analysis assumed equal diagnostic accuracy for LATP with the CamPROBE device and LATRUS.

Unit costs were taken from routine NHS sources for the price year 2018–9. The costs of biopsy were estimated from a sample of 17 CamPROBE and 17 LATRUS biopsies. Consumables were excluded from the incremental analysis if they were common to both procedures. Given the small sample, both procedures were assumed to take the same time and use the same volume of local anaesthetic. The price of the CamPROBE LATP biopsy device was unknown and set to zero for the base-case analysis, with sensitivity analysis used to estimate the maximum price for the device at which it would be cost-neutral, or cost saving compared with LATRUS. The incremental cost of LATRUS was therefore the difference in remaining consumable costs between the two biopsy techniques (£16.71). QALYs were based on disutility and duration of biopsy complications, and a disutility due to metastatic disease (MD).

Base-case results indicated that LATP (with the CamPROBE device at zero price) dominates LATRUS biopsy. At a threshold of £20,000 per QALY gained, the estimated probability that LATP is cost-effective compared with LATRUS was 59.0% and the maximum cost-effective price for CamPROBE was £81.17 per procedure (or £40.59 per CamPROBE device, as two are required per procedure). The maximum price at which CamPROBE was estimated to be cost-neutral was £40.82 per procedure. Two-way sensitivity analysis was used to explore uncertainty relating to the RR of infections and price of the CamPROBE device. At the £20,000 per QALY threshold, this indicated a maximum cost-effective procedure price of £14.50 for LATP with CamPROBE if the risk of infection was the same as with LATRUS. The results from the study by Wilson *et al.* are subject to a high degree of uncertainty. They also exclude other relevant comparators for the current evaluation, as specified in the two NICE decision questions.

Overview of other published economic studies of interest

Other studies retrieved by the systematic review were considered as possible sources of evidence to inform our model structure and inputs (see *Appendix 6*, *Table 65*). Most of these studies are evaluations of the use of mpMRI to inform TRUS biopsies versus TRUS alone in people with suspected prostate cancer, a prior negative or inconclusive biopsy or undergoing active surveillance. The remaining studies assessed screening or other diagnostic tests and assays (vs. TRUS or a PSA test) in men with suspected prostate cancer. Eight out of 13 studies used a decision tree plus a Markov model, while 2 used a decision tree only and another two used a Markov model only. One of the studies used a microsimulation model. Most studies applied a lifetime horizon and a 1-year Markov cycle length. All the studies reported costs and utilities and estimated the cost per QALY gained. Two economic studies were very influential in the development of our model and are discussed below.

Summary of other studies of interest: the PROMIS model

Firstly, the cost-effectiveness analysis conducted alongside the PROMIS study was reported in Brown *et al.*' Health Technology Assessment (HTA) report and in Faria *et al.*' paper.[64,65] This analysis

assessed the cost-effectiveness of a range of diagnostic strategies using mpMRI, TRUS biopsy and/or a template prostate mapping biopsy (TPM) for men referred to secondary care in the UK NHS with suspected prostate cancer. It used a decision tree to model alternative diagnostic pathways consisting of sequences of up to three tests, followed by a Markov model that extrapolated from diagnostic outcomes to estimate long-term costs and QALYs. The PROMIS Markov model is illustrated in Faria *et al.* supplementary figure 1. It includes three basic health states: progression-free or localised disease, MD and death. But this simple three-state model is replicated for five groups of patients, based on 'true disease' status and treatment allocated at the end of the diagnostic pathway: patients with low-risk (LR) cancer on 'watchful waiting' and patients with intermediate-risk (IR) and high-risk (HR) cancer on either watchful waiting or with radical prostatectomy.

The analysis by Wilson *et al.*, described above, relied heavily on the model structure and input parameters from Faria *et al.*' model. We also used parameters from the PROMIS economic analysis to inform estimates of baseline prevalence of prostate cancer and diagnostic yield of TRUS biopsy in our model (see *Baseline prevalence* and *Cancer detection rates*). These estimates provided the baseline diagnostic outcomes for TRUS, against which other biopsy methods in the current scope were compared.

Summary of other studies of interest: the NG131 model

The second analysis that informed our model structure and parameters was that developed by the NICE Guideline Updates Team for the NICE guideline on prostate cancer published in May 2019 (NG131) to estimate the cost-effectiveness of follow-up protocols for people with a raised PSA, negative mpMRI and/or negative biopsy.[67]

The NG131 Markov model includes 11 health states grouped in four categories: 'true negatives' (no prostate cancer or undiagnosed LR disease); 'false negatives (FNs)' (undiagnosed IR, HR or MD); 'true positives' (diagnosed disease from LR to metastatic); and death related to prostate cancer or from other causes (see NG131 health economic model report Table HE03).[67] We adapted this Markov model to predict long-term costs and outcomes based on diagnostic yield of the biopsy methods in the current decision problems (see *Long-term consequences: the Markov model* and *Markov model structure*).

Systematic review of health-related quality of life

Methods for review of health-related quality of life

We undertook searches to identify data on HRQoL for patients undergoing screening and diagnosis of prostate cancer, and for patients with diagnosed prostate cancer. The aim of these searches was to identify utility values that were suitable for use in the economic model.

A sequential approach was used to identify HRQoL studies:

1. Systematic searches of bibliographic databases were conducted for HRQoL data in people with suspected prostate cancer (searches 'HRQoL 1').
2. Additional systematic searches of bibliographic databases were conducted for HRQoL data in people with both suspected as well as diagnosed prostate cancer (searches 'HRQoL 2'), to find additional utility values suitable for the economic model not identified in the 'HRQoL 1' searches.

The first set of searches (HRQoL 1) used the clinical-effectiveness search strategies with the addition of the CADTH search filter for Health Utilities/Quality of Life applied to the MEDLINE and EMBASE strategies and amended versions of the filter applied to the Cochrane Library and Web of Science strategies. The second set of database searches (HRQoL 2) were subsequently run with the biopsy terms removed to retrieve studies that would cover the whole disease pathway in addition to the diagnostic process. In order to save time, HRQoL 2 included terms specific to the European Quality of Life Working

Group Health Status Measure 5 Dimensions (EQ-5D) utility measure (the CADTH search filter was not used), to reflect the NICE preferred method for utility assessment,[68] with the option to expand the search to other utility measures if needed. The searches were carried out in MEDLINE, EMBASE, Web of Science and the Cochrane Library, and they were limited to the most recent 10 years. The strategies for HRQoL 1 and HRQoL 2 are shown in *Appendix 1* (see *Tables 48* and *49*).

The inclusion and exclusion criteria for eligibility screening are given in *Appendix 7*, *Table 66*. The same eligibility criteria were used for screening both titles and abstracts and full-text records. Only primary research studies were included. The relevant population was people who had undergone screening or diagnostic tests for prostate cancer, or with diagnosed prostate cancer. We planned to extract data related to the study design, country and sample size, HRQoL instruments used, and health states assessed.

Results of the review of health-related quality-of-life studies

The systematic searches 'HRQoL 1' identified 244 potentially relevant studies (see *Appendix 7*, *Figure 20*). Of the 244 references, 34 were retrieved for full-text screening and 9 studies were included.[69–77] The excluded references and reasons for exclusion are shown in *Appendix 7*, *Table 67*. Study characteristics and results from the included studies are summarised in *Appendix 7*, *Tables 68* and *69*. However, these studies did not provide suitable utility values for our economic model.

The systematic searches 'HRQoL 2' identified 369 potentially relevant studies, of which 21 were retrieved for full-text screening, and 6 studies[78–83] were included (see *Appendix 7*, *Figure 21*). The excluded references and reasons for exclusion are shown in *Appendix 7* (*Table 70*).

The main characteristics and results of the six studies included from 'HRQoL 2' are presented in *Tables 27* and *28* (further detail in *Appendix 7*, *Table 71*). Three studies were conducted in the UK and

TABLE 27 Characteristics of included HRQoL studies (searches 'HRQoL 2')

First author, Year	*N*[a]	Country	Instrument	Health state(s) described
Booth *et al.* 2014[78]	5516	Finland	EQ-5D	No prostate cancer (screened and not screened); prostate cancer (screened and not screened); organ-confined prostate cancer (screened and not screened); advanced prostate cancer (screened and not screened)
Drummond *et al.* 2015[79]	3348	Republic of Ireland and Northern Ireland	EQ-5D-5L	Invasive prostate cancer (at least 20-month survivors)
Farkkila *et al.* 2014[80]	30	Finland	EQ-5D-3L	End-stage prostate cancer
Gavin *et al.* 2016[81]	3348	Republic of Ireland and Northern Ireland	EQ-5D-5L	Invasive prostate cancer, 2–18 years post treatment: early disease at diagnosis (stage I/II and Gleason grade 2–7), late disease at diagnosis (stage III/IV and any Gleason grade at diagnosis)
Torvinen *et al.* 2013[82]	621	Finland	EQ-5D-3L	Localised disease 6 months after diagnosis; localised disease in the following 12 months; remission; MD; palliative care
Watson *et al.* 2016[83]	316	UK	EQ-5D-5L	No/mild and moderate/severe problems due to prostate cancer treatment in patients diagnosed at least 9 months before

N, sample size.
a Corresponds to the total number of participants who completed the HRQoL questionnaires.

TABLE 28 Included HRQoL studies: summary of utility values (searches 'HRQoL 2')

Health states	Utility	Source
No prostate cancer		
No PC (screening programme)	0.830	Booth *et al.* 2014[78]
No PC (no screening programme)	0.857	Booth *et al.* 2014[78]
Prostate cancer		
Difference of PC vs. no PC (screening programme)	+ 0.005	Booth *et al.* 2014[78]
Difference of PC vs. no PC (no screening programme)	− 0.031	Booth *et al.* 2014[78]
Early disease		
Difference of organ-confined PC vs. no PC (screening programme)	+ 0.010	Booth *et al.* 2014[78]
Difference of organ-confined PC vs. no PC (no screening programme)	− 0.031	Booth *et al.* 2014[78]
Early disease PC (2–18 years post treatment)	0.877	Gavin *et al.* 2016[81]
Localised disease (6 months after diagnosis) *n* = 46	0.900 (0.840–0.960)	Torvinen *et al.* 2013[82]
Localised disease (18 months after diagnosis) *n* = 91	0.890 (0.860–0.920)	Torvinen *et al.* 2013[82]
Localised disease (remission) *n* = 309	0.870 (0.850–0.890)	Torvinen *et al.* 2013[82]
Advanced disease		
Difference of advanced PC vs. no PC (screening programme)	− 0.039	Booth *et al.* 2014[78]
Difference of advanced PC vs. no PC (no screening programme)	− 0.051	Booth *et al.* 2014[78]
Invasive PC (at least 20 months after diagnosis)	0.820	Drummond *et al.* 2015[79]
Late disease PC (2–18 years post treatment)	0.777	Gavin *et al.* 2016[81]
MD *n* = 85	0.740 (0.690–0.800)	Torvinen *et al.* 2013[82]
Palliative disease *n* = 17	0.590 (0.480–0.700)	Torvinen *et al.* 2013[82]
End-stage PC	0.551 (0.405–0.664)	Farkkila *et al.* 2014[80]
Adverse events after treatment for PC (diagnosed at least 9 months before)		
Urine function (no/mild problems)	0.868 (SD, 0.160)	Watson *et al.* 2016[83]
Urine function (moderate/severe problems)	0.773 (0.222)	Watson *et al.* 2016[83]
Bowel function (no/mild problems)	0.862 (0.166)	Watson *et al.* 2016[83]
Bowel function (moderate/severe problems)	0.653 (0.195)	Watson *et al.* 2016[83]
Sexual function (no/mild problems)	0.861 (0.176)	Watson *et al.* 2016[83]
Sexual function (moderate/severe problems)	0.838 (0.170)	Watson *et al.* 2016[83]

PC, prostate cancer.

used the EQ-5D-5L, and three were conducted in Finland, from which two used the EQ-5D-3L version with a UK tariff and the other did not specify the version used. Overall, the studies reported EQ-5D scores associated with no cancer, early/localised prostate cancer and late/metastatic prostate cancer. All the studies, except one, have a sample size > 300. These papers are discussed in relation to their applicability to the EAG economic model in *Utilities*.

Overview of economic evidence in the company submissions

BXTAccelyon, the company that produces PrecisionPoint, submitted a cost-minimisation study. This was developed in 2020 by the York Health Economics Consortium (YHEC) using an economic model that compared the costs of LATP (with the PrecisionPoint device) against different combinations of LATRUS and GATP for UK NHS Trusts. YHEC assumed that LATP and GATP have the same rate of achieving a successful biopsy (with no need to repeat the procedure) and fewer complications than LATRUS biopsies. The majority of clinical experts providing feedback to the EAG reported that they would expect better diagnostic yield for transperineal biopsies compared with LATRUS. This suggests that the assumption of equal diagnostic yield may be conservative.

The YHEC model included costs associated with carrying out prostate biopsies and costs associated with biopsy complications from an HTA report by Ramsay *et al.*[84] YHEC concluded that it was not possible to calculate a cost per case that could be multiplied by the number of cases to show the total cost of each biopsy, as the costs of complications and the capital cost of a stepping device vary according to the number of cases. In addition, different NHS Trusts undertake different proportions of TRUS and GATP. Therefore, they conducted scenarios to estimate the economic impact of different combinations.

The results suggested that LATP using the PrecisionPoint device is cost saving, yielding higher savings as the proportion of biopsies that were previously performed as GATP increases. Assuming that an NHS Trust undertakes 500 biopsies per year (250 TRUS and 250 GATP), adopting PrecisionPoint yields a cost saving of £81,027.

We note that this study does not compare costs against LATP with grid and stepping device or with another freehand device.

Economic evaluation approach and rationale

The EAG developed a health economic model to compare the cost-effectiveness of alternative biopsy methods for people with suspected prostate cancer, as specified in the NICE scope (see *Definition of the decision problem*). The model comprises a decision tree to estimate short-term diagnostic outcomes and a cohort health state transition (Markov) model to predict the long-term consequences of the diagnostic pathway on disease progression and associated costs and patient outcomes. In this section, we introduce the EAG economic evaluation. Further detail and explanation are provided in subsequent sections of this chapter.

The modelled cohort

The base case population entering the model is a cohort referred for a first prostate biopsy for suspected localised prostate cancer after mpMRI with Likert score of 3 or more. We also conduct analysis for three other subgroups: mpMRI Likert score of 1 or 2 at first biopsy; mpMRI Likert score of 3 or more after a previous negative biopsy; and mpMRI Likert score of 1 or 2 after a previous negative biopsy. For our base case, we assume that there are no people with metastatic prostate cancer in the cohort because it is likely that people with overt MD and those for whom active treatment for diagnosed disease would not be appropriate would have been screened out of the cohort prior to biopsy. We tested the impact of including a proportion of people with pre-existing MD in scenario analysis (see *Appendix 9*, *Table 88*).

The diagnostic pathway: decision tree

The structure of the decision tree is described in detail in *Decision tree structure*. The design and parameter sources are largely based on the PROMIS economic analysis reported by Faria and colleagues,

and the version of this analysis adapted by Wilson *et al.* to estimate cost-effectiveness for LATP (see *Results of the review of economic studies* and *Overview of other published economic studies of interest* above for discussion of these studies).[63–65]

The cohort entering the decision tree is first stratified by baseline prevalence of LR, IR and HR localised disease, and MD (if included). The tree then models the diagnostic pathway with the alternative biopsy methods specified in the scope, and estimates resulting complication and cancer detection rates, costs and QALYs. The tree includes a second biopsy for a proportion of patients with a negative first biopsy, with the assumption that the second biopsy would be conducted with the LATRUS method. This is a simplification. In practice, methods for repeat biopsies are likely to vary, but evidence for the diagnostic yield of other biopsy methods after a previous negative first biopsy is sparse. The proportion undergoing repeat biopsy can be changed.

Inputs to the decision tree are:

- Baseline prevalence stratified by level of risk, estimated from data reported by Faria *et al.* (see *Baseline prevalence*).[64,65,94]
- Probabilities of detecting CS and clinically non-significant (CNS) prostate cancer (see *Cancer detection rates*). For LATRUS, these probabilities are also estimated from data reported by Faria *et al.*[64,65,94] These baseline probabilities are adjusted for other biopsy methods using RR estimates from the EAG systematic reviews and meta-analyses (see *Intermediate outcomes*).
- The probability of a repeat biopsy if the first biopsy is negative is estimated from a paper by Jimenez *et al.*, identified from our clinical review.[85] Assumptions about how this probability differs according to the first biopsy method and result were tested in scenario analysis (see discussion in *Probability of a repeat biopsy*).
- Probabilities of biopsy-related complications were estimated from various sources.[66,96–100] Relevant papers were identified from our clinical review and the review of economic evaluations (see *Clinical outcomes, Results of the review of economic studies* and *Overview of other published economic studies of interest*), with alternative sources tested in scenario analysis (see discussion in *Biopsy-related complications*).
- Costs of the biopsy procedures and treatment for complications, see *Costs of the biopsy procedure* and Resource use and costs for management of suspected prostate cancer. We developed detailed cost estimates for different LATP approaches in decision question 2.
- The impact of biopsy-related complications on patient HRQoL and survival (QALY loss) is based on assumptions as in the analysis by Wilson *et al.* (see *Utilities*).[63]

Long-term consequences: the Markov model

We considered two designs for the Markov model based on existing studies:

1. a model with three health states (progression-free, MD and death), stratified by initial level of cancer risk and treatment, developed for the PROMIS economic evaluation by Faria *et al.*; and
2. a model developed by the NICE Guideline Updates Team for the 2019 update of the NICE prostate cancer guideline (NG131) evaluation of follow-up strategies for people with a negative mpMRI or biopsy result.[64,65,67]

The NG131 model structure includes some features that make it more appropriate for the current decision problem. In particular, it explicitly models subsequent diagnosis for people with FN results after the biopsy pathway, based on estimated rates of symptomatic presentation and routine follow-up in primary care. This enables quantification of the monetary and QALY costs of a biopsy failing to diagnose CS disease and the resulting delay in treatment. The NG131 model also includes costs for diagnosis and follow-up and a wider range of treatments that reflect NICE guidance. We therefore decided to adapt the NG131 Markov model structure for our analysis.

The structure and input parameters of the NG131 model are described in the health economic model report available on the NICE website.[67] We also had access to a copy of the model. Input parameters and assumptions in our model were aligned with those in the NG131 model, except where more recent or relevant sources were identified. We included parameters to specify a schedule of primary care follow-up for people with one or more negative biopsy result. For our base-case analysis, we assumed a PSA test at 6 months, then annual tests for a maximum of 10 years for everyone with a FN biopsy result. Modelled treatment for diagnosed prostate cancer reflected NICE guidance at the time of the 2019 guideline update, with additional treatments for MD based on more recent technology appraisals.[86–88]

See *Markov model structure* for further description of the NG131 model structure and explanation of how we adapted it for the current decision problem.

Parameters for the Markov model include:

- Transition probabilities between the 11 health states. We used the same probabilities as in the NG131 model (Table HE07 in the online model report).[67] See *Long-term transition probabilities* for details and explanation of how these probabilities were derived.
- Resource use and costs, including monitoring and follow-up, treatment of diagnosed prostate cancer, management of adverse events and end-of-life costs (see *Resource use and costs for management of suspected prostate cancer* for details).
- Health outcomes are estimated in the form of QALYs, incorporating modelled survival and the impact of symptoms and adverse effects on utility.[91,92,109] See *Utilities*.

Framework for economic analysis

Analysis followed the NICE reference case at the time of analysis, as specified in section 15 of the Diagnostics Assessment Programme (DAP) manual.[68]

- The model uses a 'lifetime' time horizon (up to a maximum age of 100 years) to reflect the life-threatening consequences of misdiagnoses or serious biopsy-related complications. The Markov model uses a 3-month model cycle.
- Health outcomes are estimated as QALYs, with utilities estimated from EQ-5D-3L data with NICE-recommended UK general population values.
- Costs are estimated from an NHS and personal social services perspective. Biopsy costs are estimated with a micro-costing approach, informed by company submissions and expert judgement. Unit costs are taken from standard national and NHS sources.[89,90] The base case uses long-term average cost estimates for the interventions and comparators, with annuitised costs for capital equipment.
- Standard rates of discounting for time preference over costs and QALYs are applied, as recommended by NICE (currently 3.5% per year for costs and QALYs).

Modelled decision problem

Population and subgroups

The model was designed to estimate costs and health outcomes for the population specified in the NICE scope: people with suspected prostate cancer referred for prostate biopsy. We aimed to reflect characteristics of this population in routine NHS practice, including age and probability of prostate cancer prior to biopsy.

The National Prostate Cancer Audit (NPCA) reported that 54% of people newly diagnosed with prostate cancer in England and Wales between April 2018 and March 2019 were aged 70 years or over (mean age at diagnosis was not reported) (NPCA 2020 Table 3).[92] However, one would expect the mean age at biopsy to be lower than the mean age at diagnosis. The mean age at referral for a first prostate biopsy in

the PROMIS study was 63.4 years, but the mean age for those diagnosed with IR and HR cancers was 64.9 and 66.8 years, respectively.[64] For the base case, we assumed a mean age of 66 years at referral for biopsy, as this matches the assumption in the NG131 update analysis, as well as feedback from a specialist committee member.[67] We tested the effect of baseline age in scenario analysis (see *Appendix 9*, *Table 88*).

For the purposes of the economic evaluation, we assumed that the cohort had already had mpMRI as an investigation for suspected clinically localised prostate cancer prior to referral for biopsy, with results reported on a five-point Likert scale. This aligns with the NICE recommendation from the 2019 update of NG131 (recommendation 1.2.2).[8] Use of the Likert scale is also consistent with evidence of the diagnostic yield of mpMRI available from the PROMIS study, which we use to estimate the baseline prevalence of prostate cancer conditional on mpMRI results (see *Baseline prevalence*). We acknowledge that this does not necessarily align with clinical practice, as some centres use PI-RADS instead of Likert to report mpMRI results. There is also uncertainty over the generalisability of evidence on the comparative diagnostic yield of biopsy methods, as some studies did not report prior mpMRI use, and those that did report results in terms of PI-RADS rather than Likert scores (see *Characteristics of studies comparing LATP prostate biopsy by any method versus LATRUS prostate biopsy (decision question 1)*, *Characteristics of studies comparing LATP prostate biopsy by any method versus GATP prostate biopsy using a grid and stepping device (decision question 1)*, *Characteristics of studies comparing LATP prostate biopsy using a freehand device versus LATRUS prostate biopsy (decision question 2)*, *Characteristics of studies comparing LATP prostate biopsy using a freehand device versus GATP prostate biopsy by grid and stepping device (decision question 2)* and *Characteristics of single-arm studies evaluating LATP prostate biopsy using a freehand device where no comparative evidence was identified*).

Faria *et al.*[65] evaluated 'true disease' status for the PROMIS population based on a combination of a TPM biopsy and TRUS biopsy (whichever was the most severe). They classified LR, IR and HR localised prostate cancer according to two sets of definitions. For the economic model, we used the following:

- LR: Gleason ≤ 6, PSA ≤ 10 ng/ml and clinical stage T1 to T2a
- IR: Gleason 7, PSA 10–20 ng/ml and clinical stage T2b
- HR: Gleason 8–10, PSA > 20 ng/ml and clinical stage T2c or higher.

Intermediate- and high-risk localised disease are grouped together as CS disease. LR disease is classed as CNS.

We assume that the referred cohort does not include people with MD. NICE guidance is that people who are not going to be able to have radical treatment should not be routinely offered mpMRI (NG131 recommendation 1.2.1), and that those for whom clinical suspicion of prostate cancer is high because of high PSA value and evidence of bone metastases should not be routinely offered prostate biopsy for histological confirmation (NG131 recommendation 1.2.8). The PROMIS, which provides baseline estimates of prevalence for the model, excluded people with MD; 5 out of 740 men registered for the study were withdrawn due to having stage T4 or nodal disease (Brown *et al.*, table 6).[64]

Patient subgroups

In our base-case analysis, we focus on people referred for a first biopsy with a prior mpMRI Likert score of 3 or more (NG131 recommendation 1.2.3). NG131 recommends considering omission of a prostate biopsy for people with a mpMRI Likert score of 1 or 2, but only as a shared decision after discussion of the risks and benefits with the person concerned (NG131 recommendation 1.2.4). The NICE scope for the current assessment reports expert opinion that around 40% of people with Likert score of 1 or 2 are discharged based on the results of the mpMRI scan. This group are less likely to have CS prostate cancer than those with a mpMRI score of 3 or more. Similarly, the risk of prostate cancer, and hence cost-effectiveness, is likely to differ for people who have never had a prostate biopsy, and for those who have had a previous negative prostate biopsy and are referred back.

We assess cost-effectiveness separately for the following subgroups:

1. people referred for a first biopsy with a Likert score of 3 or more (base case)
2. people referred for a first biopsy with a Likert score of 1 or 2
3. people referred after a previous negative biopsy with a Likert score of 3 or more
4. people referred after a previous negative biopsy with a Likert score of 1 or 2.

We do not present subgroup analysis by location of lesions or enlarged prostate, due to a lack of evidence to differentiate prognosis or diagnostic yield for these groups.

The model uses prevalence of LR, IR and HR localised prostate cancer in subgroups A to D estimated from data on true disease status in the PROMIS cohort and diagnostic yield characteristics of mpMRI and TRUS biopsy reported by Faria *et al.* See *Baseline prevalence* for details of the prevalence calculations.

Biopsy methods and devices

The model was designed to evaluate the decision questions defined in the NICE scope. Following the naming conventions for interventions and comparators used in the pairwise and network meta-analyses in *Intermediate outcomes*, we conducted the following comparisons.

Decision question 1:

- LATP prostate biopsy with a freehand device, grid and stepping device or coaxial needle (LATP-any)
- LATRUS biopsy (LATRUS)
- GATP using a grid and stepping device (GATP).

Decision question 2:

- LATP prostate biopsy with a freehand device (LATP-freehand)
- LATP prostate biopsy without a freehand device (LATP-other), including LATP conducted with a grid and stepping device or coaxial needle
- LATRUS biopsy (LATRUS)
- GATP with a grid and stepping device (GATP).

Model structure

The model comprises a decision tree which maps out the initial diagnostic pathway and a Markov model which estimates long-term treatment costs and health outcomes. See *Model parameters* for model input parameters and *Model assumptions* for a list of model assumptions.

Decision-tree structure

A simplified overview of the decision tree is shown in *Figure 4*. This tree is replicated for each biopsy method under comparison.

The model starts with a cohort of interest, one of four subgroups A–D defined by mpMRI Likert score and history of previous biopsy. The cohort is first stratified by true prostate cancer status (no cancer, LR, IR or HR localised disease or MD). The decision tree then estimates diagnostic outcomes (the proportions of correct and FN biopsy results) and complications from the biopsy process. The end points of the decision tree, correct diagnoses (Dx) or FNs, represent the initial health states in the Markov model.

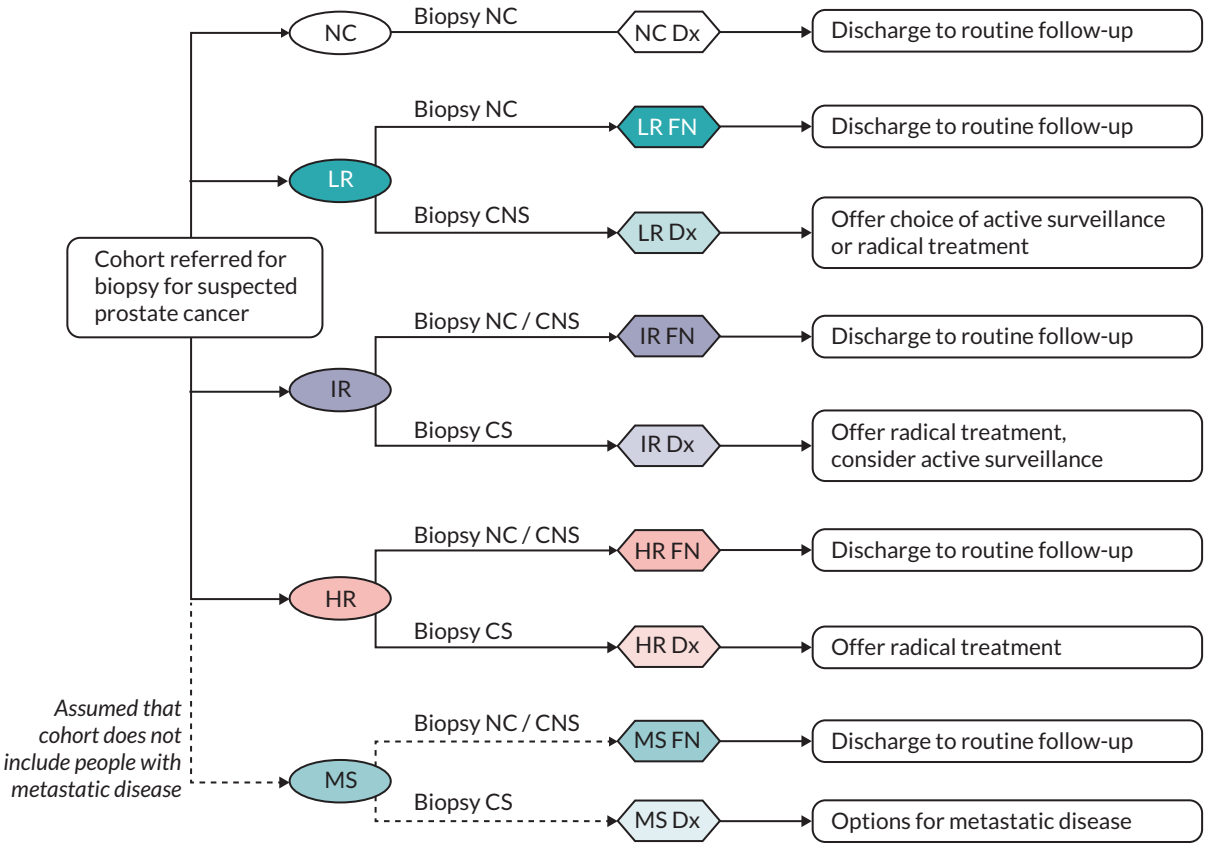

FIGURE 4 Overview of decision tree. CNS, clinically non-significant cancer; HR, true high-risk; HR Dx, high-risk correctly diagnosed; HR FN, misdiagnosed intermediate-risk; IR, true intermediate-risk; IR Dx, intermediate-risk correctly diagnosed; IR FN, misdiagnosed intermediate-risk; LR, true low-risk; LR Dx, low-risk correctly diagnosed; LR FN, misdiagnosed low-risk; MS, true metastatic disease; MS Dx, metastatic correctly diagnosed; MS FN, misdiagnosed metastatic; NC Dx, no cancer correctly diagnosed.

Biopsy-related complications are categorised as:

- no adverse event: no or minor events for which the patient does not seek treatment
- mild adverse events: mild/moderate events treated outside hospital
- admission: admission within 28 days of the biopsy
- mortality within 28 days of the biopsy.

Costs are estimated for the biopsy process, including costs of the initial and repeat biopsies, and costs for management of any biopsy-related complications. QALYs accumulated within the biopsy process are also estimated, based on initial utility values assigned to the cohort and allowing for any QALY loss attributable to complications, including disutility for transient adverse events and lifetime QALY loss for rare biopsy-related deaths.

The following sections describe the structure of the subtrees for people without prostate cancer (NC) and for those with CNS (LR) or CS (IR, HR) localised prostate cancer. The model also includes a subtree for MD, but this is not used in the current analysis.

No prostate cancer

See *Figure 5* for an illustration of the biopsy process for people who do not have prostate cancer. We assume that all biopsy methods are perfectly specific: so there cannot be false positive results for people who truly do not have prostate cancer. However, it is possible that a patient may be referred for a repeat

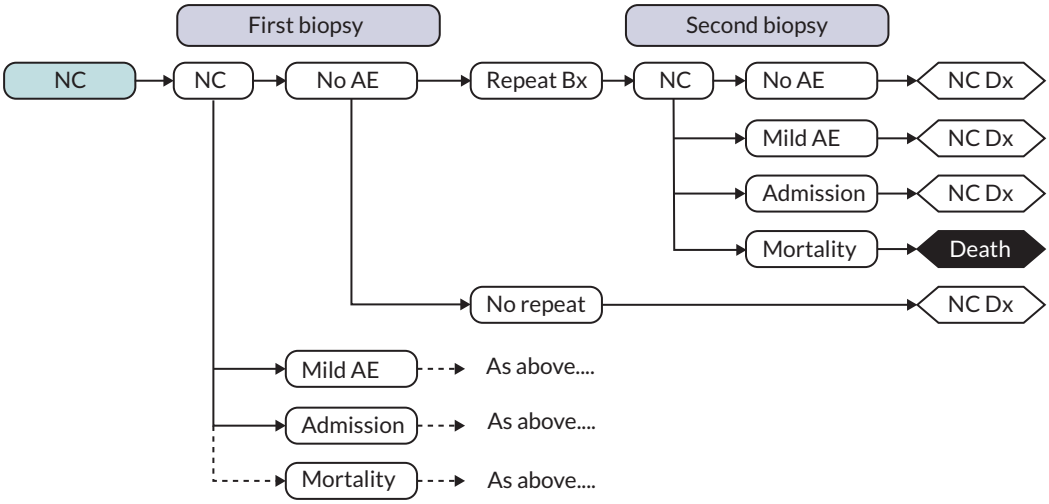

FIGURE 5 Illustration of decision tree for people without prostate cancer. AE, adverse events; Bx, biopsy; NC Dx, no cancer correctly diagnosed.

biopsy if there is a high level of clinical suspicion. Biopsy-related complications may occur, classified as above (mild, admission or mortality). End points for people without prostate cancer are correct diagnosis (NC Dx) or death from biopsy-related complications.

Clinically non-significant prostate cancer

Figure 6 illustrates the biopsy process for people with CNS disease (LR prostate cancer). For this population, the biopsy may give a correct diagnosis, a false positive result of CS disease or a FN result of no cancer. In practice, there were no cases of people with LR cancer receiving a CS biopsy result in the PROMIS study (see *Table 30*).[64] Hence, the probability of this event in our model is zero.

If the biopsy is negative (CNS or no cancer), a repeat biopsy may be performed. We assumed that the probability of a repeat biopsy is higher if the result of the first biopsy is CNS or if the prior mpMRI Likert score was 3 or more, than if the first biopsy result is 'no cancer' and the Likert score is < 3. A second biopsy may give a CS, CNS or no cancer result, although the estimated probability of a CS result for a second TRUS biopsy with LR cancer is zero (as in the PROMIS model, based on the systematic review and meta-analysis by Schoots *et al.*).[65,93]

Complications may occur after the first and/or second biopsy, classified as above (none, mild, admission or mortality). End points for people with LR disease are correct diagnosis (LR Dx), false positive (LR FP), false negative (LR FN) or death.

Clinically significant prostate cancer

The structure of the decision tree is the same for people with IR prostate cancer (illustrated in *Figure 7*) as for those with HR disease (figure not shown). We assume that the incidence of complications does not differ by cancer risk group. End points for intermediate and high risk are correct diagnosis (IR Dx; HR Dx), false negative (IR FN; HR FN) or death.

Markov model structure

As discussed above (see *Long-term consequences: the Markov model*), we considered two designs for the Markov model to estimate long-term costs and QALYs from the diagnostic outcomes from our decision tree: the model developed for the economic evaluation of the PROMIS study by Faria *et al.*, later adapted by Wilson *et al.*; and the model developed for the 2019 update of the NICE prostate cancer guideline (NG131).[63–65,67] We chose to use a replicated version of the NG131 Markov model as this gives a more flexible structure to model the costs and consequences of missed diagnoses, allowing for possible future diagnosis.

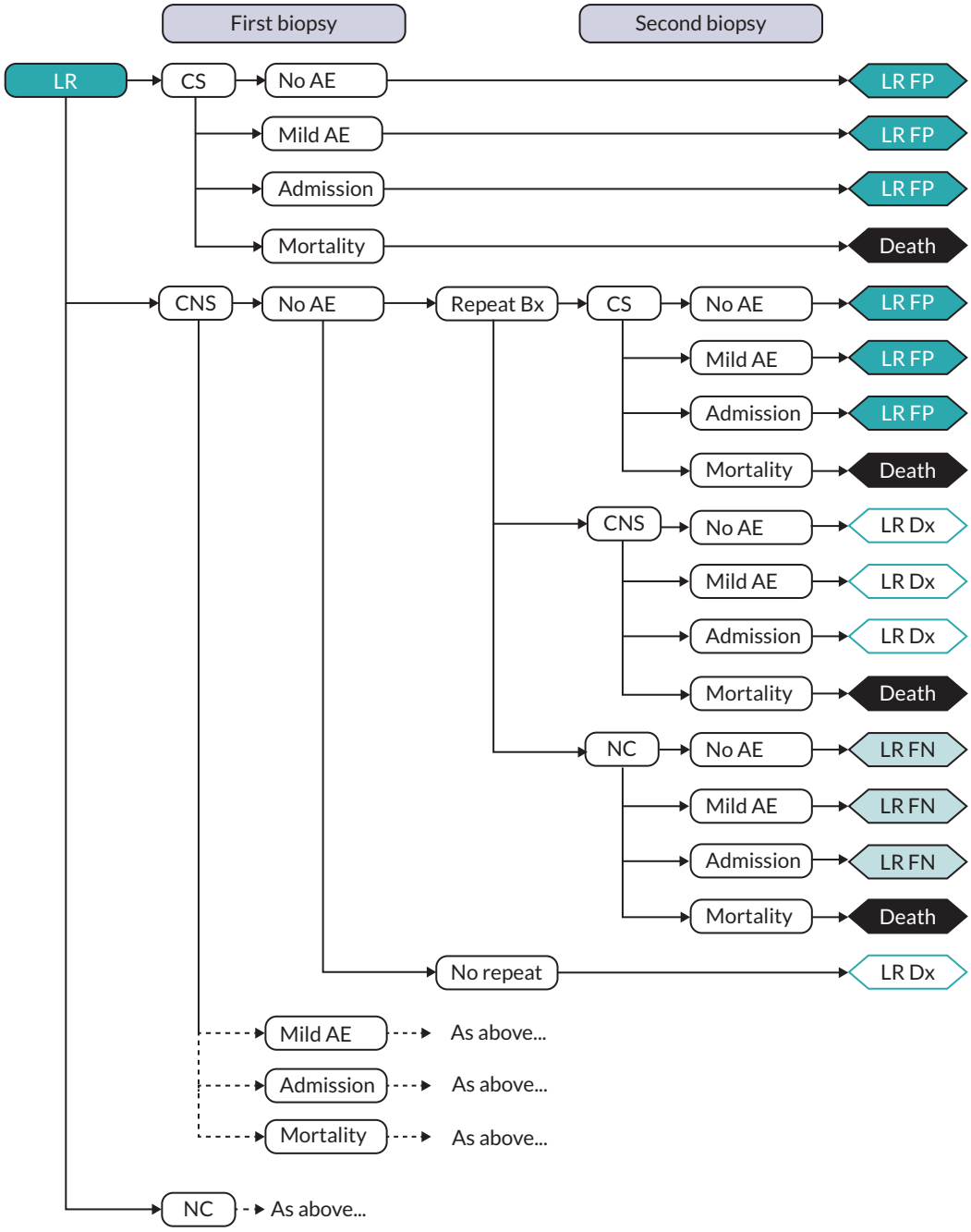

FIGURE 6 Illustration of decision tree for people with LR prostate cancer. AE, adverse event; Bx, biopsy; LR, true low-risk; LR Dx, low-risk correctly diagnosed (classified as CNS); LR FN, low-risk false negative (classified as no cancer); LR FP, low-risk false positive (classified as CS).

The structure of this model is illustrated in *Figure 8*. It includes health states based on prostate cancer and diagnostic status: no cancer (NC) and diagnosed and undiagnosed LR, IR and HR localised disease and MD. The initial distribution of the cohort across the Markov states is determined by the output from the biopsy pathway modelled in the decision tree: with some 'overdiagnosis' of LR disease and some missed diagnoses of CS disease. Rates of transition from undiagnosed to diagnosed health states can be set to reflect primary care monitoring and symptomatic presentation. The model includes simplified assumptions about sequential progression of prostate cancer: from incident LR disease through IR and HR localised disease to MD. Death from prostate cancer is assumed to only occur with MD, although death from other causes occurs from all states.

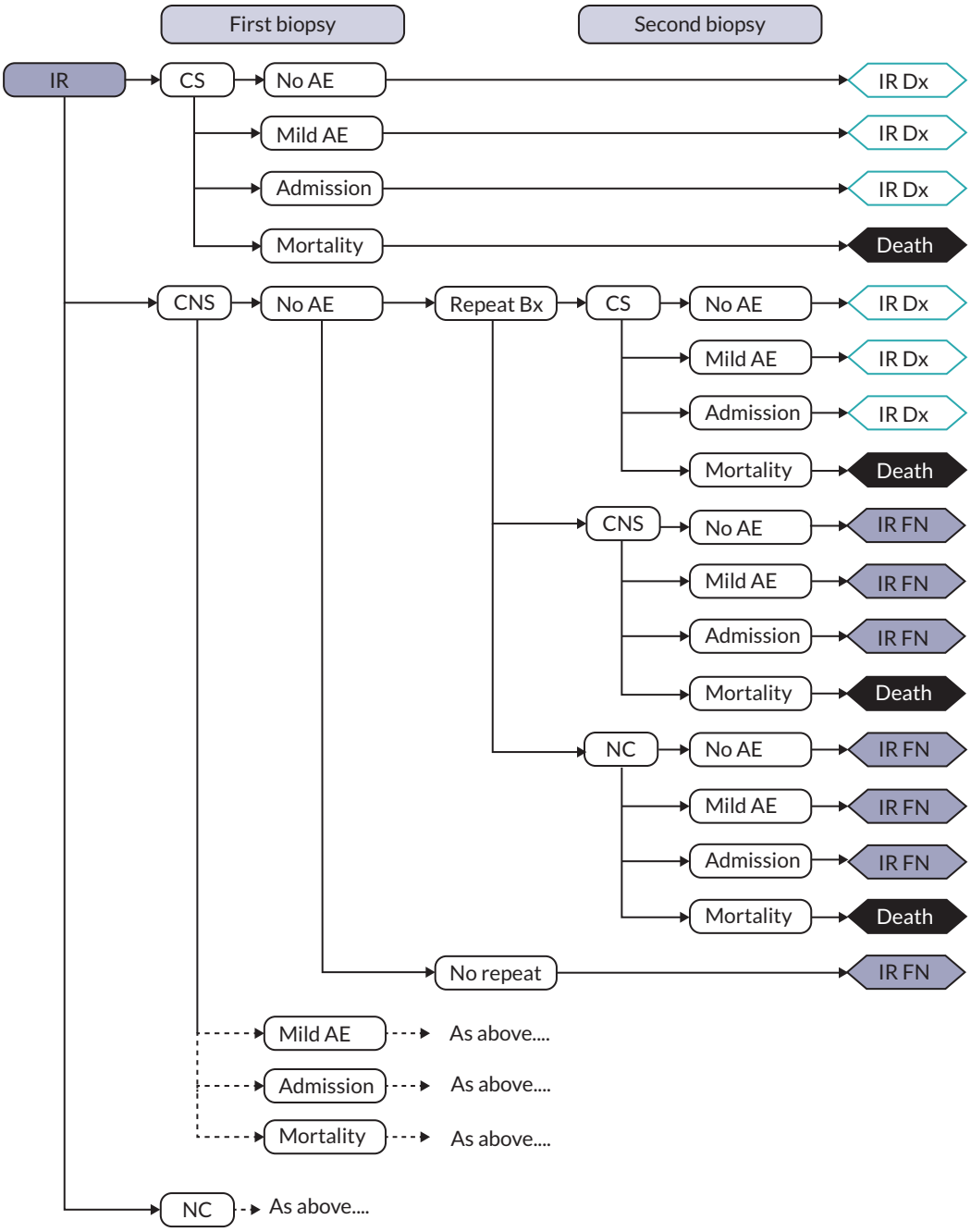

FIGURE 7 Illustration of decision tree for people with IR prostate cancer. AE, adverse event; Bx, biopsy; IR, true intermediate-risk; IR Dx, intermediate-risk correctly diagnosed (classified as CS); IR FN, intermediate-risk FN (classified as CNS or no cancer).

Model parameters

Baseline prevalence

Estimates of the true prevalence of prostate cancer for each of the subgroups, A–D, are shown in *Table 29*. These provide the starting proportions of the cohort allocated to LR, IR and HR disease in the decision-tree model. They were derived from the following PROMIS results reported by Faria *et al.*:[65]

- True cancer status in the PROMIS cohort defined by the most severe of the template mapping biopsy and TRUS biopsy results (Faria *et al.* supplement table 5).[65]

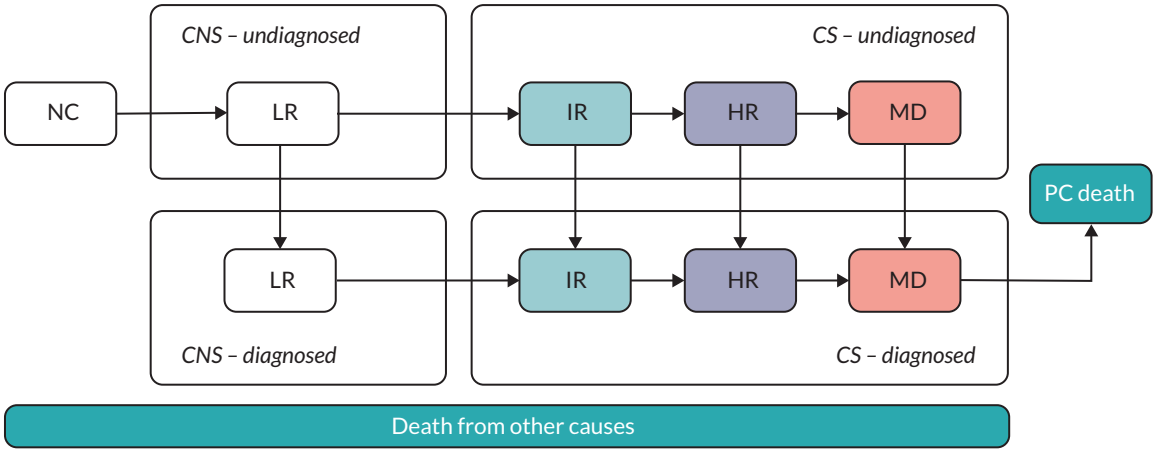

FIGURE 8 Schematic of Markov model structure. PC, prostate cancer. Source: adapted from NG131 health economic model report[67] figure HE01.

TABLE 29 Prevalence of prostate cancer for included subgroups

	First biopsy		Previous negative biopsy	
	Likert 3+	Likert 1 or 2	Likert 3+	Likert 1 or 2
True disease status	Subgroup A (%)	Subgroup B (%)	Subgroup C (%)	Subgroup D (%)
No cancer	19.4	47.7	40.0	59.4
LR cancer	12.4	25.7	25.7	32.0
IR cancer	63.8	26.6	34.3	8.6
HR cancer	4.4	0.0	0.0	0.0

Source
Estimated by EAG from prevalence and diagnostic yield of mpMRI and TRUS biopsy from PROMIS (Faria *et al.* supplementary tables 5, 6 and 7).[65]

- Diagnostic yield of mpMRI: probability of mpMRI result of no cancer, CNS or CS disease, given true cancer status (Faria *et al.* table 3, CNS definition 2, Likert cut-off ≥ 3).[65]
- Diagnostic yield of first TRUS biopsy: probability of finding of no cancer, CNS or CS disease, given true cancer status (Faria *et al.* table 2, Type 4, CNS definition 2).[65]

We combined these results using Bayes formula. For example, the probability that a member of subgroup A does not have cancer is calculated from the probability that someone with no cancer had Likert ≥ 3, the proportion of the cohort with no cancer and the overall probability of Likert ≥ 3: p(NC | Likert ≥ 3) = (p(Likert ≥ 3 | NC) * p(NC))/p(Likert ≥ 3).

We note the zero probability of true HR localised prostate cancer for people with a Likert 1 or 2 result from mpMRI (Faria *et al.*, supplementary table 7). We understand that such cases may occur in practice, although this may reflect inaccurate mpMRI scoring.

Cancer detection rates

Cancer detection rates for LATRUS prostate biopsy

Estimates of diagnostic yield for LATRUS biopsy were taken from the PROMIS economic evaluation (*Table 30*). These results correspond with definition 2 for a CS TRUS result, which reflects the definition in the optimal cost-effective strategy identified by Faria *et al.*. Methods of calculation for these results are reported in supplementary section 2.2 of Faria *et al.*.[65]

TABLE 30 Cancer detection rates for LATRUS biopsy

True cancer status	Probability of TRUS result		
	No cancer	CNS	CS
First biopsy after a suspicious mpMRI result[a]			
LR cancer	0.79 (0.66 to 0.89)	0.21 (0.11 to 0.34)	
IR cancer	0.15 (0.09 to 0.21)	0.11 (0.06 to 0.16)	0.74 (0.65 to 0.84)
HR cancer	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	1.00 (1.00 to 1.00)
Second biopsy after a negative first biopsy and suspicious mpMRI result[b]			
LR cancer	0.68 (0.02 to 1.00)	0.32 (0.02 to 0.91)	
IR cancer	0.05 (0.02 to 0.11)	0.08 (0.03 to 0.18)	0.87 (0.71 to 0.95)
HR cancer	0.05 (0.02 to 0.11)	0.08 (0.03 to 0.18)	0.87 (0.71 to 0.95)

a Test 4, PROMIS data and Schoots *et al.* 2015.
b Test 5 based on Schoots *et al.* 2015.[93]
Source
Faria *et al.* 2018, supplementary table 6.[65]

Relative risks for cancer detection with other biopsy methods

Cancer detection rates for the other biopsy methods in decision questions 1 and 2 are estimated by adjusting the LATRUS rates using RRs from the EAG evidence synthesis described in *Intermediate outcomes*. Our original base case used results from the NMA of RCTs reported in *Figures 13* and *18 in Appendix 4*. These include results from the Hara *et al.*[26] and Takenaka *et al.*[28] trials classified as comparisons between LATP (without freehand device) and LATRUS. However, there are uncertainties over this classification due to the types of anaesthesia used in the Hara and Takenaka trials (spinal injection in the transperineal arm and caudal block in the transrectal arm). We therefore used a NMA excluding these two trials in a revised EAG economic base case. The results of the revised network meta-analyses results excluding the Hara and Takenaka trials are shown in *Table 31*, alongside two alternative NMA scenarios. We also conducted a scenario analysis based on the pairwise meta-analyses of observational studies. See *Scenario analysis: cancer detection rates* for discussion of these scenario analyses.

There is high uncertainty over comparative cancer detection rates between the included biopsy methods, as indicated by the confidence intervals in *Table 31*. In addition, there is uncertainty related to the nature of the evidence base, including potential risks to internal validity of the RCTs and clinical heterogeneity between studies, and various assumptions and simplifications that we had to make.

TABLE 31 Relative risks for cancer detection

	Base case NMA excluding Hara and Takenaka[26,28]	Scenario 1 Hara and Takenaka[26,28] trials included as LATP vs. LATRUS	Scenario 2 Hara and Takenaka[26,28] trials included as GATP vs. LATRUS
Decision question 1			
LATP-any	1.15 (0.93 to 1.41)	1.01 (0.85 to 1.18)	1.09 (0.91 to 1.30)
GATP	1.09 (0.75 to 1.60)	0.96 (0.64 to 1.44)	0.92 (0.77 to 1.09)
Decision question 2			
LATP-freehand	1.40 (0.96 to 2.04)	1.40 (0.96 to 2.04)	1.40 (0.96 to 2.04)
LATP-other	1.05 (0.83 to 1.34)	0.94 (0.81 to 1.10)	1.01 (0.82 to 1.24)
GATP	1.01 (0.67 to 1.51)	0.90 (0.63 to 1.29)	0.90 (0.76 to 1.08)

a Relative risk for GATP vs. LATP adjusted for comparison with LATRUS.

- The NMA value for 'LATP-freehand' is based on a single RCT (Lam *et al.*), which used the PrecisionPoint device.[27] It is not clear whether this is representative of the list of freehand devices included in the scope. Given the lack of evidence for other devices, we model LATP-freehand for decision question 2 as a single intervention but test the impact of using different prices for the respective devices in scenario analyses (see *Scenario analysis: biopsy costs*).
- The scope specifies LATP biopsy with a grid and stepping device as a comparator for decision question 2. However, reporting of LATP methods and devices in the clinical evidence base made it difficult to separate evidence relating to grid and stepping devices. We therefore use a pooled estimate for studies that did not report use of a freehand device ('LATP-other').
- The value for GATP is based on a single RCT (Lv *et al.*), which compared with LATP.[42] This means that RR estimates from the NMA compared with LATRUS differ for decision questions 1 and 2.

Probability of a repeat biopsy

The probability of patients having a second biopsy after a negative first biopsy is based on a prospective cohort study reported by Jimenez *et al.*.[85] They assessed whether an initial GATP biopsy (systematic TP with 30 cores taken in theatre under general or spinal anaesthetic) translated into a lower risk of re-biopsy compared with LATRUS (systematic transrectal biopsy with 12–18 cores taken in office under local anaesthetic). Repeat biopsy was indicated based on a protocol defined by the authors (see table 1 in Jimenez *et al.*).[85] The number of patients having GATP in the cohort was much smaller than those having LATRUS, and patients with larger prostates were preferably selected for GATP. During the study period, 15.5% (95/615) and 5.4% (3/56) of patients had repeat biopsies after LATRUS and GATP respectively ($p = 0.06$). This difference was statistically significant in a multivariate analysis with adjustment for PSA density ($p = 0.03$). However, there are uncertainties over the generalisability of this result due to the lower sample size for GATP and differences in prostate volume and the numbers of core samples. We applied the LATRUS re-biopsy rate (15.5%) in our base case for all biopsy methods and varied this in scenario analyses (see *Appendix 9*, *Table 87*).

Biopsy-related complications

Comparative rates of complications from our systematic review are reported in *Clinical outcomes*. The included studies reported a variety of adverse outcomes, but the studies were too heterogeneous for meta-analysis and the individual studies lacked power to reliably estimate adverse-event rates. We therefore used other observational sources identified from our clinical and economic searches to estimate complication rates for the model. See *Table 32* for a summary of sources used in our base case analysis.

For admission and mortality, we used results from an analysis of NHS Hospital Episode Statistics by Tamhankar *et al.*.[94] They included all patients with a code of M702 (transperineal needle biopsy of prostate) or M703 (transrectal needle biopsy of prostate) between April 2008 and March 2019, and identified those who were readmitted or attended accident and emergency within 28 days after the biopsy. These data do not distinguish between transperineal biopsies conducted under local or general anaesthetic. We used results from the two most recent years (April 2017–March 2019), following advice that these are more reflective of current practice. In the 2017–9 cohort, non-elective admissions were lower after TP than after transrectal biopsy, but the difference was not statistically significant (3.54% and 3.74% respectively, $p = 0.11$). Infections were the main cause of non-elective admissions after transrectal biopsy, while urinary retention was the main cause after TP. Mortality within 28 days of the procedure was rare and similar after transperineal and transrectal biopsy (0.05% and 0.07%, respectively).

The decision-tree model also included biopsy-related complications treated outside hospital ('mild' adverse events) (see *Decision tree structure*). For this outcome, we used complication rates from different sources for transrectal and transperineal biopsies, as we could not identify a suitable source that included both. Rosario *et al.* reported healthcare contacts within 35 days of a TRUS biopsy for a prospective cohort of 1147 patients nested within the ProtecT trial.[95] Pepe and Aragona reported complications within 15–20 days of a TP in a single-centre study in Italy.[96] This cohort included

TABLE 32 Biopsy complication rates

Biopsy		*n*	Mean (%)	95% CI
Tamhankar et al. 2020, analysis of Hospital Episode Statistics data (2017–9)[94]				
TRUS	Non-elective admission	2845/76,106	3.74	3.60 to 3.87
	Mortality	53/76,106	0.07	0.05 to 0.09
TP	Non-elective admission	1314/37,077	3.54	3.36 to 3.73
	Mortality	19/37,077	0.05	0.03 to 0.08
Rosario et al. 2012, prospective cohort associated with ProtecT study[95]				
TRUS	Consultation with GP or nurse	119/1147	10.4	8.7 to 12.3
	Hospital admission	15/1147	1.3	0.8 to 2.1
Pepe and Aregona 2013, cohort study[96]				
TP	Emergency department visit	274/3000	9.1	8.1 to 10.2
	Hospital admission	37/3000	1.2	0.9 to 1.7

n, sample size.

3000 patients who underwent biopsy under general or local anaesthetic, with 12, 18 or 24 or more biopsy cores.

In the base case, we assumed the same rates of complications for LATP and GATP. We have received conflicting expert advice over the relative incidence of complications for transperineal biopsies under local or general anaesthetic, although Pepe and Aragona reported that these rates were 'superimposable'.[96]

Scenario analyses for other estimates of biopsy-related hospital admission rates are reported in *Scenario analysis: probability of biopsy complications*. In addition to scenarios with admission rates from the Rosario and Pepe and Aragona studies (as reported in *Table 32*), we report scenarios based on a study by Berry *et al.*.[97]

Berry *et al.* used data from the NPCA linked to Hospital Episode Statistics to compare readmission rates within 30 days of a transrectal or TP (type of anaesthesia not reported) conducted prior to a new diagnosis of prostate cancer. People who underwent a TP were less likely to be readmitted to hospital because of sepsis, but more likely to be readmitted because of urinary retention than patients who underwent a transrectal biopsy. The analysis also showed that an overnight stay was significantly more likely immediately after a TP than after a transrectal biopsy (12.25% and 2.36%, respectively, $p < 0.001$). However, NICE specialist committee members advised that this difference is not reflective of current practice, as the Berry *et al.* analysis used data from a period prior to March 2017 when TP was conducted under general anaesthetic.

Long-term transition probabilities

Transition probabilities for the Markov model were based on values used in the NICE 2019 guideline update NG131.[8] The natural history parameters used to calculate transition probabilities are reported in Table HE07 of the health economic model report available on the NICE website.[67]

The base-case transition probabilities (per 3-month model cycle) are shown in *Table 33*. The matrix differs for model cycles in which primary care follow-up (PSA testing and LATRUS biopsy if indicated) is expected for people with a negative diagnosis, because the probability of diagnosis for FN cases is higher than in the other model cycles, when diagnosis is only related to symptomatic presentation.

TABLE 33 Markov model transition probabilities (per 3-month model cycle)

Non-screening cycle (diagnosis through symptomatic presentation only)													
	Per cycle probability			Undiagnosed				Diagnosed					
	Progression	Diagnosis	NC	LR FN	IR FN	HR FN	MS FN	LR Dx	IR Dx	HR Dx	MS Dx	PC death	Other death
NC	–	–	1.000	–				–					General population mortality
LR FN	0.038	0.001		0.960	0.038			0.001	0.000				
IR FN	0.085	0.010			0.906	0.084			0.009	0.001			
HR FN	0.014	0.010				0.976	0.014			0.010	0.000		
MS FN		0.073					0.927				0.073	13.380	
LR Dx	0.035							0.965	0.035				
IR Dx	0.031								0.969	0.031			
HR Dx	0.008									0.992	0.008		
MS Dx											1.000	9.060	
Screening cycle (diagnosis through primary care follow-up or symptomatic presentation)													
	Per cycle probability			Undiagnosed				Diagnosed					
	Progression	Diagnosis	NC	LR FN	IR FN	HR FN	MS FN	LR Dx	IR Dx	HR Dx	MS Dx	PC death	Other death
NC	–	–	1.000	–				–					General population mortality
LR FN	0.038	0.222		0.748	0.030			0.213	0.009				
IR FN	0.085	0.604			0.362	0.034			0.553	0.051			
HR FN	0.014	0.604				0.390	0.006			0.596	0.009		
MS FN		0.630					0.370				0.630	13.380	
LR Dx	0.035							0.965	0.035				
IR Dx	0.031								0.969	0.031			
HR Dx	0.008									0.992	0.008		
MS Dx											1.000	9.060	

MS Dx, metastatic correctly diagnosed; MS FN, metastatic false negative; PC, prostate cancer.

Source

Estimated by EAG based on parameter estimates reported by the NICE Guideline Update Team for the NG131 economic model.[67]

Costs of the biopsy procedure

We estimated the cost of each biopsy method using a micro-costing approach, including the following components:

- cost of device (where applicable)
- cost of general consumables (needles, antibiotics, anaesthesia, ultrasound, lithotomy bed, etc.)
- staff time for training
- staff time to perform biopsy (urologists, nurses, anaesthetists)
- cost of the place of biopsy (outpatient room, theatre session)
- cost of reprocessing for reusable devices
- cost of histopathological analysis
- urologist consultation to discuss biopsy results and disease management.

Estimates were based on information provided to NICE by the companies (including the YHEC study),[84] from clinical experts, and from the study by Wilson *et al.*.[63] Where information was not available, we made assumptions. More details on the assumptions used in the estimation of biopsy costs are shown in *Appendix 8*. Costs of consumables are summarised in *Appendix 8*, *Table 72*.

We estimated a cost of £681 for LATRUS biopsy and £1251 for GATP (*Table 34*). The estimated cost varies between LATP methods and devices.

- For decision question 1, we used a base case cost of £776 for LATP-any, which is the mean of the named LATP devices (CamPROBE, PrecisionPoint, EZY-PA3, UA1232, Trinity Perine and SureFire Guide), LATP with a grid and stepping device and LATP with a coaxial needle ('double freehand').
- For decision question 2, we used a cost of £781 for 'LATP freehand': the mean cost for all named LATP devices (CamPROBE, PrecisionPoint, EZY-PA3, UA1232, Trinity Perine and SureFire Guide). For 'LATP other', we used the estimated cost for LATP with a grid and stepping device (£791).

See *Scenario analysis: biopsy costs* for scenario analysis with different estimates of biopsy costs.

Resource use and costs for management of suspected prostate cancer

In addition to the cost of biopsies, the model includes costs for subsequent follow-up and monitoring, diagnosis and the treatment of prostate cancer and adverse events. In this section, we summarise the key assumptions used for costing. Full details of resource use inputs to the base-case model are listed in *Appendix 8*, *Table 73*. Unit costs are listed in *Appendix 8*, *Table 74*.

Monitoring of suspected and diagnosed prostate cancer

We based our assumptions regarding the monitoring of suspected and diagnosed prostate cancer on the recommendations outlined in the 2019 update of NICE guideline NG131[8] and the assumptions of the decision model that informed NG131.[67]

Initial diagnostic pathway in the decision tree:

- A proportion of patients with a first biopsy result of no cancer or CNS disease were assumed to repeat the biopsy.
    - MRI Likert score 3+: base-case assumption is that 5.0% of patients with biopsy result no cancer and 15.5% of patients with CNS repeat the biopsy.
    - MRI Likert score 1 or 2: base-case assumption is that 1.3% of patients with biopsy result no cancer and 5.0% of patients with CNS repeat the biopsy.
- Patients without cancer are assumed to receive a correct diagnosis at first or second biopsy and are discharged with no additional costs at the end of the decision tree.

TABLE 34 Micro-costing analysis: cost components and total cost of biopsy methods

	Cost per biopsy									
	LATP									
Cost component	CamPROBE	PrecisionPoint	EZU-PA3U	UA1232	Trinity Perine	SureFire Guide	Grid and stepping device	Double freehand	GATP	LATRUS
Device	£70	£200	£19	£14	£8	£135	£80	–	£80	–
Consumables	£87	£87	£108	£87	£89	£87	£87	£109	£170	£86
Training	£2	£5	£1	£1	£1	£5	£5	£5	£5	£1
Biopsy staff										
Urologist	£49	£40	£44	£44	£44	£44	£44	£44	£119	£37
Nurse	£25	£21	£23	£23	£23	£23	£23	£23	£62	£19
Anaesthetist	–	–	–	–	–	–	–	–	£119	–
Place of biopsy	£53	£43	£48	£48	£48	£48	£48	£48	£194	£40
Reprocessing	–	–	£5	£5	£5	–	£5	–	£5	–
Histopathology	£439	£439	£439	£439	£439	£439	£439	£439	£439	£439
Urologist consult	£60	£60	£60	£60	£60	£60	£60	£60	£60	£60
Total	**£785**	**£894**	**£746**	**£721**	**£715**	**£826**	**£791**	**£727**	**£1251**	**£681**

Primary care follow-up for suspected prostate cancer in the Markov model:

- There is a probability that patients with undiagnosed prostate cancer (LR, IR, HR and metastatic) can be diagnosed in each 3-month model cycle due to symptomatic presentation or follow-up in primary care (*Table 33*).
- We assume that primary care follow-up consists of a PSA velocity test after 6 months, and yearly thereafter. Patients with a positive PSA (threshold 0.75 mg/ml/year) are assumed to have a TRUS biopsy for disease confirmation. The proportion of patients having a positive PSA (69%) is the sensitivity of the PSA velocity test used in the NG131 economic model.[67]

Monitoring of diagnosed disease in the Markov model:

- Once diagnosed, patients are offered active surveillance, radical treatment, treatment for MD or watchful waiting, depending on their level of risk. We made the following assumptions regarding subsequent monitoring.
- Active surveillance was assumed to include: PSA measurement every 3 months and DRE and mpMRI at 12 months in the first year; and subsequently, PSA measurement every 6 months and DRE every 12 months.
- Following radical treatment, patients were assumed to have a PSA test every 6 months for 2 years and once a year thereafter.
- Patients diagnosed with prostate cancer on watchful waiting were assumed to require a PSA measurement once a year.
- Half of the patients diagnosed with IR, 70.0% diagnosed with HR and 100.0% diagnosed with metastatic prostate cancer were assumed to have a computerised tomography (CT) and a bone scan to monitor for metastases once.

The costs of repeat biopsy were based on the microcosting analysis (as in *Table 34*). The cost of PSA involves the costs of the test kit and the cost of a primary care nurse appointment to take the blood sample (assumed to last 10 minutes). Costs for PSA tests, mpMRI, CT and bone scans were obtained from NHS National Cost Collection Data Publication 2019–20.[90] The cost of DRE was assumed to be the cost of a 20-minute GP appointment. The costs of nurse and GP appointments were obtained from Personal Social Services Research Unit (PSSRU) 2020.[89] See *Appendix 8*, *Table 74* for the unit costs.

Treatment for diagnosed prostate cancer

Patients with LR or IR localised prostate cancer will have one of the following treatments: active surveillance, radical prostatectomy or radical radiotherapy. Patients with HR localised prostate cancer will have radical prostatectomy or radical radiotherapy. Patients with no intent of curative treatment in the IR and HR groups may choose a watchful waiting approach.

The distributions of patients by risk group across treatments for localised disease were obtained from the NPCA Annual Report 2020.[92] This reported that around 5.0% of patients with LR and 71.0% of patients with HR localised disease have radical treatment. The distribution across radical treatments (radical prostatectomy and radical radiotherapy) were informed by a study by Gnanapragasam *et al.* (see *Appendix 8*, *Table 73*).[98]

Radical prostatectomy was estimated as a robotic surgery.[92] Radical radiotherapy includes both brachytherapy and of hypofractionated radiotherapy using image-guided intensity-modulated radiation therapy. During radical radiotherapy, patients were assumed to receive androgen-deprivation therapy (ADT): bicalutamide 50 mg for 21 days followed by leuprorelin/triptorelin 11.25 mg or goserelin 3.6 mg for 3 months to patients with LR prostate cancer, 6 months to patients with IR prostate cancer and 2 years to patients with HR prostate cancer.[67,99]

The management of MD, according to NG131, includes a course of docetaxel plus ADT for patients without significant comorbidities or ADT alone for patients not suitable to receive docetaxel. In addition, two drugs were more recently recommended for metastatic hormone-sensitive prostate cancer – apalutamide plus ADT (ID1534)[86] and enzalutamide plus ADT (TA712).[87] The proportion of patients taking docetaxel for metastatic hormone-sensitive prostate cancer (36.0%) was obtained from the NPCA Annual Report 2020,[92] while the proportion of patients taking ADT alone was assumed to be 50.0% and the remaining treatment options were assumed to be taken by the remaining patients (7.0% each).

The treatment with docetaxel consists of six cycles of 3 weeks at a dose of 75 mg/m^2. ADT alone, apalutamide plus ADT and enzalutamide plus ADT were taken until disease progression, which we assumed to occur after 2 years.

Once patients progress to metastatic hormone-relapsed prostate cancer, we assumed that they could have one of the following:

- abiraterone for 8 months
- enzalutamide for 14 months
- docetaxel for 9.5 cycles
- best supportive care.

The distribution across metastatic treatments for hormone-relapse disease were informed by NICE Technology Appraisal (TA712)[87] as reported in *Appendix 8*, *Table 73*. We assumed that patients could only have abiraterone or enzalutamide at this stage if they had not previously received these treatments.

The costs for radical treatment were obtained from NHS National Cost Collection Data Publication 2019–20,[90] while the costs for ADT and drugs for MD were obtained from British National Formulary (BNF) 2020 and electronic market information tool (eMIT) 2020 (see *Appendix 8*, *Table 74*).[100,101]

Managing adverse events associated with prostate biopsy and radical and metastatic treatment

Biopsy-related adverse events were categorised into mild (requiring consultation with a GP or other healthcare professional), hospital admission (including haematuria, urinary retention, sepsis) and death. See *Biopsy-related complications* for the estimated incidence of biopsy-related adverse events used in the base case model.

We modelled the most common adverse events associated with radical treatment: sexual, urinary and bowel dysfunction. Incidence data were sourced from the ProtecT study.[102] For metastatic treatment, we considered the adverse events from STAMPEDE[103] for ADT and docetaxel plus ADT, from TITAN for apalutamide plus ADT[104] and from ARCHES for enzalutamide plus ADT.[105] See *Appendix 8*, *Table 73* for rates of treatment-related adverse events used in the base-case model.

The costs of biopsy-related adverse events were taken from the Tamhankar study (estimated cost per patient of non-elective admission), inflated to the cost year 2019–20 using inflation indices from PSSRU 2020.[89,94] Costs of the remaining adverse events were taken from the NHS National Cost Collection 2019–20[90] and the decision model that informed NG131[67] (see *Appendix 8*, *Table 74*).

We assume the same cost of adverse events for misdiagnosed patients (FN LR, IR, HR and metastatic) on primary care follow-up as for patients undergoing active surveillance.

End-of-life costs

End-of-life costs were applied to the number of new deaths per cycle. We considered the end-of-life costs estimated by Round *et al.* in 2015[106] (£14,859) and inflated the cost to the cost year 2019/20, based on the inflation indices from PSSRU 2020[89] (£16,052).

Utilities

Health-related quality-of-life (utility) values for the decision model were derived from studies identified from the systematic review 'HRQoL 2' (see *Tables 27* and *28*) and from references in relevant economic evaluations (see *Results of the review of economic studies* and *Overview of other published economic studies of interest*).

Decision tree

The initial utility of the cohort on entry to the decision tree was based on age and gender-related utilities for the general population in England, estimated by Ara and Brazier.[107] This source was also used to adjust utility as the cohort aged within the Markov model.

We did not apply a direct loss of utility associated with the yield of a prostate biopsy, regardless of the method used (LATP, GATP or LATRUS). Evidence on the degree of pain and discomfort or tolerability of different prostate biopsy methods is sparse (see *Tables 25* and *26*). Faria *et al.* assumed that the impact on patient-reported EQ-5D from the PROMIS study was associated with the transperineal mapping biopsy, and assumed no utility loss from TRUS biopsy, based on results from a large European screening study.[65,70]

The model does account for the utility impact of biopsy-related adverse events. The utility decrement for mild adverse events (treated without admission) and adverse events requiring admission was based on the estimates used by Wilson *et al.*[63] and Lee *et al.*[108] for urinary-tract infection (−0.289 for 3 days) and sepsis (−0.490 for 30 days) respectively. The decrement for urinary-tract infection is based on a study from 1997,[109] which assessed suspected urinary-tract infection in healthy adult women. The decrement applied to sepsis is based on a study from 2001,[110] which assessed the change in health status among sepsis survivors over a 6-month period.

We assumed a utility decrement of −0.490 for 30 days for patients who died due to biopsy adverse events, in addition to the QALY loss associated with lost years of life.

Markov model

For the localised disease health states (including LR, IR and HR), utilities were based on population norms with adjustment for age,[107] since there is no evidence of worse HRQoL than in the general population.[81,82] We have, however, included utility decrements for adverse effects associated with treatments for localised disease. These were calculated as the difference between the EQ-5D utilities reported for no/mild complications and moderate/severe complications reported by Watson *et al.*[83] Utility decrements of 0.023, 0.095 and 0.209 were applied to sexual, urinary and bowel dysfunction, respectively (*Table 28*). Incidences of these complications with active monitoring, prostatectomy and radiotherapy were estimated from the ProtecT study:[102] see *Appendix 8*, *Table 73*.

For the metastatic health state, we applied a utility decrement of 0.137 obtained from the study by Torvinen *et al.*[82] This decrement was calculated as the difference between the average EQ-5D score reported for localised cancer (0.877) and the EQ-5D score reported for metastatic cancer (0.740) (*Table 28*).

For patients with undiagnosed disease (FN LR, IR, HR localised or metastatic), we assumed the same disutility as for patients on active surveillance. This results in patients with undiagnosed MD having a much lower disutility (−0.019) than patients with diagnosed MD (−0.137). This can be explained as undiagnosed patients do not experience treatment-related adverse effects and patients with severe symptoms are unlikely to be undiagnosed. We have tested the impact of this assumption in scenario analysis, applying the disutility of diagnosed metastatic patients (−0.137) to undiagnosed metastatic patients.

Model assumptions

Table 35 lists the key assumptions in the de novo economic model.

Model validation

The model was developed by two health economists (JL and IR). The model was developed sequentially, starting with the cost and utility calculation sheets, then the parameter sheet, one copy of the decision tree, one copy of the Markov trace and the results sheets. Each element of the model was created

TABLE 35 Model assumptions

Population	Initial cohort have had mpMRI as a first-line investigation for suspected clinically localised prostate cancer.
	Initial cohort does not include people with evidence of MD.
	Initial cohort does not include people for whom active treatment would not be appropriate – they would not be referred for biopsy.
	Initial mean age of the cohort is 66 years.
Diagnostic accuracy	All biopsies are assumed to be perfectly specific – if the biopsy result is positive (CNS or CS), the person has true disease (LR, IR, HR or metastatic). Although we classify diagnosis of LR localised disease as a 'true positive', we note that treatment would not usually be indicated for this patient group. Hence, in NG131 a correct diagnosis of LR was labelled as a 'true negative'. Despite this different terminology, assumptions about treatment for this group within our model are the same as in the NG131 analysis.
Biopsy pathway	A proportion of patients with a negative result from a first biopsy have a repeat biopsy. Second biopsies are assumed to be conducted with an LATRUS method.
Biopsy complications	The incidence of biopsy complications does not differ by true disease status (LR, IR or HR localised prostate cancer).
Natural history	The NG131 model makes the following assumptions about disease incidence and progression. True negative patients are at continuous risk of developing the disease; this is included in our model although we set the probability of incidence to zero for our base case. True negative patients who develop the disease must pass through FN states, starting on LR, before moving to true positive states. People with true disease (diagnosed or undiagnosed) are at continuous risk of progression. Progression occurs from LR to IR to HR and then to metastatic. Prostate-cancer-specific death occurs only among people with MD.
Utilities	Utility for localised disease is assumed equal to that of the general population plus disutilities from radical treatment adverse events.
	Patients with a FN biopsy result (LR, IR, HR and metastatic) have the same disutility as patients on active surveillance.
Follow-up pathway	A proportion of patients with a first biopsy result NC or CNS repeat the biopsy. The probability of a repeat biopsy will be higher with a prior mpMRI Likert score of 3 or more (5.0–15.5%) than with a score of 1 or 2 (1.3–5.0%).
	Patients without cancer and a biopsy result NC are discharged and no additional costs are incurred.
	Patients with LR prostate cancer and a biopsy result NC as well as patients with IR, HR or metastatic and a biopsy result NC or CNS are followed up in primary care.
	Patients with LR prostate cancer and a biopsy result CNS as well as patients with IR and a biopsy result CS are offered a choice between radical treatment or active surveillance, while patients with HR prostate cancer and a biopsy result CS are not offered active surveillance. A proportion of patients with no intent of curative treatment have watchful waiting. Patients with MD are offered drugs for MD.
	Primary care follow-up consists of a PSA velocity test measurement at 6 months and yearly thereafter. Patients with a positive PSA (threshold 0.75 mg/ml/year) have a LATRUS biopsy for disease confirmation.

continued

TABLE 35 Model assumptions (*continued*)

Follow-up resource use	Active surveillance costs consist of a PSA measurement every 3 months, DRE and mpMRI at 12 months in the first year and PSA measurement every 6 months and DRE every 12 months in the subsequent years.
	Patients having radical treatment have a PSA every 6 months for 2 years and once a year thereafter.
	Patients on watchful waiting require a PSA measurement once a year.
	Half of the patients diagnosed with IR disease, 70.0% of the patients with HR disease and 100.0% of the patients with MD have one CT and bone scan.
Prostate cancer treatment	The proportion of patients taking ADT alone for metastatic hormone-sensitive prostate cancer is 50.0% and the proportions taking apalutamide plus ADT and enzalutamide plus ADT are 7.0% each.
	ADT alone, apalutamide plus ADT and enzalutamide plus ADT are taken until disease progression, which we assumed to occur after 2 years of having metastatic hormone-sensitive disease.
	Once patients progress to metastatic hormone-relapsed prostate cancer, they can only have abiraterone or enzalutamide if they have not received apalutamide or enzalutamide before.
	All patients receiving radical radiotherapy receive ADT.
Micro-costing analysis	A co-axial needle was assumed to be used for biopsies using double freehand devices and EZU-PA3U.
	Antibiotic prophylaxis for TP biopsies is one prophylactic dose of ciprofloxacin (500 mg), while for LATRUS biopsies it is a course of ciprofloxacin 500 mg twice a day for 3 days.
	We assumed the average cost of the ultrasound machine costs of EZU-PA3U, UA1232 and Trinity Perine as the cost of the ultrasound machine and transducer of the remaining biopsy methods and devices. We also assumed the same lifetime, number of procedures and proportion of biopsies as for a stepper.
	We assumed that an average of five urologists per hospital have training each year regardless of the biopsy method. We assumed that a whole day (8 hours) of training would be required per person for SureFire Guide, LATP using grid and stepping device, LATP using double freehand devices and GATP. For LATRUS, we assumed that this would only require 1 hour of training – based on the assumption that urologists will already be familiar with this technique.
	We assumed that all biopsies are carried out by one urologist and that there are two nurses in the room for assistance.
	We assumed the mean procedure time for CamPROBE and PrecisionPoint (0.37 hours) for the remaining LATP devices and 1.00 hour for GATP.
	The cost of reprocessing was assumed to be £5, as advised by a Specialist Committee Member.
	For the base case, we assumed that 12 samples were taken from a prostate biopsy regardless of the biopsy method.
	We assumed that 1000 biopsies are carried out per year on average per hospital. This informed estimates of the cost per patient for capital equipment.

independently by one member of the team and checked by the other before proceeding. One version of the decision-tree sheets was developed and double-checked before duplicating for other arms of the analysis. Similarly, one version of the Markov model was developed and checked first, and then duplicated. Calculations of the Markov probabilistic input parameters, the transition matrix and Markov trace were cross-checked against the calculations in the NG131 model, to which we had access.

Economic analysis results

Base-case results for decision question 1

Deterministic results

Deterministic cost-effectiveness results for decision question 1 are shown in *Table 36*. LATP-any is more costly but yields more QALYs than LATRUS for all subgroups. The incremental cost-effectiveness

TABLE 36 Base-case cost-effectiveness (deterministic): decision question 1

	Total		Incremental		INHB (QALYs)		ICERs
Biopsy method	**Cost**	**QALYs**	**Cost**	**QALYs**	**£20k**	**£30k**	**£/QALY**
Subgroup A: MRI Likert 3 + first biopsy							
LATRUS	£19,878	9.299					
LATP-any	£19,919	9.306	£40	0.007	0.005	0.006	£5859
GATP	£20,405	9.304	£486	−0.002	−0.021	−0.013	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,753	9.478					
LATP-any	£15,805	9.483	£51	0.004	0.002	0.003	£11,610
GATP	£16,286	9.482	£482	−0.001	−0.023	−0.014	Dominated
Subgroup C: MRI Likert 3 + previous negative biopsy							
LATRUS	£16,653	9.456					
LATP-any	£16,703	9.461	£50	0.004	0.002	0.003	£11,111
GATP	£17,185	9.460	£482	−0.001	−0.023	−0.014	Dominated
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	£14,066	9.547					
LATP-any	£14,121	9.550	£55	0.003	0.001	0.001	£16,792
GATP	£14,601	9.550	£480	0.000	−0.024	−0.015	Dominated

Notes
ICER (fully incremental).
INHB vs. LATRUS, at thresholds £20,000–30,000/QALY gained.

ratio (ICER) for LATP-any versus LATRUS increases from £5859 per QALY gained in subgroup A up to £16,792 per QALY gained for subgroup D. LATP-any dominates GATP in all subgroups, as it is less costly but no less effective.

Probabilistic results

Results of the probabilistic sensitivity analysis for decision question 1 are shown in *Appendix 9*, *Table 75*. The results are similar to the deterministic results, with slightly higher ICERs for LATP-any compared with LATRUS: £6710 per QALY gained in subgroup A up to £19,126 in subgroup D. GATP is dominated in all subgroups. The probabilistic results for subgroup A are illustrated in the scatterplot and cost-effectiveness acceptability curves (CEAC) in *Appendix 9*, *Figures 22* and *23*, respectively.

Intermediate outcomes

Outcomes related to the decision-tree biopsy pathway for decision question 1 are shown in *Appendix 9*, *Table 77*. The mean numbers of biopsies per person are lower for subgroup B than for subgroup A, reflecting base-case assumptions that the probability of repeat biopsy after a negative (no cancer or CNS) first biopsy result is lower for people with a Likert score of 1 or 2 than for people with a Likert score of 3 or more. Subgroups C and D, with a previous negative biopsy, are assumed not to have a repeat biopsy within the decision tree. The proportion of the cohort with undiagnosed CS prostate cancer at the end of the decision tree declines from subgroup A to D, in accordance with expected prevalence between the subgroups. The differences between the biopsy methods in the estimated proportions of undiagnosed CS prostate cancer (FNs) are due to small, non-statistically significant differences in cancer detection estimates (*Table 31*). We note that these parameters are highly

uncertain; see *Scenario analysis: cancer detection rates* for scenario analysis using alternative estimates of comparative cancer detection rates.

Base-case estimates of biopsy-related adverse events result in a lower proportion of people with 'mild' adverse events (not requiring hospital admission) with TP than with transrectal biopsy. The estimated rate of admissions is also lower with the transperineal methods than with LATRUS. There is high uncertainty over differences in adverse-event rates with different biopsy methods, see scenario analyses in *Scenario analysis: probability of biopsy complications*.

Outcomes from the Markov model for decision question 1 are summarised in *Appendix 9*, *Table 78*. Deaths from prostate cancer decline and mean LYs and QALYs increase for the subgroups with lower baseline prevalence of CS prostate cancer. There are small differences in these outcomes between the biopsy methods, driven by the proportions of the cohort with FN biopsy results estimated from the decision tree.

Appendix 9, *Table 79* summarises costs estimated from the decision tree and Markov models for decision question 1. Although the estimated costs of treating prostate cancer are high, cost differences between the biopsy methods from the Markov model are very small. Total costs are therefore driven by costs of the biopsy pathway, as estimated from the decision tree. We explore the impact of uncertainty over biopsy costs in Scenario analysis: cost of core samples and Scenario analysis: biopsy costs.

Base-case results for decision question 2

Deterministic results

For decision question 2, LATP-freehand dominates both LATP-other and GATP, yielding lower costs and more QALYs in all subgroups (*Table 37*). The ICER for LATP-freehand versus LATRUS is below £20,000 per QALY gained for all the subgroups (A–D). The QALY advantage for LATP-freehand in this analysis is driven by the favourable RR of cancer detection based on a single study;[27] see *Table 31*.

Probabilistic results

Appendix 9, *Table 76* shows probabilistic results for decision question 2. As with question 1, the probabilistic results are similar to the deterministic results, with slightly higher ICERs for LATP-freehand compared with LATRUS in all subgroups, although these ICERs remain well under £20,000 per QALY gained: £2184 per QALY in subgroup A rising to £11,022 per QALY in subgroup D. LATP-other and GATP are dominated in all subgroups. The probabilistic results for this decision question are illustrated for subgroup A in *Appendix 9*, *Figures 24* and *25*.

Intermediate outcomes

Outcomes and costs for decision question 2 are shown in *Appendix 9*, *Tables 80–82*. Cancer detection rates for LATP-freehand are more favourable than for other comparators – driven by RR estimates from the NMA (*Table 31*). Other decision-tree results are very similar for LATP-freehand, LATP-other and GATP, as we use the same repeat biopsy and adverse-event rates for the transperineal methods in our base case. This might not be realistic, and we explore alternative scenarios in *Scenario analysis: cancer detection rates* and *Scenario analysis: probability of biopsy complications*.

The Markov outcomes for decision question 2 show the impact of the more favourable cancer detection rates for LATP-freehand biopsy, as deaths from prostate cancer are lower and life expectancy and QALYs are higher than for other comparators (see *Appendix 9*, *Table 81*). Costs of treatment from the Markov model are also slightly lower for LATP-freehand than for other comparators, although estimated biopsy costs are higher for LATP-freehand than for LATRUS (see *Appendix 9*, *Table 82*). We investigate alternative biopsy cost estimates in Scenario analysis: cost of core samples and Scenario analysis: biopsy costs.

Scenario analysis: cancer detection rates

Our original base case used RRs of cancer detection estimated from NMA of six RCTs, including the Hara 2008[26] and Takenaka 2008[28] trials classified as comparisons between LATP (without freehand

device) and LATRUS. There are uncertainties over this approach due to the types of anaesthesia used in the Hara and Takenaka trials (spinal injection in the transperineal arm and caudal block in the transrectal arm). We therefore excluded the Hara and Takenaka trials from the revised base case, as reported above.

Alternative NMA scenarios were reported in *Table 31*:

1. Hara and Takenaka classified as LATP-any versus LATRUS (for decision question 1) and LATP-other versus LATRUS (for decision question 2).
2. Hara and Takenaka classified as GATP versus LATRUS.

Results of these scenarios for subgroup A decision question 1 are reported in *Table 38*. For NMA scenario 1, the ICER for LATP versus LATRUS is £28,322 per QALY in subgroup A, increasing to £31,261 per QALY in subgroup D. For NMA scenario 2, the ICER for LATP versus LATRUS is £10,096 per QALY in subgroup A, increasing to £21,322 per QALY in subgroup D. GATP remains dominated in NMA scenarios 1 and 2 for all subgroups.

TABLE 37 Base-case cost-effectiveness (deterministic): decision question 2

	Total		Incremental		INHB (QALYs)		ICERs
Biopsy method	**Cost**	**QALYs**	**Cost**	**QALYs**	**£20k**	**£30k**	**£/QALY**
Subgroup A: MRI Likert 3 + first biopsy							
LATRUS	£19,878	9.299					
LATP-freehand	£19,888	9.312	£10	0.013	0.013	0.013	£743
LATP-other	£19,952	9.303	£63	−0.010	0.000	0.001	Dominated
GATP	£20,420	9.301	£468	−0.001	−0.025	−0.016	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,753	9.478					
LATP-freehand	£15,788	9.486	£35	0.008	0.006	0.006	£4595
LATP-other	£15,830	9.481	£42	−0.005	−0.001	0.000	Dominated
GATP	£16,295	9.480	£465	−0.001	−0.025	−0.016	Dominated
Subgroup C: MRI Likert 3 + previous negative biopsy							
LATRUS	£16,653	9.456					
LATP-freehand	£16,699	9.461	£46	0.005	0.003	0.003	£9284
LATP-other	£16,729	9.459	£30	−0.002	−0.001	0.000	Dominated
GATP	£17,195	9.458	£466	−0.001	−0.025	−0.016	Dominated
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	£14,066	9.547					
LATP-freehand	£14,112	9.552	£46	0.004	0.002	0.003	£10,640
LATP-other	£14,144	9.550	£32	−0.002	−0.001	0.000	Dominated
GATP	£14,608	9.549	£464	0.000	−0.025	−0.016	Dominated

Notes
ICER (fully incremental).
INHB vs. LATRUS, at thresholds £20,000–30,000/QALY gained.

For decision question 2, results are not sensitive to the NMA scenarios. This is because the RR for cancer detection with LATP-freehand versus LATRUS does not change between NMA scenarios and other comparators are dominated in all scenarios and subgroups (see *Table 39* for subgroup A).

We also investigated the effect of using observational data to estimate cancer detection rates: see *Appendix 9*, *Tables 83* and *84*. Results were not sensitive to the observational scenarios. For decision question 1, the ICER for LATP-any versus LATRUS was well below £30,000 per QALY for all observational scenarios and subgroups. For decision question 2, the ICER for LATP-freehand versus LATRUS was below £20,000 per QALY for all observational scenarios and subgroups. GATP and LATP-other in decision question 2 had high ICERs or were dominated in all observational analyses.

Scenario analysis: probability of biopsy complications

The rationale for choosing sources for the incidence of biopsy-related complications is explained in *Biopsy-related complications* above. For the base case, we used admission rates reported by Tamhankar *et al.*.[80]

TABLE 38 Network meta-analysis scenarios for decision question 1, subgroup A (deterministic)

		Total		Incremental		ICERs
Biopsy method	RR[a]	cost	QALYs	cost	QALYs	£/QALY
Network meta-analysis scenario 1: Hara and Takenaka classified as LATP-any vs. LATRUS[26,28]						
LATRUS	1.00	£19,878	9.299			
LATP-any	1.01	£19,944	9.301	£66	0.002	£28,322
GATP	0.96	£20,430	9.299	£486	−0.002	Dominated
Network meta-analysis scenario 2: Hara and Takenaka classified as GATP vs. LATRUS[26,28]						
LATRUS	1.00	£19,878	9.299			
LATP-any	1.09	£19,929	9.304	£51	0.005	£10,096
GATP	0.92	£20,439	9.298	£510	−0.006	Dominated

a Relative risk for cancer detection compared with LATRUS.

TABLE 39 Network meta-analysis scenarios for decision question 2, subgroup A (deterministic)

		Total		Incremental		ICERs
Biopsy method	RR[a]	cost	QALYs	cost	QALYs	£/QALY
Network meta-analysis scenario 1: Hara and Takenaka classified as LATP-other vs. LATRUS[26,28]						
LATRUS	1.00	£19,878	9.299			
LATP-freehand	1.40	£19,888	9.312	£10	0.013	£743
LATP-other	0.94	£19,974	9.299	£86	−0.014	Dominated
GATP	0.90	£20,444	9.297	£470	−0.002	Dominated
Network meta-analysis scenario 2: Hara and Takenaka classified as GATP vs. LATRUS[26,28]						
LATRUS	1.00	£19,878	9.299			
LATP-freehand	1.40	£19,888	9.312	£10	0.013	£743
LATP-other	1.01	£19,960	9.301	£71	−0.011	Dominated
GATP	0.90	£20,444	9.297	£484	−0.004	Dominated

a Relative risk for cancer detection compared with LATRUS.

Additional scenario analyses to test the effect of alternative estimates of biopsy-related admission rates are reported below:

1. Inclusion of additional overnight stays immediately after biopsy as reported by Berry *et al.*.[94,97] This increases the overall admission rate for transperineal biopsies more than for transrectal biopsies.
2. Inclusion of additional overnight stays from the Berry study applied to GATP only.[97]
3. Rosario *et al.*[95] used as the source of admissions. This reduces the admission rate for LATRUS compared with the base case.
4. Pepe and Aragona[96] used as the source of admissions for transperineal biopsies. This reduces the admission rate for LATP and GATP.
5. Rosario study and Pepe and Aragona study as the sources of admissions for LATRUS and transperineal biopsies respectively.

Table 40 (decision question 1) and *Table 41* (decision question 2) show the results of these scenarios for subgroup A (MRI Likert score 3+ at first biopsy).

TABLE 40 Admission scenarios: alternative sources for serious biopsy complications, subgroup A (deterministic) – decision question 1

Biopsy method	Admission rate (%)	Total		Incremental		ICERs £/QALY
		cost	QALYs	cost	QALYs	
Scenario 1: include overnight stay from Berry et al. for LATRUS, LATP and GATP[97]						
LATRUS	6.10	£19,940	9.298			
LATP all	15.61	£20,149	9.301	£210	0.003	£70,257
GATP	15.61	£20,635	9.299	£486	−0.002	Dominated
Scenario 2: include overnight stay from Berry et al. for GATP only[97]						
LATRUS	3.74	£19,878	9.299			
LATP all	3.54	£19,919	9.306	£40	0.007	£5859
GATP	15.61	£20,633	9.299	£715	−0.007	Dominated
Scenario 3: Rosario et al. admission rate for LATRUS[95]						
LATRUS	1.31	£19,815	9.300			
LATP all	3.54	£19,917	9.306	£101	0.006	£17,119
GATP	3.54	£20,403	9.304	£486	−0.002	Dominated
Scenario 4: Pepe and Aragona admission rate for LATP and GATP[96]						
LATP all	1.23	£19,875	9.307			
LATRUS	3.74	£19,878	9.299	£3	−0.008	Dominated
GATP	1.23	£20,361	9.305	£483	0.006	Dominated[a]
Scenario 5: Rosario et al. for LATRUS; Pepe and Aragona for LATP and GATP[95,96]						
LATRUS	1.31	£19,815	9.300			
LATP all	1.23	£19,873	9.307	£57	0.007	£8395
GATP	1.23	£20,359	9.305	£486	−0.002	Dominated

a Extendedly dominated by LATRUS and LATP-any.

TABLE 41 Scenario: alternative sources for serious biopsy complications, subgroup A (deterministic) – decision question 2

		Total		Incremental		ICERs
Biopsy method	**Admission rate (%)**	**cost**	**QALYs**	**cost**	**QALYs**	**£/QALY**
Scenario 1: include overnight stay from Berry et al. for LATRUS, LATP and GATP[97]						
LATRUS	6.10	£19,940	9.298			
LATP-freehand	15.61	£20,119	9.307	£179	0.009	£19,140
LATP-other	15.61	£20,182	9.298	£63	−0.010	Dominated
GATP	15.61	£20,651	9.296	£468	−0.001	Dominated
Scenario 2: include overnight stay from Berry et al. for GATP only[97]						
LATRUS	3.74	£19,878	9.299			
LATP-freehand	3.54	£19,888	9.312	£10	0.013	£743
LATP-other	3.54	£19,952	9.303	£63	−0.010	Dominated
GATP	15.61	£20,649	9.296	£697	−0.006	Dominated
Scenario 3: Rosario et al. admission rate for LATRUS[95]						
LATRUS	1.31	£19,815	9.300			
LATP-freehand	3.54	£19,886	9.312	£71	0.012	£5750
LATP-other	3.54	£19,950	9.303	£64	−0.010	Dominated
GATP	3.54	£20,418	9.301	£468	−0.001	Dominated
Scenario 4: Pepe and Aragona admission rate for LATP and GATP[96]						
LATP-freehand	1.23	£19,844	9.313			
LATRUS	3.74	£19,878	9.299	£34	−0.014	Dominated
LATP-other	1.23	£19,908	9.304	£30	0.005	Dominated
GATP	1.23	£20,376	9.302	£468	−0.001	Dominated
Scenario 5: Rosario et al. for LATRUS; Pepe and Aragona for LATP and GATP[95,96]						
LATRUS	1.31	£19,815	9.300			
LATP-freehand	1.23	£19,842	9.313	£27	0.013	£2035
LATP-other	1.23	£19,906	9.304	£64	−0.010	Dominated
GATP	1.23	£20,374	9.302	£468	−0.001	Dominated

For decision question 1, results are sensitive to the difference in admission rates between LATP and LATRUS. In scenario 1 with additional overnight stays included, the ICER for LATP is over £70,000 per QALY for subgroup A, and higher for other subgroups. In scenario 3, with a lower admission rate for LATRUS, the ICER for LATP versus LATRUS is £17,119 per QALY for subgroup A, and over £30,000 per QALY for other subgroups.

GATP is dominated in all scenarios.

For decision question 2, ICERs for LATP-freehand are higher in scenario 1 with the overnight stay included: £19,140 per QALY for subgroup A and over £30,000 for other subgroups. LATP-other and GATP are dominated in all scenarios.

We note that the excess overnight stays after TP from the Berry *et al.* study relate to Hospital Episode Statistics from 2014 to 2017, when the use of local anaesthetic for TP was rare. This suggests that scenario 2 may be a more appropriate interpretation of results from the Berry study than scenario 1.

Scenario analysis: cost of core samples

Number of core samples by biopsy method

The base-case assumption of equal numbers of core samples (12) per patient for all biopsy methods was based on a lack of data on the mean number of core samples taken in the clinical trials that contributed to the effectiveness (cancer detection) estimates in the model. Five of the six RCTs in the network meta-analyses reported protocols with the same number of cores for intervention and comparator arms. The exception was the Lam 2021 study, which used a 'modified Ginsburg' protocol for the LATP arm (with the PrecisionPoint freehand device), but a standard 12-core protocol for LATRUS.[27] The mean number of cores taken for patients in the LATP arm in the Lam study was not reported. The other RCT protocols included between 8 and 14 core samples,[24–26,28,42] although two of these trials included additional targeted sampling as needed (mean per patient not reported).[25,42]

Experts advising NICE reported that in practice the number of cores is likely to differ between biopsy methods. We understand that LATRUS biopsy is 'almost always' 10–12 cores, and that TP usually follows one of two protocols: the RAPID protocol (12–16 biopsies), mostly used for grid and stepping device LATP or GATP; and the Ginsburg protocol (24–34 biopsies), mostly used for freehand LATP or GATP. In a recent study, Lopez *et al.* reported a median of 24 cores (range 1–47) in a multicentre prospective cohort of 1218 patients who underwent LATP biopsy with the PrecisionPoint device according to the Ginsburg protocol (7 out of 10 centres from the UK).[111]

We consider three alternative scenarios including costs for different numbers of core samples taken for the different biopsy procedures:

1. 24 cores for LATP and GATP, 12 for LATRUS.
2. 24 cores for LATP-freehand and 12 for the LATP-other, GATP and LATRUS.
3. 24 cores for LATP-freehand, 16 for LATP-other and GATP and 12 for LATRUS.

Note that these scenarios only model changes to histopathology costs; we were not able to model the impact of the number of core samples on patient outcomes. In practice one would expect clinical parameters, including rates of repeat biopsy and adverse events as well as cancer detection rates, to be affected by the number of cores sampled. It may be argued that the scenario analyses with costs for 24 cores for LATP-freehand and 12 for LATRUS are more consistent with the clinical evidence from the Lam *et al.* trial.[27]

Results are highly sensitive to the scenarios with 24 cores for transperineal biopsies and 12 for LATRUS. For decision question 1, the ICER for LATP-any versus LATRUS in subgroup A is over £60,000 per QALY (*Table 42*), and in decision question 2 the ICER for LATP-freehand compared with LATRUS is £33,813 per QALY (*Table 43*). These ICERs are higher for other subgroups.

Histopathology costs

The above scenario results depend on histopathology costs in addition to the number of core samples. In the base case and core scenarios, we assumed £36.58 per core (code DAPS2, NHS cost collection 2019–20):[90] £439 for 12 cores and £878 for 24 cores. However, it has been suggested that these are overestimates, as the unit cost may be applied per sample pot, which may contain more than one core.

An alternative source for estimating histopathology costs is available from an online report by the University of Surrey.[112] This reported a cost of £37.50 for 'standard histology' (1–2 sites/lesions) and £7 per additional site/lesion. Assuming that each core sample is one 'site/lesion', this gives a cost of £108

for 12 cores and £192 for 24 cores. There is uncertainty over the appropriateness of these estimates, as we had previously received feedback that they underestimate histopathology costs.

The ICERs for LATP in the core sample scenarios are more favourable with the Surrey histopathology costs (see *Appendix 9*, *Tables 85* and *86*) than with our base-case costs (see *Tables 42* and *43*). For example, the ICER for LATP-freehand (24 cores) versus LATRUS (12 cores) with Surrey costs is £8052 in subgroup A, increasing to £33,545 in subgroup D.

Scenario analysis: biopsy costs

Decision question 1

The cost of LATP in the base case for decision question 1 assumes an equal mix of methods, including grid and stepping device, double freehand and the six named devices included in the scope. The costs

TABLE 42 Core scenarios for decision question 1, subgroup A (deterministic)[90]

		Total		Incremental		ICERs
Biopsy method	Biopsy samples	cost	QALYs	cost	QALYs	£/QALY
Core scenario 1: 24 core samples for all transperineal methods						
LATRUS	12	£19,878	9.299			
LATP-any	24	£20,358	9.306	£479	0.007	£69,547
GATP	24	£20,844	9.304	£486	−0.002	Dominated

TABLE 43 Core scenarios for decision question 2, subgroup A (deterministic)

		Total		Incremental		ICERs
Biopsy method	Biopsy samples	cost	QALYs	cost	QALYs	£/QALY
Core scenario 1: 24 cores for all transperineal methods						
LATRUS	12	£19,878	9.299			
LATP-freehand	24	£20,327	9.312	£449	0.013	£33,813
LATP-other	24	£20,391	9.303	£63	−0.010	Dominated
GATP	24	£20,859	9.301	£468	−0.001	Dominated
Core scenario 2: 24 cores for LATP-freehand only						
LATRUS	12	£19,878	9.299			
LATP-other	12	£19,952	9.303	£73	0.004	£19,716
LATP-freehand	24	£20,327	9.312	£375	0.010	£39,304
GATP	12	£20,420	9.301	£93	−0.011	Dominated
Core scenario 3: 24 cores for LATP-freehand and 16 for LATP-other and GATP						
LATRUS	12	£19,878	9.299			
LATP-other	16	£20,098	9.303	£220	0.004	Dominated[a]
LATP-freehand	24	£20,327	9.312	£229	0.010	£33,813
GATP	16	£20,566	9.301	£239	−0.011	Dominated

a Extendedly dominated by LATRUS and LATP-freehand.

were obtained from our micro-costing analysis. We conducted two scenario analyses for the overall cost of the biopsy procedure for decision question 1 (*Table 44*).

1. Biopsy costs from the National Schedule of NHS costs 2019–20:[90] £332 for LATRUS (outpatient procedure LB76Z 101, urology), £329 for LATP (outpatient procedure B77Z, 101, urology) and £1512 for GATP (day-case procedure LB77Z). In this scenario, the cost for LATRUS is slightly higher than the cost for LATP, so LATP is dominant in all subgroups.
2. Microcosting, but with different assumptions about the proportion of LATP methods used: 10% conducted with a grid and stepping device and 30% with each of the transperineal devices that we understand are currently most common in the UK (CamPROBE, PrecisionPoint and UA1232). This increases the mean cost of LATP by £23 per biopsy, which increases the ICER for LATP in subgroup A from £5859 per QALY to £9245. The ICER for LATP in this scenario remains below £20,000 per QALY for subgroups B and C and below to £30,000 per QALY in subgroup D.

Decision question 2

For decision question 2, we report three scenarios for biopsy costs.

The first scenario relates to the cost of LATP-freehand. In our base case, we used a simple average of the cost of each named device as the cost for the LATP-freehand arm. In this scenario, we use the cost of the PrecisionPoint device, which was used in the clinical trial that provided the evidence on diagnostic yield for LATP-freehand.[27] This is the most costly of the included freehand devices: £200 for the device and total cost of the procedure estimated at £894. This increases the ICER for LATP-freehand versus LATRUS in subgroup A to £9230 per QALY (*Table 45*). The ICER for LATP-freehand remains below £20,000 per QALY for subgroup B, but exceeds £30,000 per QALY for subgroups C and D.

The second and third scenarios relate to the cost of LATP-other. In the base case, we grouped evidence relating to LATP biopsy without a named freehand device together as 'LATP-other', but we based the cost for this grouped comparator only on the cost for LATP biopsy using grid and stepping device (£791). We report additional scenarios below, using the cost of LATP biopsy with a double freehand technique (£727) or LATP biopsy with the CamPROBE double freehand device (£785) for the LATP-other comparator. These scenarios do not affect the cost-effectiveness results (see *Table 45* for subgroup A). This is because LATP-other remains dominated for both scenarios, and for all subgroups.

TABLE 44 Scenario: biopsy costs from NHS Costs (deterministic) – decision question 1

		Total		Incremental		ICERs
Biopsy method	**Cost per biopsy**	**Cost**	**QALYs**	**Cost**	**QALYs**	**£/QALY**
Cost scenario 1: NHS cost data 2019–20[90]						
LATP-any	£329	£19,460	9.306			
LATRUS	£332	£19,518	9.299	£58	−0.007	Dominated
GATP	£1512	£20,654	9.304	£1136	0.005	Dominated
Cost scenario 2: LATP mix (30% each for CamPROBE, PrecisionPoint and UA1232; and 10% grid and stepping device)						
LATRUS	£681	£19,878	9.299			
LATP-any	£799	£19,942	9.306	£64	0.007	£9245
GATP	£1251	£20,405	9.304	£463	−0.002	Dominated

Other scenario analysis

Other scenario analyses are presented in *Appendix 9*, including the probability of repeat biopsy, and RR of cancer detection from observational studies. *Appendix 9*, *Table 88* presents scenario analyses conducted for decision questions 1 and 2 in subgroup A with a lower impact in the model results and that did not impact the final conclusions. The results for the other subgroups (B, C and D) follow the same tendency as the results presented in *Appendix 9*, *Table 88*.

TABLE 45 Scenarios on the cost of LATP-freehand and LATP-other for decision question 2, subgroup A (deterministic)

		Total		Incremental		ICERs
Biopsy method	**Cost per biopsy**	**Cost**	**QALYs**	**Cost**	**QALYs**	**£/QALY**
Cost of LATP-freehand: cost of PrecisionPoint device						
LATRUS	£681	£19,878	9.299			
LATP-other	£791	£19,952	9.303	£73	0.004	Dominated[a]
LATP-freehand	£894	£20,001	9.312	£49	0.010	£9230
GATP	£1251	£20,420	9.301	£419	−0.011	Dominated
Cost of LATP-other scenario 1: cost of double freehand device						
LATRUS	£681	£19,878	9.299			
LATP-other	£727	£19,888	9.303	£10	0.004	Dominated[a]
LATP-freehand	£781	£19,888	9.312	£0	0.010	£743
GATP	£1251	£20,420	9.301	£532	−0.011	Dominated
Cost of LATP-other scenario 2: cost of CamPROBE						
LATRUS	£681	£19,878	9.299			
LATP-freehand[b]	£780	£19,887	9.312	£9	0.013	£682
LATP-other	£785	£19,946	9.303	£59	−0.010	Dominated
GATP	£1251	£20,420	9.301	£474	−0.001	Dominated

a Extendedly dominated by LATRUS and LATP-freehand.
b Cost of LATP-freehand does not include the cost of CamPROBE.

Note
ICER (fully incremental).

Chapter 6 Discussion

Clinical effectiveness evidence

We conducted a comprehensive systematic review of studies assessing the diagnostic yield and clinical effectiveness outcomes of LATP prostate biopsy for people in whom prostate cancer is suspected.

We included 23 studies which we grouped into 5 pairwise comparisons of LATP prostate biopsy versus an alternative biopsy modality relevant to the decision problem. Each pairwise comparison was of primary relevance to one of two decision questions on the clinical and cost-effectiveness of LATP prostate biopsy.

The largest volume of available evidence is for comparison 1: LATP-any versus LATRUS. As its title suggests, this comparison incorporates the spectrum of LATP biopsy methods and hence has a diverse evidence base. The majority of the available LATP prostate-biopsy studies are relevant here. The strength of this evidence is mixed – some are RCTs, but the majority are observational studies of varying designs. The RCTs appear well designed and executed, but we are unclear on the potential for bias due to limitations in study reporting, as is the case for the observational studies. Decision question 2, nested within decision question 1, has a more specific focus – on the use of freehand biopsy devices. This is a smaller evidence base, in terms of number of studies, and less heterogeneous than that of the broader decision question.

We identified few differences between LATP prostate biopsy and alternatives, principally, LATRUS, in terms of key outcome measures, notably cancer detection rates. Our meta-analyses estimated RRs close to 1 for cancer detection rates, indicating similar effects. Our overall interpretation of the decision question 1 evidence is that LATP biopsy is similar to LATRUS biopsy in diagnostic yield, a conclusion shared by previous studies in this field. The strength of the evidence is adequate and there is reasonable certainty (based on relatively narrow confidence intervals in our meta-analyses).

Regarding post-biopsy complications, we discerned no definitive association between specific complications and biopsy modalities. Rates of complications were low, often occurring in a handful of participants; it would be unwise to interpret very small differences seen between biopsy methods as being definitive. This is a limitation of clinical trials and evaluations – they are often not statistically powered to detect differences in relatively rare events. Larger cohort studies and data sets often provide more certain estimates of rare events; hence we use these to inform estimates of complication rates in our cost-effectiveness analysis.

Generalisability

The TP protocols (e.g. device used/sampling method/number of cores taken) varied between studies, which may partly reflect local clinical practice guidelines in study host institutions, but also the evolution of transperineal prostate biopsy practices over time (e.g. increases in the number of cores sampled over time as protocols evolve). Some of the more recently published studies used pre-biopsy mpMRI to inform biopsy sampling, but this constitutes a small proportion of the whole evidence base. This presents a challenge to the applicability of the evidence to UK clinical practice, where mpMRI is recommended for routine use to inform the decision to refer for biopsy and may also be used to target biopsy sampling.

The studies were typically conducted in single centres by clinical investigators using local biopsy protocols to evaluate the optimum biopsy modality in their centre, on a range of outcomes such as use of general or local anaesthesia protocols, procedure time and related resources, biopsy complications

and the patient's ability to tolerate pain and discomfort during and after the biopsy. Many studies pre-date the introduction of mpMRI into prostate biopsy protocols, and given the preponderance of studies from East Asia use of mpMRI worldwide may differ from practice in the UK.

The multicentre UK study (TRANSLATE[52–54]) will provide evidence for freehand LATP using any ultrasound probe-mounted needle guidance device, including the PrecisionPoint and UA1232 devices. As the study uses freehand devices to perform the biopsies, it is expected to inform any future consideration of both decision question 1 (LATP-any vs. LATRUS) and decision question 2 (LATP-freehand vs. LATRUS). This will be the first available comparative evidence for the UA1232 device, and is expected to provide information on cancer detection, infection rates and other outcomes including cost.

Cost-effectiveness evidence

We developed an economic model to assess the cost-effectiveness of LATP prostate biopsies and freehand TP devices. The model includes a decision tree to evaluate short-term diagnostic outcomes and biopsy-related costs and adverse effects, and a Markov model that estimates the long-term costs and health consequences of failing to detect CS disease. The Markov model was replicated from a model previously developed by the NICE Guidelines Update Team to evaluate different follow-up strategies for people at increased risk of prostate cancer.[67] The model was also informed by the results and cost-effectiveness analysis of the PROMIS trial,[65] and a recent economic evaluation that compared transperineal and transrectal prostate biopsies conducted under local anaesthetic.[63]

We estimated cost-effectiveness for four subgroups of patients with suspected prostate cancer. The subgroups vary by prior likelihood of having CS prostate cancer: from the highest risk in the subgroup with mpMRI Likert 3 + and no previous biopsy to lowest in the subgroup with mpMRI Likert 1 or 2 and previous negative biopsy.

The model is designed to address both decision questions in the NICE scope, although limitations in the clinical evidence do impose some restrictions on the analysis for decision question 2: in particular, we do not have comparative evidence of the diagnostic yield or adverse-event rates of LATP with different freehand TP devices or with a grid and stepping device. Cancer detection rates for the different biopsy methods are estimated from our network meta-analyses in the base case, with scenarios using RRs from pairwise meta-analysis of observational evidence.

Relative rates of complications and repeat biopsy associated with the different biopsy methods are difficult to assess. There is good evidence from NHS practice, based on Hospital Episode Statistics and observational cohort studies.[94–96,113,114] However, this does not reliably distinguish between type of anaesthesia as well as biopsy route (transrectal vs. transperineal).

For decision question 1, the economic base-case analysis indicated that GATP is more expensive and less effective (yielding fewer QALYs) than LATP in all four subgroups. This result was based on sparse comparative evidence, with a single RCT reporting on the diagnostic yield of GATP compared with LATP.[42] The ICER for LATP based on pooled evidence for all LATP methods compared with LATRUS was below £20,000 per QALY gained in all subgroups, within the lower limit used for decision-making by NICE advisory committees. This conclusion was supported by probabilistic sensitivity analysis and a range of scenario analyses, although the results are sensitive to some uncertainties over relative cancer detection rates, rates of hospital admissions, the number of core samples and pathology costs.

For decision question 2, the economic analysis indicated that LATP with a freehand device was the most cost-effective strategy, with an ICER of £743 per QALY compared with LATRUS for the highest-risk

subgroup with MRI Likert score of 3 or more at first biopsy, and £4595 per QALY for the subgroup with a MRI Likert score 1 or 2 at first biopsy. For the subgroups with a previous negative biopsy, the ICER remained below £20,000 per QALY. These favourable ICER estimates are driven by cancer detection rates from a single RCT for LATP with a freehand device (PrecisionPoint).[27] In the scenario based on observational evidence of cancer detection rates, the ICERs for LATP with a freehand device were higher but still below £20,000 per QALY in all subgroups. However, these results were sensitive to the number of core samples per biopsy and the cost of processing them, and to the cost of the freehand device.

Strengths and limitations of the assessment

Strengths

We conducted a systematic review of evidence related to the decision questions specified in the NICE scope, with pairwise and NMA of cancer detection outcomes from both randomised and observational studies.

A major strength of the economic analysis is that we could build on the work of previous researchers to develop an appropriate decision-tree structure and model parameters, including the economic evaluation of the PROMIS study by Faria *et al.*, the adaptation of the PROMIS analysis by Wilson *et al.* and the economic model that informed the update of the NICE guideline (NG131).[63,65,67,115] The decision tree is based on prevalence and diagnostic yield data for TRUS from the PROMIS study, which used estimates of true disease status based on a template mapping biopsy as the reference standard.

Another strength is that the predicted impact of diagnostic yield on long-term costs and outcomes was based on the recent and high-quality economic model that was developed to inform an update of the NICE guideline for prostate cancer (NG131). The NICE economic model has gone through a rigorous process of development, review and discussion by members of the guideline committee (including topic specialists and methodological, patient and public experts) and consultation with stakeholders. We appreciate that the NICE Centre for Guidelines provided a copy of this model, as this helped us to replicate the transition probabilities accurately (in particular it provided access to the covariance matrices for the calibrated parameters).

The RR of cancer detection was directly informed by the clinical effectiveness systematic review and therefore we believe that the most relevant studies reporting data on cancer detection rates were considered.

Limitations

The clinical evidence base and economic model have several limitations. As discussed above, there are limitations to the generalisability of the clinical evidence to UK practice, including variations between centres and over time in TP protocols and the use of mpMRI to inform referral for biopsy, and biopsy sampling.

The definition of patient subgroups in the model was based on mpMRI Likert scores, in order to align with epidemiological data from the PROMIS study. However, we are aware that some UK centres use the PI-RADS method to summarise mpMRI results. We have not provided results for subgroups according to lesion site or prostate volume, due to lack of data to differentiate prognosis or diagnostic yield of the biopsy methods under assessment.

We extrapolated data on repeat biopsy from LATRUS and GATP (based on the Jimenez *et al.*' study) to LATP, in the absence of specific evidence for LATP.[113] Moreover, the Jimenez *et al.* study assesses a Spanish cohort that may not be wholly generalisable to UK practice. However, a scenario analysis on the probability of repeat biopsy showed that the model results are not sensitive to this parameter.

We have assumed that patients with a negative biopsy result were discharged and no additional costs were incurred, since we are uncertain about the extent and nature of the follow-up of these patients in primary care. However, it is likely that a substantial proportion of people with a negative biopsy who develop prostate cancer later have a diagnosis based on symptoms, which is considered in the model. Lastly, although we included costs for recently recommended treatments for metastatic hormone-sensitive prostate cancer (apalutamide and enzalutamide), we did not incorporate survival benefit from these treatments in our model. Our scenario analysis showed that excluding apalutamide and enzalutamide from the treatment options for mHSPC has a low impact in the model results.

Uncertainties

Uncertainties in the clinical evidence base contribute to uncertainties in cost-effectiveness estimates. In particular, the RR for cancer detection for LATP-freehand is based on a single RCT which used the PrecisionPoint device.[27] The RR for 'LATP-other' is a pooled estimate of studies that did not report the use of a freehand device, so it is unclear whether this corresponds with the LATP using grid and stepping device comparator for decision question 2.

Sources of evidence for biopsy complications for the economic model were difficult to interpret, as results were not reported for LATP and GATP separately and therefore it is unclear how many complications (and which ones) relate to LATP or GATP.

The microcosting analysis is also associated with some uncertainty, although the majority of assumptions relate to values that cancel out across biopsy methods. A key uncertainty is the number of cores taken, which we assume to be 12 for every biopsy method. This is potentially an important factor, as the number of cores taken may have an impact on cancer detection rates, but oversampling can make the procedure more difficult for the patient to tolerate, as well as having a cost impact related to the duration of the procedure and pathology costs. The cost-effectiveness results were very sensitive to assumptions about differences in the number of core samples for LATP and LATRUS, and to estimates of the cost of histopathology.

There was no evidence on the disutility of biopsy procedures and limited evidence on the disutilities of biopsy complications. Although we have used the same disutilities for biopsy complication as Wilson *et al.*,[63] these estimates were obtained from old studies not conducted in the population of interest. We assumed that misdiagnosed patients have the same rate of adverse events and disutility from adverse events as patients undergoing active surveillance, although it is uncertain if that reflects real practice.

Chapter 7 Conclusions

Pooled evidence from randomised trials indicates that transperineal prostate biopsy (using any available method) performed under local anaesthetic is equally effective at detecting prostate cancer as TRUS-guided prostate biopsy under local anaesthetic. One RCT estimated a non-significant improvement in the cancer detection rate for transperineal prostate biopsy using a freehand device under local anaesthetic compared with TRUS-guided prostate biopsy under local anaesthetic. This finding was supported by observational evidence. Comparative evidence on cancer detection rates with transperineal prostate biopsy conducted under local versus general anaesthetic is sparse. What evidence there is does not indicate a difference.

Evidence on complications associated with the different biopsy methods is sparse and difficult to interpret, for example because studies do not specify the anaesthetic approach or whether any specific device was used. The available evidence, supported by clinical opinion, suggests that LATP prostate biopsy is associated with more urinary retention whereas local anaesthetic TRUS-guided prostate biopsy has higher infection rates.

Based on pooled evidence for all types of LATP biopsy (with or without a specified freehand device), LATP is estimated to meet conventional criteria for cost-effectiveness in a UK context, with an incremental cost below £20,000 per QALY gained in comparison with LATRUS. LATP with a freehand device was also estimated to meet conventional criteria as a cost-effective alternative to LATRUS. These results are subject to some uncertainties over the cost of the freehand device, the number of core samples, and the sources for cancer detection rates and biopsy complication rates.

Implications for service provision

This analysis suggests that the use of LATP freehand TP devices is potentially cost-effective compared to LATRUS, with costs per QALY within the range generally considered acceptable by health services decision-makers. This conclusion is more certain for PrecisionPoint because, of all the freehand devices, it had most of the available evidence. Furthermore, until more evidence is available the comparative cost-effectiveness of the freehand TP devices is unknown. Our study also suggests that the additional expense of more costly biopsy procedures may not be warranted for patients at lower risk of having prostate cancer (according to Likert or PI-RADS scores, previous negative biopsy, prostate volume and site of lesions).

Suggested research priorities

- *Evidence for freehand devices*. There was no evidence for several of the freehand devices in the NICE scope. The TRANSLATE study may address this question to some extent, as it is evaluating the PrecisionPoint, UA1232 and 'any ultrasound probe-mounted needle guidance device'.
- *Outcomes not covered in included available evidence*. We suggest that incidence of defined complications (standardised for grading of severity and length of follow-up), health-related quality of life, and longer-term clinical outcomes could be defined in a core outcome set.
- *LATP versus GATP*. Evidence for this comparison is sparse (we identified one RCT reporting cancer detection rates).
- *Repeat biopsy population*. There is a need for separate reporting of results for this subgroup, or a separate prospective RCT.
- *UK NHS setting*. The three UK studies included in our review were single-centre observational studies with a limited set of outcomes. The TRANSLATE study is expected to remedy this; it is a multicentre randomised study across nine NHS Trusts in England.

Additional information

Contributions of authors

Inês Souto-Ribeiro (https://orcid.org/0000-0001-8464-4513) (Senior Research Assistant, health economics) carried out the review of economic evaluations, developed the independent economic model, and drafted the report.

Lois Woods (https://orcid.org/0000-0002-4587-9149) (Senior Research Assistant, evidence synthesis) conducted literature searches, carried out the systematic review of diagnostic test evaluation and clinical effectiveness, and drafted the report.

Emma Maund (https://orcid.org/0000-0002-3998-6669) (Research Fellow, evidence synthesis) carried out the systematic review of diagnostic test evaluation and clinical effectiveness, and drafted the report.

David Alexander Scott (https://orcid.org/0000-0001-6475-8046) (Principal Research Fellow, evidence synthesis) conducted the network meta-analysis and drafted the report.

Joanne Lord (https://orcid.org/0000-0003-1086-1624) (Professorial Research Fellow, health economics) carried out the review of economic evaluations, developed the independent economic model, and drafted the report.

Joanna Picot (https://orcid.org/0000-0001-5987-996X) (Senior Research Fellow, evidence synthesis) wrote the research protocol, carried out systematic review of diagnostic test evaluation and clinical effectiveness, drafted the report and provided a quality assurance review of the draft report.

Jonathan Shepherd (https://orcid.org/0000-0003-1682-4330) (Principal Research Fellow, evidence synthesis) carried out the systematic review of diagnostic test evaluation and clinical effectiveness, drafted the report, managed the project, and is the project guarantor.

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Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to completed data extractions for all studies included in the systematic review of diagnostic test and clinical effectiveness may be provided following review.

Ethics statement

Ethical approval was not sought for this study as this is not a requirement for secondary research, including economic modeling. There was no direct access to human participants for data collection or analysis.

Information governance statement

The University of Southampton is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

Under the Data Protection legislation the University of Southampton is the Data Processor; the NIHR is the Data Controller and we process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: www.southampton.ac.uk/about/governance/policies/privacy-policy.page.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/ZKTW8214.

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The other authors have no competing interests to declare.

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Appendix 1 Literature search strategies for the systematic reviews of clinical effectiveness, cost-effectiveness and health-related quality of life

All the database search strategies for the clinical effectiveness, cost-effectiveness and HRQoL searches are reported below. Each strategy was first developed in MEDLINE (Ovid) and then adapted for the other databases. Reference management and deduplication of search results were carried out in EndNote (Clarivate).

Searches for diagnostic test evaluation and clinical effectiveness studies

The searches for diagnostic test evaluation and clinical effectiveness had no date limits and the databases were searched from inception. An English-language limit was applied to the search strategy as a pragmatic decision due to the fixed time and resources available to this assessment for study-language translation. In order to be sensitive and retrieve all relevant studies, no study design search filters were used. *Table 46* details the search strategies for the databases and the conference hand searches. See also the section *Identification of studies* in this report.

Searches for cost-effectiveness studies

The database search strategies for the cost effectiveness searches were based on an early version of the clinical effectiveness searches with the addition of the CADTH filter for Economic Evaluations/Cost/Economic Models[60] applied to the MEDLINE and EMBASE strategies, and amended versions of the filter applied to the Cochrane Library and Web of Science strategies. An English language limit was applied. In addition, the EconLit database was searched. The full strategies are in *Table 47*.

Searches for health-related quality-of-life studies

The first search for relevant HRQoL studies ('HRQoL 1') was carried out on 17 June 2021 and was similar to the clinical effectiveness searches but with the CADTH filter for Health Utilities/Quality of Life added. This was not sufficient as it only covered the biopsy aspects of the disease pathway. Therefore, a second search was performed on 15 September 2021 ('HRQoL 2') where the biopsy terms were removed in order to retrieve studies that would cover the whole disease pathway in addition to the diagnostic process. In order to save time, search terms were applied specifically for the EQ-5D utility measure, as the preferred method according to NICE guidance. The option to expand the search to other utility measures was considered, but after screening the results it was not deemed necessary. The searches were carried out in MEDLINE, EMBASE, Web of Science, and the Cochrane Library, and they were limited to the most recent 10 years. The strategies are in *Tables 48* and *49*.

TABLE 46 Search strategies for diagnostic accuracy/efficacy and clinical effectiveness

Database, host, years searched, date searched	Literature search strategy	Results
Ovid MEDLINE(R) and Epub Ahead of Print, In-process, In-data-review & Other Non-indexed Citations, Daily and Versions(R) 1946–8 July 2021 Date of original search: 9 July 2021 Date of update search: 19 October 2021	1 exp Prostatic Neoplasms/ 2 (prostat* adj3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)).tw. 3 1 or 2 4 (PrecisionPoint or 'Precision Point').tw. 5 BXTAccelyon.tw. 6 UA1232.tw. 7 'BK Medical'.tw. 8 ((Trinity or Perine) and prostat*).tw. 9 Koelis.tw. 10 CamPROBE.tw. 11 'cambridge prostate biopsy device'.tw. 12 JEB.tw. 13 SureFire.tw. 14 LeapMed*.tw. 15 EZU-PA3U.tw. 16 (Hitachi and prostat*).tw. 17 (needle adj (device or grid or guide or template)).tw. 18 (stepping adj (device or grid or guide or template)).tw. 19 (device adj2 (grid or guide or stepping or template)).tw. 20 ((freehand or free?hand) adj2 (device* or needle* or biops*)).tw. 21 'local an?esthetic transperineal'.tw. 22 'local an?esthesia transperineal'.tw. 23 'general an?esthetic transperineal'.tw. 24 'general an?esthesia transperineal'.tw. 25 (LATP adj5 (biops* or prostat*)).tw. 26 (transperineal adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')).tw. 27 (transperineal adj2 biops* adj12 ('general an?esthesia' or 'general an?esthetic')).tw. 28 (perineal adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')).tw. 29 (perineal adj2 biops* adj12 ('general an?esthesia' or 'general an?esthetic')).tw. 30 (('transrectal ultraso*' or TRUS) adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')).tw. 31 'cognitive MRI-targeted biops*'.tw. 32 'cognitive fusion biops*'.tw. 33 (cognitive* adj2 biops*).tw. 34 or/4-33 35 3 and 34 36 congress.pt. 37 limit 36 to yr='1860 – 2017' 38 35 not 37 39 limit 38 to animals 40 38 not 39 41 limit 40 to english language	Original search: 205 Update search: 6
Ovid Embase Classic + Embase 1947–8 July 2021 Date of original search: 9 July 2021 Date of update search: 19 October 2021	1 exp prostate cancer/ 2 (prostat* adj3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)).tw. 3 1 or 2 4 (PrecisionPoint or 'Precision Point').tw. 5 BXTAccelyon.tw. 6 UA1232.tw. 7 'BK Medical'.tw. 8 ((Trinity or Perine) and prostat*).tw. 9 Koelis.tw. 10 CamPROBE.tw. 11 'cambridge prostate biopsy device'.tw. 12 JEB.tw. 13 SureFire.tw. 14 LeapMed*.tw.	Original search: 1348 Update search: 17

TABLE 46 Search strategies for diagnostic accuracy/efficacy and clinical effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	15 EZU-PA3U.tw. 16 (Hitachi and prostat*).tw. 17 (needle adj (device or grid or guide or template)).tw. 18 (stepping adj (device or grid or guide or template)).tw. 19 (device adj2 (grid or guide or stepping or template)).tw. 20 ((freehand or free?hand) adj2 (device* or needle* or biops*)).tw. 21 'local an?esthetic transperineal'.tw. 22 'local an?esthesia transperineal'.tw. 23 'general an?esthetic transperineal'.tw. 24 'general an?esthesia transperineal'.tw. 25 (LATP adj5 (biops* or prostat*)).tw. 26 (transperineal adj2 biops* adj12 'local an?esthesia').tw. 27 (transperineal adj2 biops* adj12 'local an?esthetic').tw. 28 (transperineal adj2 biops* adj12 'general an?esthesia').tw. 29 (transperineal adj2 biops* adj12 'general an?esthetic').tw. 30 (perineal adj2 biops* adj12 'local an?esthesia').tw. 31 (perineal adj2 biops* adj12 'local an?esthetic').tw. 32 (perineal adj2 biops* adj12 'general an?esthesia').tw. 33 (perineal adj2 biops* adj12 'general an?esthetic').tw. 34 *transrectal ultrasonography/ 35 (('transrectal ultraso*' or TRUS) adj2 biops* adj12 'local an?esthetic').tw. 36 (('transrectal ultraso*' or TRUS) adj2 biops* adj12 'local an?esthesia').tw. 37 'cognitive MRI-targeted biops*'.tw. 38 'cognitive fusion biops*'.tw. 39 (cognitive* adj2 biops*).tw. 40 or/4-39 41 3 and 40 42 conference paper.pt. 43 conference abstract.pt. 44 42 or 43 45 limit 44 to yr='1883 - 2017' 46 41 not 45 47 limit 46 to animals 48 limit 46 to animal studies 49 47 or 48 50 46 not 49 51 limit 50 to english language	
Cochrane Library, Wiley **(CDSR and CENTRAL)** Date of original search: 9 July 2021 Date of update search: 19 October 2021	#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees #2 (prostat* near/3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)):ti,ab,kw (Word variations have been searched) #3 #1 or #2 #4 (precisionpoint or 'precision point'):ti,ab,kw (Word variations have been searched) #5 (BXTAccelyon):ti,ab,kw (Word variations have been searched) #6 (UA1232):ti,ab,kw (Word variations have been searched) #7 ('BK Medical'):ti,ab,kw (Word variations have been searched) #8 ((Trinity or Perine) and prostat*):ti,ab,kw (Word variations have been searched) #9 (Koelis):ti,ab,kw (Word variations have been searched) #10 (CamPROBE):ti,ab,kw (Word variations have been searched) #11 ('cambridge prostate biopsy device'):ti,ab,kw (Word variations have been searched) #12 (JEB):ti,ab,kw (Word variations have been searched) #13 (SureFire):ti,ab,kw (Word variations have been searched) #14 (LeapMed*):ti,ab,kw (Word variations have been searched) #15 (EZU-PA3U):ti,ab,kw (Word variations have been searched) #16 (Hitachi and prostat*):ti,ab,kw (Word variations have been searched) #17 (needle near/1 (device or grid or guide or template)):ti,ab,kw (Word variations have been searched) #18 (stepping near/1 (device or grid or guide or template)):ti,ab,kw (Word variations have been searched)	Original search: Reviews: 2 Trials: 122 Update search: Reviews: 0 Trials: 2

continued

TABLE 46 Search strategies for diagnostic accuracy/efficacy and clinical effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	#19 (device near/2 (grid or guide or stepping or template)):ti,ab,kw (Word variations have been searched) #20 ((freehand or free?hand) near/2 (device* or needle* or biops*)):ti,ab,kw (Word variations have been searched) #21 ('local an?esthetic transperineal'):ti,ab,kw (Word variations have been searched) #22 ('local an?esthesia transperineal'):ti,ab,kw (Word variations have been searched) #23 ('general an?esthetic transperineal'):ti,ab,kw (Word variations have been searched) #24 ('general an?esthesia transperineal'):ti,ab,kw (Word variations have been searched) #25 (LATP near/5 (biops* or prostat*)):ti,ab,kw (Word variations have been searched) #26 (transperineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')):ti,ab,kw (Word variations have been searched) #27 (transperineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic')):ti,ab,kw (Word variations have been searched) #28 (perineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')):ti,ab,kw (Word variations have been searched) #29 (perineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic')):ti,ab,kw (Word variations have been searched) #30 (('transrectal ultraso*' or TRUS) near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')):ti,ab,kw (Word variations have been searched) #31 ('cognitive MRI-targeted biops*'):ti,ab,kw (Word variations have been searched) #32 ('cognitive fusion biops*'):ti,ab,kw (Word variations have been searched) #33 (cognitive* near/2 biops*):ti,ab,kw (Word variations have been searched) #34 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 807 #35 #3 and #34	
Web of Science ***Indexes = SCI-EXPANDED, CPCI-S Timespan = 1970–2021*** Date of original search: 9 July 2021 Date of update search: 19 October 2021	1 TS = (prostat* near/3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)) 2 TS = (precisionpoint or 'precision point') 3 TS = (BXTAccelyon) 4 TS = (UA1232) 5 TS=('BK Medical') 6 TS=((Trinity or Perine) and prostat*) 7 TS = (Koelis) 8 TS = (CamPROBE) 9 TS=('cambridge prostate biopsy device') 10 TS = (JEB) 11 TS = (SureFire) 12 TS = (LeapMed*) 13 TS = (EZU-PA3U) 14 TS = (Hitachi and prostat*) 15 TS = (needle near/1 (device or grid or guide or template)) 16 TS = (stepping near/1 (device or grid or guide or template)) 17 TS = (device near/2 (grid or guide or stepping or template)) 18 TS=((freehand or free?hand) near/2 (device* or needle* or biops*)) 19 TS=('local an?esthetic transperineal') 20 TS=('local an?esthesia transperineal') 21 TS=('general an?esthetic transperineal') 22 TS=('general an?esthesia transperineal') 23 TS = (LATP near/5 (biops* or prostat*)) 24 TS = (transperineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')) 25 TS = (transperineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic'))	Original search: 491 Update search: 34

TABLE 46 Search strategies for diagnostic accuracy/efficacy and clinical effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	26 TS = (perineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic'))	
	27 TS = (perineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic'))	
	28 TS=(('transrectal ultraso*' or TRUS) near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic'))	
	29 TS=('cognitive MRI-targeted biops*')	
	30 TS=('cognitive fusion biops*')	
	31 TS = (cognitive* near/2 biops*)	
	32 #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2	
	33 #32 AND #1	
	34 (#33) AND LANGUAGE: (English)	
Epistemonikos www.epistemonikos.org/ Date of original search: 9 July 2021 Date of update search: 19 October 2021	title:((prostate or prostatic) AND (cancer* OR carcinoma* OR malignan* OR neoplasm* OR tumour* OR tumor*)) AND ((title:(biops* AND (transperineal or perineal or transrectal)) OR (title:(precisionpoint OR 'precision point' OR BXTAccelyon OR UA1232 OR 'BK Medical' OR Trinity OR Perine OR Koelis OR camprobe OR 'cambridge prostate biopsy device' OR JEB OR SureFire OR LeapMed* OR EZU-PA3U OR Hitachi))) OR abstract:(precisionpoint OR 'precision point' OR BXTAccelyon OR UA1232 OR 'BK Medical' OR Trinity OR Perine OR Koelis OR camprobe OR 'cambridge prostate biopsy device' OR JEB OR SureFire OR LeapMed* OR EZU-PA3U OR Hitachi))	Original search: 43 Update search: 2
DARE and NHS EED www.crd.york.ac.uk/CRDWeb/ Date of original search: 9 July 2021 Date of update search: Not applicable (Database ceased to be updated after March 2015)	1 MeSH DESCRIPTOR prostatic neoplasms EXPLODE ALL TREES IN DARE,NHSEED	Original search: 2
	2 (prostat* adj3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)) IN DARE, NHSEED	
	3 #1 OR #2	
	4 (precisionpoint or 'precision point' or bxtaccelyon) IN DARE, NHSEED	
	5 (UA1232 or 'BK Medical') IN DARE, NHSEED	
	6 (Trinity or Perine or Koelis) IN DARE, NHSEED	
	7 (camPROBE or 'cambridge prostate biopsy device' or JEB) IN DARE, NHSEED	
	8 (SureFire or LeapMed*) IN DARE, NHSEED	
	9 (EZU-PA3U or (Hitachi and prostat*)) IN DARE, NHSEED	
	10 (needle adj (device or grid or guide or template)) IN DARE, NHSEED	
	11 (stepping adj (device or grid or guide or template)) IN DARE, NHSEED	
	12 (device adj2 (grid or guide or stepping or template)) IN DARE, NHSEED	
	13 ((freehand or free?hand) adj2 (device* or needle* or biops*)) IN DARE, NHSEED	
	14 ('local anaesthe* transperineal') IN DARE, NHSEED	
	15 ('local anesthe* transperineal') IN DARE, NHSEED	
	16 ('general anaesthe* transperineal') IN DARE, NHSEED	
	17 ('general anesthe* transperineal') IN DARE, NHSEED	
	18 (LATP adj5 (biops* or prostat*)) IN DARE, NHSEED	
	19 (transperineal adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')) IN DARE, NHSEED	
	20 (transperineal adj2 biops* adj12 ('general an?esthesia' or 'general an?esthetic')) IN DARE, NHSEED	
	21 (perineal adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')) IN DARE, NHSEED	
	22 (perineal adj2 biops* adj12 ('general an?esthesia' or 'general an?esthetic')) IN DARE, NHSEED	
	23 (('transrectal ultraso*' or TRUS) adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')) IN DARE, NHSEED	
	24 (cognitive* adj2 biops*) IN DARE, NHSEED	
	25 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	
	26 #3 AND #25	

continued

TABLE 46 Search strategies for diagnostic accuracy/efficacy and clinical effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
International HTA Database (INAHTA) www.inahta.org/hta-database/ Date of original search: 9 July 2021 Date of update search: 19 October 2021	(((cognitive* and biops*)) OR ('cognitive fusion biops*') OR ('cognitive MRI-targeted biops*') OR (('transrectal ultraso*' or TRUS) and biops* and ('local an?esthesia' or 'local an?esthetic')) OR (perineal and biops* and ('general an?esthesia' or 'general an?esthetic')) OR (perineal and biops* and ('local an?esthesia' or 'local an?esthetic')) OR (transperineal and biops* and ('general an?esthesia' or 'general an?esthetic')) OR (transperineal and biops* and ('local an?esthesia' or 'local an?esthetic')) OR (LATP and (biops* or prostat*)) OR ('general an?esthesia transperineal') OR ('general an?esthetic transperineal') OR ('local an?esthesia transperineal') OR ('local an?esthetic transperineal') OR ((freehand or free?hand) and (device* or needle* or biops*)) OR (device and (grid or guide or stepping or template)) OR (stepping and (device or grid or guide or template)) OR (needle and (device or grid or guide or template)) OR (Hitachi and prostat*) OR (EZU-PA3U) OR (LeapMed*) OR (SureFire) OR (JEB) OR (CamPROBE or 'cambridge prostate biopsy device') OR (Koelis) OR ((Trinity or Perine) and prostat*) OR (UA1232 or 'BK Medical') OR (Precisionpoint or BXTAccelyon)) AND ((((prostat* and (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*))) OR ('Prostatic Neoplasms'[mhe]))) English language filter	Original search: 30 Update search: 0
OpenGrey (DANS EASY Archive) Date of original search: 9 July 2021	Prostate and biops* – only useful search terms 82 results: 71 in French, 14 in English, 1 in German 0 relevant	Original search: 0
PROSPERO www.crd.york.ac.uk/prospero/ Date of original search: 9 July 2021	1 MeSH DESCRIPTOR prostatic neoplasms EXPLODE ALL TREES 2 prostat* and (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*) 3 #1 OR #2 4 biops* AND (transperineal or perineal or transrectal) 5 PrecisionPoint or 'precision point' or BXTAccelyon or UA1232 or 'BK Medical' or CAMProbe or 'cambridge prostate biopsy device' or JEB or SureFire or LeapMed* or EZU-PA3U or (Hitachi and prostat*) or (Koelis and (Trinity or Perine)) 6 biops* and (LATP or TRUS or freehand or cognitive) 7 #4 OR #5 OR #6 8 #3 AND #7	Original search: 73
ClinicalTrials.gov www.clinicaltrials.gov/ Date of original search: 10 June 2021	Prostate cancer | transperineal = 93 studies Prostate cancer | perineal = 34 studies Prostate cancer | transrectal = 254 studies Prostate cancer | TRUS = 209 NB 'Also searched for **Prostatic Neoplasm**, **Prostatic**, and **Neoplasm**' Total 590, deduplicated = 346	Original search: 346
Be Part of Research https://bepartofresearch.nihr.ac.uk/ Date of original search: 10 June 2021	Search terms: prostate cancer, biopsy, biopsies, prostate biopsy, transperineal, perineal, transrectal, TRUS	Original search: 0
NIHR CRN Portfolio Search (NIHR website) Date of original search: 10 June 2021	272 results for prostate cancer. Title screen = 0 relevant/biopsy-related.	Original search: 0
ASCO Genitourinary Cancers Symposium Date of original search: June 2021 Date of update search: Not applicable, no further conferences in 2021	Hand-search proceedings published in the *Journal of Clinical Oncology* supplements for 2018–21 Keywords: prostat*, biopsy, biopsies, transperineal, TRUS, etc.	Original search: 16

TABLE 46 Search strategies for diagnostic accuracy/efficacy and clinical effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
AUA Annual Meeting Date of original search: June 2021 Date of update search: 19 October 2021	Hand-search proceedings published in *The Journal of Urology* supplements for 2018–21 Keywords: prostat*, biopsy, biopsies, transperineal, TRUS, etc.	Original search: 54 Update search: 3
BAUS has an Annual Scientific meeting Date of original search: June 2021 Date of update search: 19 October 2021	Hand-search proceedings published in the *Journal of Clinical Oncology* supplements for 2018–21 Keywords: prostat*, biopsy, biopsies, transperineal, TRUS, etc.	Original search: 9 Update search: 2
EAU Annual Meeting Date of original search: June 2021 Date of update search: 19 October 2021	Hand-search proceedings published in *European Urology Open Science* (2020-), formerly *European Urology Supplements* (-2019). Keywords: prostat*, biopsy, biopsies, transperineal, TRUS, etc.	Original search: 35 Update search: 4

TABLE 47 Search strategies for cost effectiveness

Database, host, years searched, date searched	Literature search strategy	Results
Ovid MEDLINE(R) and Epub Ahead of Print, In-process, In-data-review & Other Non-indexed Citations, Daily and Versions(R) 1946–16 June 2021 Date of original search: 17 June 2021 Date of update search: 2 November 2021	1 exp Prostatic Neoplasms/ 2 (prostat* adj3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)).tw. 3 1 or 2 4 (prostat* adj3 biops*).tw. 5 Biopsy/ 6 exp Biopsy, Needle/ 7 ((needle or puncture or aspiration) adj3 biops*).tw. 8 or/4-7 9 (transperineal or perineal or transrectal).tw. 10 8 and 9 11 PrecisionPoint.tw. 12 BXTAccelyon.tw. 13 UA1232.tw. 14 'BK Medical'.tw. 15 ((Trinity or Perine) and prostat*).tw. 16 Koelis.tw. 17 CamPROBE.tw. 18 'cambridge prostate biopsy device'.tw. 19 JEB.tw. 20 SureFire.tw. 21 LeapMed*.tw. 22 EZU-PA3U.tw. 23 (Hitachi and prostat*).tw. 24 (needle adj (device or grid or guide or template)).tw. 25 (stepping adj (device or grid or guide or template)).tw. 26 (device adj2 (grid or guide or stepping or template)).tw. 27 ((freehand or free?hand) adj2 (device* or needle* or biops*)).tw. 28 'local an?esthetic transperineal'.tw. 29 'local an?esthesia transperineal'.tw. 30 'general an?esthetic transperineal'.tw. 31 'general an?esthesia transperineal'.tw. 32 (LATP adj5 (biops* or prostat*)).tw. 33 (transperineal adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')).tw.	Original search: 144 Update search: 10

continued

TABLE 47 Search strategies for cost effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	34 (transperineal adj2 biops* adj12 ('general an?esthesia' or 'general an?esthetic')).tw. 35 (perineal adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')).tw. 36 (perineal adj2 biops* adj12 ('general an?esthesia' or 'general an?esthetic')).tw. 37 (('transrectal ultraso*' or TRUS) adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')).tw. 38 'cognitive MRI-targeted biops*'.tw. 39 'cognitive fusion biops*'.tw. 40 (cognitive* adj2 biops*).tw. 41 or/11-40 42 10 or 41 43 Economics/ 44 exp 'Costs and Cost Analysis'/ 45 Economics, Nursing/ 46 Economics, Medical/ 47 Economics, Pharmaceutical/ 48 exp Economics, Hospital/ 49 Economics, Dental/ 50 exp 'Fees and Charges'/ 51 exp Budgets/ 52 budget*.ti,ab,kf. 53 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. 54 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq = 2 55 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. 56 (value adj2 (money or monetary)).ti,ab,kf. 57 exp models, economic/ 58 economic model*.ab,kf. 59 markov chains/ 60 markov.ti,ab,kf. 61 monte carlo method/ 62 monte carlo.ti,ab,kf. 63 exp Decision Theory/ 64 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. 65 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 66 3 and 42 and 65 67 limit 66 to english language Update search: 68 limit 67 to dt = 20210618-20211102	
Ovid Embase Classic + Embase 1947–2021 Week 23 Date of original search: 17 June 2021 Date of update search: 2 November 2021	1 exp prostate cancer/ 2 (prostat* adj3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)).tw. 3 1 or 2 4 prostate biopsy/ 5 (prostat* adj3 biops*).ti. 6 4 or 5 7 biopsy device/ 8 biopsy needle/ 9 ((needle or puncture or aspiration) adj3 biops*).tw. 10 or/6-9 11 (transperineal or perineal or transrectal).tw. 12 10 and 11 13 PrecisionPoint.tw. 14 BXTAccelyon.tw. 15 UA1232.tw.	Original search: 378 Update search: 8

TABLE 47 Search strategies for cost effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	16 'BK Medical'.tw. 17 ((Trinity or Perine) and prostat*).tw. 18 Koelis.tw. 19 CamPROBE.tw. 20 'cambridge prostate biopsy device'.tw. 21 JEB.tw. 22 SureFire.tw. 23 LeapMed*.tw. 24 EZU-PA3U.tw. 25 (Hitachi and prostat*).tw. 26 (needle adj (device or grid or guide or template)).tw. 27 (stepping adj (device or grid or guide or template)).tw. 28 (device adj2 (grid or guide or stepping or template)).tw. 29 ((freehand or free?hand) adj2 (device* or needle* or biops*)).tw. 30 'local an?esthetic transperineal'.tw. 31 'local an?esthesia transperineal'.tw. 32 'general an?esthetic transperineal'.tw. 33 'general an?esthesia transperineal'.tw. 34 (LATP adj5 (biops* or prostat*)).tw. 35 (transperineal adj2 biops* adj12 'local an?esthesia').tw. 36 (transperineal adj2 biops* adj12 'local an?esthetic').tw. 37 (transperineal adj2 biops* adj12 'general an?esthesia').tw. 38 (transperineal adj2 biops* adj12 'general an?esthetic').tw. 39 (perineal adj2 biops* adj12 'local an?esthesia').tw. 40 (perineal adj2 biops* adj12 'local an?esthetic').tw. 41 (perineal adj2 biops* adj12 'general an?esthesia').tw. 42 (perineal adj2 biops* adj12 'general an?esthetic').tw. 43 *transrectal ultrasonography/ 44 (('transrectal ultraso*' or TRUS) adj2 biops* adj12 'local an?esthetic').tw. 45 (('transrectal ultraso*' or TRUS) adj2 biops* adj12 'local an?esthesia').tw. 46 'cognitive MRI-targeted biops*'.tw. 47 'cognitive fusion biops*'.tw. 48 (cognitive* adj2 biops*).tw. 49 or/12-48 50 Economics/ 51 Cost/ 52 exp Health Economics/ 53 Budget/ 54 budget*.ti,ab,kw. 55 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. 56 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq = 2 57 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. 58 (value adj2 (money or monetary)).ti,ab,kw. 59 Statistical Model/ 60 economic model*.ab,kw. 61 Probability/ 62 markov.ti,ab,kw. 63 monte carlo method/ 64 monte carlo.ti,ab,kw. 65 Decision Theory/ 66 Decision Tree/ 67 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. 68 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 69 3 and 49 and 68 70 limit 69 to english language	

continued

TABLE 47 Search strategies for cost effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	Update search: 71 limit 70 to dd = 20210618-20211102	
Cochrane Library for CDSR and CENTRAL, Wiley Date of original search: 17 June 2021 Date of update search: 2 November 2021	#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees #2 (prostat* near/3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)):ti,ab,kw (Word variations have been searched) #3 #1 or #2 #4 (prostat* near/3 biops*):ti,ab,kw (Word variations have been searched) #5 MeSH descriptor: [Biopsy] this term only #6 MeSH descriptor: [Biopsy, Needle] explode all trees #7 ((needle or puncture or aspiration) near/3 biops*):ti,ab,kw (Word variations have been searched) #8 #4 or #5 or #6 or #7 #9 (transperineal or perineal or transrectal):ti,ab,kw (Word variations have been searched) #10 #8 and #9 #11 (precisionpoint):ti,ab,kw (Word variations have been searched) #12 (BXTAccelyon):ti,ab,kw (Word variations have been searched) #13 (UA1232):ti,ab,kw (Word variations have been searched) #14 ('BK Medical'):ti,ab,kw (Word variations have been searched) #15 ((Trinity or Perine) and prostat*):ti,ab,kw (Word variations have been searched) #16 (Koelis):ti,ab,kw (Word variations have been searched) #17 (CamPROBE):ti,ab,kw (Word variations have been searched) #18 ('cambridge prostate biopsy device'):ti,ab,kw (Word variations have been searched) #19 (JEB):ti,ab,kw (Word variations have been searched) #20 (SureFire):ti,ab,kw (Word variations have been searched) #21 (LeapMed*):ti,ab,kw (Word variations have been searched) #22 (EZU-PA3U):ti,ab,kw (Word variations have been searched) #23 (Hitachi and prostat*):ti,ab,kw (Word variations have been searched) #24 (needle near/1 (device or grid or guide or template)):ti,ab,kw (Word variations have been searched) #25 (stepping near/1 (device or grid or guide or template)):ti,ab,kw (Word variations have been searched) #26 (device near/2 (grid or guide or stepping or template)):ti,ab,kw (Word variations have been searched) #27 ((freehand or free?hand) near/2 (device* or needle* or biops*)):ti,ab,kw (Word variations have been searched) #28 ('local an?esthetic transperineal'):ti,ab,kw (Word variations have been searched) #29 ('local an?esthesia transperineal'):ti,ab,kw (Word variations have been searched) #30 ('general an?esthetic transperineal'):ti,ab,kw (Word variations have been searched) #31 ('general an?esthesia transperineal'):ti,ab,kw (Word variations have been searched) #32 (LATP near/5 (biops* or prostat*)):ti,ab,kw (Word variations have been searched) #33 (transperineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')):ti,ab,kw (Word variations have been searched) #34 (transperineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic')):ti,ab,kw (Word variations have been searched) #35 (perineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')):ti,ab,kw (Word variations have been searched) #36 (perineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic')):ti,ab,kw (Word variations have been searched) #37 (('transrectal ultraso*' or TRUS) near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')):ti,ab,kw (Word variations have been searched) #38 ('cognitive MRI-targeted biops*'):ti,ab,kw (Word variations have been searched) #39 ('cognitive fusion biops*'):ti,ab,kw (Word variations have been searched)	Original search: Reviews: 1 Trials: 69 Update search: Reviews: 0 Trials: 3

TABLE 47 Search strategies for cost effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	#40 (cognitive* near/2 biops*):ti,ab,kw (Word variations have been searched) #41 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 #42 MeSH descriptor: [Economics] this term only #43 MeSH descriptor: [Costs and Cost Analysis] explode all trees #44 MeSH descriptor: [Economics, Nursing] this term only #45 MeSH descriptor: [Economics, Medical] this term only #46 MeSH descriptor: [Economics, Pharmaceutical] this term only #47 MeSH descriptor: [Economics, Hospital] explode all trees #48 MeSH descriptor: [Economics, Dental] this term only #49 MeSH descriptor: [Fees and Charges] explode all trees #50 MeSH descriptor: [Budgets] explode all trees #51 (budget*):ti,ab,kw (Word variations have been searched) #52 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed):ti,ab,kw (Word variations have been searched) #53 (cost* near/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)):ti,ab,kw (Word variations have been searched) #54 (value near/2 (money or monetary)):ti,ab,kw (Word variations have been searched) #55 MeSH descriptor: [Models, Economic] explode all trees #56 ('economic model*'):ti,ab,kw (Word variations have been searched) #57 MeSH descriptor: [Markov Chains] this term only #58 (markov):ti,ab,kw (Word variations have been searched) #59 MeSH descriptor: [Monte Carlo Method] this term only #60 ('monte carlo'):ti,ab,kw (Word variations have been searched) #61 MeSH descriptor: [Decision Theory] explode all trees #62 (decision* near/2 (tree* or analy* or model*)):ti,ab,kw (Word variations have been searched) #63 #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 #64 #3 and #41 and #63 Update search: #64 #3 and #41 and #63 with Cochrane Library publication date Between Jun 2021 and Nov 2021 **3**	
EconLit, EBSCO Date of original search: 17 June 2021 Date of update search: 2 November 2021	S1 TI (prostat* N3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)) OR AB (prostat* N3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)) S2 TI biops* OR AB biops* S3 TI (transperineal or perineal or transrectal) OR AB (transperineal or perineal or transrectal) S4 TI (PrecisionPoint or BXTAccelyon or UA1232 or 'BK Medical' or ((Trinity or Perine) and prostat*) or Koelis or CamPROBE or 'cambridge prostate biopsy device' or JEB or SureFire or LeapMed* or EZU-PA3U or (Hitachi and prostat*)) OR AB (PrecisionPoint or BXTAccelyon or UA1232 or 'BK Medical' or ((Trinity or Perine) and prostat*) or Koelis or CamPROBE or 'cambridge prostate biopsy device' or JEB or SureFire or LeapMed* or EZU-PA3U or (Hitachi and prostat*)) S5 S2 OR S3 OR S4 S6 S1 AND S5 Update search: S7 S1 AND S5 – Published Date: 20210601-20211131	Original search: 4 Update search: 0

continued

TABLE 47 Search strategies for cost effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
Web of Science ***Indexes*** **=** ***SCI-EXPANDED, CPCI-S*** ***Timespan*** **=** ***1970–2021*** Date of original search: 17 June 2021 Date of update search: 2 November 2021	Custom year range 2021–2021 (+ deduplication in EndNote) Update search: (#45) AND LANGUAGE: (English) #45 #1 AND #37 AND #44 #44 #38 OR #39 OR #40 OR #41 OR #42 OR #43 #43 TS=(decision near/2 (tree* or analy* or model*)) #42 TS=(markov or 'monte carlo') #41 TS=(value near/2 (money or monetary)) #40 TS=(cost* near/2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)) #39 TS=(budget*) #38 TS=(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed) #37 #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 #36 TS=(cognitive* near/2 biops*) #35 TS=('cognitive fusion biops*') #34 TS=('cognitive MRI-targeted biops*') #33 TS=(('transrectal ultraso*' or TRUS) near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')) #32 TS=(perineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic')) #31 TS=(perineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')) #30 TS=(transperineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic')) #29 TS=(transperineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')) #28 TS=(LATP near/5 (biops* or prostat*)) #27 TS=('general an?esthesia transperineal') #26 TS=('general an?esthetic transperineal') #25 TS=('local an?esthesia transperineal') #24 TS=('local an?esthetic transperineal') #23 TS=((freehand or free?hand) near/2 (device* or needle* or biops*)) #22 TS=(device near/2 (grid or guide or stepping or template)) #21 TS=(stepping near/1 (device or grid or guide or template)) #20 TS=(needle near/1 (device or grid or guide or template)) #19 TS=(Hitachi and prostat*) #18 TS=(EZU-PA3U) #17 TS=(LeapMed*) #16 TS=(SureFire) #15 TS=(JEB) #14 TS=('cambridge prostate biopsy device') #13 TS=(CamPROBE) #12 TS=(Koelis) #11 TS=((Trinity or Perine) and prostat*) #10 TS=('BK Medical') #9 TS=(UA1232) #8 TS=(BXTAccelyon) #7 TS=(precisionpoint) #6 #5 AND #4 #5 TS=(transperineal or perineal or transrectal) #4 #3 OR #2 #3 TS=((needle or puncture or aspiration) near/3 biops*) #2 TS=(prostat* near/3 biops*) #1 TS=(prostat* near/3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*))	Original search: 86 Update search: 21

TABLE 47 Search strategies for cost effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
DARE and NHS EED www.crd.york.ac.uk/CRDWeb/ Date of original search: 7 June 2021 Date of update search: not applicable (Database ceased to be updated after March 2015)	1 MeSH DESCRIPTOR prostatic neoplasms EXPLODE 1 IN DARE,NHSEED 2 (prostat* adj3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)) IN DARE, NHSEED 3 #1 OR #2 4 (suspected or suspicion or suspicious) IN DARE, NHSEED 5 #3 AND #4 6 (prostat* adj3 biops*) IN DARE, NHSEED 7 MeSH DESCRIPTOR biopsy IN DARE,NHSEED 8 MeSH DESCRIPTOR biopsy, needle EXPLODE ALL TREES IN DARE,NHSEED 9 ((needle or puncture or aspiration) adj3 biops*) IN DARE, NHSEED 10 #6 OR #7 OR #8 11 (transperineal or perineal or transrectal) IN DARE, NHSEED 12 #10 AND #11 13 (PrecisionPoint or BXTAccelyon) IN DARE, NHSEED 14 (UA1232 or 'BK Medical') IN DARE, NHSEED 15 (((Trinity or Perine) and prostat*) OR Koelis) IN DARE, NHSEED 16 (CamPROBE or 'cambridge prostate biopsy device') IN DARE, NHSEED 17 (JEB) IN DARE, NHSEED 18 (SureFire) IN DARE, NHSEED 19 (LeapMed*) IN DARE, NHSEED 20 (EZU-PA3U) IN DARE, NHSEED 21 (Hitachi and prostat*) IN DARE, NHSEED 22 (needle adj (device or grid or guide or template)) IN DARE, NHSEED 23 (stepping adj (device or grid or guide or template)) IN DARE, NHSEED 24 (device adj2 (grid or guide or stepping or template)) IN DARE, NHSEED 25 ((freehand or free?hand) adj2 (device* or needle* or biops*)) IN DARE, NHSEED 26 ('local an?esthetic transperineal') IN DARE, NHSEED 27 ('local an?esthesia transperineal') IN DARE, NHSEED 28 ('general an?esthetic transperineal') IN DARE, NHSEED 29 ('general an?esthesia transperineal') IN DARE, NHSEED 30 (LATP adj5 (biops* or prostat*)) IN DARE, NHSEED 31 (transperineal adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')) IN DARE, NHSEED 32 (transperineal adj2 biops* adj12 ('general an?esthesia' or 'general an?esthetic')) IN DARE, NHSEED 33 (perineal adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')) IN DARE, NHSEED 34 (perineal adj2 biops* adj12 ('general an?esthesia' or 'general an?esthetic')) IN DARE, NHSEED 35 (('transrectal ultraso*' or TRUS) adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')) IN DARE, NHSEED 36 ('cognitive MRI-targeted biops*') IN DARE, NHSEED 37 ('cognitive fusion biops*') IN DARE, NHSEED 38 (cognitive* adj2 biops*) IN DARE, NHSEED 39 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 40 #5 AND #39	Original search: 6

continued

TABLE 47 Search strategies for cost effectiveness (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
International HTA Database (INAHTA) www.inahta.org/hta-database/ Date of original search: 7 June 2021 Date of update search: 2 November 2021	(((cognitive* and biops*)) OR ('cognitive fusion biops*') OR ('cognitive MRI-targeted biops*') OR (('transrectal ultraso*' or TRUS) and biops* and ('local an?esthesia' or 'local an?esthetic')) OR (perineal and biops* and ('general an?esthesia' or 'general an?esthetic')) OR (perineal and biops* and ('local an?esthesia' or 'local an?esthetic')) OR (transperineal and biops* and ('general an?esthesia' or 'general an?esthetic')) OR (transperineal and biops* and ('local an?esthesia' or 'local an?esthetic')) OR (LATP and (biops* or prostat*)) OR ('general an?esthesia transperineal') OR ('general an?esthetic transperineal') OR ('local an?esthesia transperineal') OR ('local an?esthetic transperineal') OR ((freehand or free?hand) and (device* or needle* or biops*)) OR (device and (grid or guide or stepping or template)) OR (stepping and (device or grid or guide or template)) OR (needle and (device or grid or guide or template)) OR (Hitachi and prostat*) OR (EZU-PA3U) OR (LeapMed*) OR (SureFire) OR (JEB) OR (CamPROBE or 'cambridge prostate biopsy device') OR (Koelis) OR ((Trinity or Perine) and prostat*) OR (UA1232 or 'BK Medical') OR (Precisionpoint or BXTAccelyon) OR ((transperineal or perineal or transrectal) AND (((needle or puncture or aspiration) and biops*) OR ('Biopsy, Needle'[mhe]) OR ('Biopsy'[mh]) OR (prostat* and biops*)))) AND ((suspected or suspicion or suspicious) AND ((((prostat* and (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)))) OR ('Prostatic Neoplasms'[mhe]))))	Original search: 4 Update search: 0
Epistemonikos www.epistemonikos.org/ Date of original search: 7 June 2021 Date of update search: 2 November 2021	title:(prostat* AND (cancer* OR carcinoma* OR malignan* OR neoplasm* OR tumour* OR tumor*)) AND (title:(suspected OR suspicion OR suspicious) OR abstract:(suspected OR suspicion OR suspicious)) AND (title:(biops* OR precisionpoint OR BXTAccelyon OR UA1232 OR 'BK Medical' OR Trinity OR Perine OR Koelis OR camprobe OR 'cambridge prostate biopsy device' OR JEB OR SureFire OR LeapMed* OR EZU-PA3U OR Hitachi) OR abstract:(biops* OR precisionpoint OR BXTAccelyon OR UA1232 OR 'BK Medical' OR Trinity OR Perine OR Koelis OR camprobe OR 'cambridge prostate biopsy device' OR JEB OR SureFire OR LeapMed* OR EZU-PA3U OR Hitachi))	Original search: 129 Update search: 2

TABLE 48 Search strategies for 'HRQoL 1'

Database, host, years searched, date searched	Literature search strategy	Results
Ovid MEDLINE(R) and Epub Ahead of Print, In-process, In-data-review & Other Non-indexed Citations, Daily and Versions(R) 1946 to 17 June 2021 Date of original search: 17 June 2021	1 exp Prostatic Neoplasms/ 2 (prostat* adj3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)).tw. 3 1 or 2 4 (prostat* adj3 biops*).tw. 5 Biopsy/ 6 exp Biopsy, Needle/ 7 ((needle or puncture or aspiration) adj3 biops*).tw. 8 or/4-7 9 (transperineal or perineal or transrectal).tw. 10 8 and 9 11 PrecisionPoint.tw. 12 BXTAccelyon.tw. 13 UA1232.tw. 14 'BK Medical'.tw. 15 ((Trinity or Perine) and prostat*).tw. 16 Koelis.tw. 17 CamPROBE.tw. 18 'cambridge prostate biopsy device'.tw. 19 JEB.tw. 20 SureFire.tw. 21 LeapMed*.tw. 22 EZU-PA3U.tw.	Original search: 75

TABLE 48 Search strategies for 'HRQoL 1' (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	23 (Hitachi and prostat*).tw. 24 (needle adj (device or grid or guide or template)).tw. 25 (stepping adj (device or grid or guide or template)).tw. 26 (device adj2 (grid or guide or stepping or template)).tw. 27 ((freehand or free?hand) adj2 (device* or needle* or biops*)).tw. 28 'local an?esthetic transperineal'.tw. 29 'local an?esthesia transperineal'.tw. 30 'general an?esthetic transperineal'.tw. 31 'general an?esthesia transperineal'.tw. 32 (LATP adj5 (biops* or prostat*)).tw. 33 (transperineal adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')).tw. 34 (transperineal adj2 biops* adj12 ('general an?esthesia' or 'general an?esthetic')).tw. 35 (perineal adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')).tw. 36 (perineal adj2 biops* adj12 ('general an?esthesia' or 'general an?esthetic')).tw. 37 (('transrectal ultraso*' or TRUS) adj2 biops* adj12 ('local an?esthesia' or 'local an?esthetic')).tw. 38 'cognitive MRI-targeted biops*'.tw. 39 'cognitive fusion biops*'.tw. 40 (cognitive* adj2 biops*).tw. 41 or/11-40 42 10 or 41 43 'Value of Life'/ 44 Quality of Life/ 45 quality of life.ti,kf. 46 ((instrument or instruments) adj3 quality of life).ab. 47 Quality-Adjusted Life Years/ 48 quality adjusted life.ti,ab,kf. 49 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. 50 disability adjusted life.ti,ab,kf. 51 daly*.ti,ab,kf. 52 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or short-form36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf. 53 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf. 54 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf. 55 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or short-form12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf. 56 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf. 57 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or short-form20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf. 58 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf. 59 (hye or hyes).ti,ab,kf. 60 (health* adj2 year* adj2 equivalent*).ti,ab,kf. 61 (pqol or qls).ti,ab,kf. 62 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf. 63 nottingham health profile*.ti,ab,kf. 64 sickness impact profile.ti,ab,kf. 65 exp health status indicators/ 66 (health adj3 (utilit* or status)).ti,ab,kf. 67 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf. 68 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	

continued

TABLE 48 Search strategies for 'HRQoL 1' (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	69 disutilit*.ti,ab,kf. 70 rosser.ti,ab,kf. 71 willingness to pay.ti,ab,kf. 72 standard gamble*.ti,ab,kf. 73 (time trade off or time tradeoff).ti,ab,kf. 74 tto.ti,ab,kf. 75 (hui or hui1 or hui2 or hui3).ti,ab,kf. 76 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. 77 duke health profile.ti,ab,kf. 78 functional status questionnaire.ti,ab,kf. 79 dartmouth coop functional health assessment*.ti,ab,kf. 80 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 81 3 and 42 and 80 82 limit 81 to english language	
Ovid Embase Classic + Embase 1947–2021 Week 23 Date of original search: 17 June 2021	1 exp prostate cancer/ 2 (prostat* adj3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)).tw. 3 1 or 2 4 prostate biopsy/ 5 (prostat* adj3 biops*).ti. 6 4 or 5 7 biopsy device/ 8 biopsy needle/ 9 ((needle or puncture or aspiration) adj3 biops*).tw. 10 or/6-9 11 (transperineal or perineal or transrectal).tw. 12 10 and 11 13 PrecisionPoint.tw. 14 BXTAccelyon.tw. 15 UA1232.tw. 16 'BK Medical'.tw. 17 ((Trinity or Perine) and prostat*).tw. 18 Koelis.tw. 19 CamPROBE.tw. 20 'cambridge prostate biopsy device'.tw. 21 JEB.tw. 22 SureFire.tw. 23 LeapMed*.tw. 24 EZU-PA3U.tw. 25 (Hitachi and prostat*).tw. 26 (needle adj (device or grid or guide or template)).tw. 27 (stepping adj (device or grid or guide or template)).tw. 28 (device adj2 (grid or guide or stepping or template)).tw. 29 ((freehand or free?hand) adj2 (device* or needle* or biops*)).tw. 30 'local an?esthetic transperineal'.tw. 31 'local an?esthesia transperineal'.tw. 32 'general an?esthetic transperineal'.tw. 33 'general an?esthesia transperineal'.tw. 34 (LATP adj5 (biops* or prostat*)).tw. 35 (transperineal adj2 biops* adj12 'local an?esthesia').tw. 36 (transperineal adj2 biops* adj12 'local an?esthetic').tw. 37 (transperineal adj2 biops* adj12 'general an?esthesia').tw. 38 (transperineal adj2 biops* adj12 'general an?esthetic').tw. 39 (perineal adj2 biops* adj12 'local an?esthesia').tw. 40 (perineal adj2 biops* adj12 'local an?esthetic').tw. 41 (perineal adj2 biops* adj12 'general an?esthesia').tw. 42 (perineal adj2 biops* adj12 'general an?esthetic').tw. 43 *transrectal ultrasonography/ 44 (('transrectal ultraso*' or TRUS) adj2 biops* adj12 'local an?esthetic').tw. 45 (('transrectal ultraso*' or TRUS) adj2 biops* adj12 'local an?esthesia').tw.	Original search: 138

TABLE 48 Search strategies for 'HRQoL 1' (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	46 'cognitive MRI-targeted biops*'.tw. 47 'cognitive fusion biops*'.tw. 48 (cognitive* adj2 biops*).tw. 49 or/12-48 50 socioeconomics/ 51 exp Quality of Life/ 52 quality of life.ti,kw. 53 ((instrument or instruments) adj3 quality of life).ab. 54 Quality-Adjusted Life Year/ 55 quality adjusted life.ti,ab,kw. 56 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. 57 disability adjusted life.ti,ab,kw. 58 daly*.ti,ab,kw. 59 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or short-form36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw. 60 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw. 61 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw. 62 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or short-form12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw. 63 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw. 64 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or short-form20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw. 65 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kw. 66 (hye or hyes).ti,ab,kw. 67 (health* adj2 year* adj2 equivalent*).ti,ab,kw. 68 (pqol or qls).ti,ab,kw. 69 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw. 70 nottingham health profile*.ti,ab,kw. 71 nottingham health profile/ 72 sickness impact profile.ti,ab,kw. 73 sickness impact profile/ 74 health status indicator/ 75 (health adj3 (utilit* or status)).ti,ab,kw. 76 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw. 77 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw. 78 disutilit*.ti,ab,kw. 79 rosser.ti,ab,kw. 80 willingness to pay.ti,ab,kw. 81 standard gamble*.ti,ab,kw. 82 (time trade off or time tradeoff).ti,ab,kw. 83 tto.ti,ab,kw. 84 (hui or hui1 or hui2 or hui3).ti,ab,kw. 85 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw. 86 duke health profile.ti,ab,kw. 87 functional status questionnaire.ti,ab,kw. 88 dartmouth coop functional health assessment*.ti,ab,kw. 89 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 90 3 and 49 and 89 91 limit 90 to english language	

continued

TABLE 48 Search strategies for 'HRQoL 1' (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
Web of Science – Science Citation Index Expanded (SCI-EXPANDED), Conference Proceedings Citation Index – Science (CPCI-S) *Timespan = 1970–2021* Date of original search: 16 September 2021	#1 TS=(prostat* near/3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)) #2 TS=(prostat* near/3 biops*) #3 TS=((needle or puncture or aspiration) near/3 biops*) #4 #3 OR #2 #5 TS=(transperineal or perineal or transrectal) #6 #5 AND #4 #7 TS=(precisionpoint) #8 TS=(BXTAccelyon) #9 TS=(UA1232) #10 TS=('BK Medical') #11 TS=((Trinity or Perine) and prostat*) #12 TS=(Koelis) #13 TS=(CamPROBE) #14 TS=('cambridge prostate biopsy device') #15 TS=(JEB) #16 TS=(SureFire) #17 TS=(LeapMed*) #18 TS=(EZU-PA3U) #19 TS=(Hitachi and prostat*) #20 TS=(needle near/1 (device or grid or guide or template)) #21 TS=(stepping near/1 (device or grid or guide or template)) #22 TS=(device near/2 (grid or guide or stepping or template)) #23 TS=((freehand or free?hand) near/2 (device* or needle* or biops*)) #24 TS=('local an?esthetic transperineal') #25 TS=('local an?esthesia transperineal') #26 TS=('general an?esthetic transperineal') #27 TS=('general an?esthesia transperineal') #28 TS=(LATP near/5 (biops* or prostat*)) #29 TS=(transperineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')) #30 TS=(transperineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic')) #31 TS=(perineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')) #32 TS=(perineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic')) #33 TS=(('transrectal ultraso*' or TRUS) near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')) #34 TS=('cognitive MRI-targeted biops*') #35 TS=('cognitive fusion biops*') #36 TS=(cognitive* near/2 biops*) #37 #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 #38 TS=((value or quality) near/1 life) #39 TS=((instrument or instruments) near/3 quality of life) #40 TS=('quality adjusted life') #41 TS=(qaly* or qald* or qale* or qtime* or 'life year' or 'life years') #42 TS=('disability adjusted life' or daly*) #43 TS=(sf36 or sf 36 or 'short form 36' or 'shortform 36' or 'short form36' or shortform36 or 'sf thirtysix' or sfthirtysix or 'sfthirty six' or 'sf thirty six' or 'shortform thirtysix' or 'shortform thirty six' or 'short form thirtysix' or 'short form thirty six') #44 TS=(sf6 or 'sf 6' or 'short form 6' or 'shortform 6' or 'sf six' or sfsix or 'short-form six' or 'short form six' or shortform6 or 'short form6') #45 TS=(sf8 or 'sf 8' or 'sf eight' or sfeight or 'shortform 8' or 'shortform 8' or shortform8 or 'short form8' or 'shortform eight' or 'short form eight') #46 TS=(sf12 or 'sf 12' or 'short form 12' or 'shortform 12' or 'short form12' or shortform12 or 'sf twelve' or sftwelve or 'shortform twelve' or 'short form twelve')	Original search:

TABLE 48 Search strategies for 'HRQoL 1' (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	#47 TS=(sf16 or 'sf 16' or 'short form 16' or 'shortform 16' or 'short form16' or shortform16 or 'sf sixteen' or sfsixteen or 'shortform sixteen' or 'short form sixteen') #48 TS=(sf20 or 'sf 20' or 'short form 20' or 'shortform 20' or 'short form20' or shortform20 or 'sf twenty' or sftwenty or 'shortform twenty' or 'short form twenty') #49 TS=(hql or hqol or 'h qol' or hrqol or 'hr qol') #50 TS=(hye or hyes) #51 TS=(health* near/2 year* near/2 equivalent*) #52 TS=(pqol or qls) #53 TS=('quality of wellbeing' or 'quality of well being' or 'index of wellbeing' or 'index of well being' or qwb) #54 TS=('nottingham health profile*' or 'duke health profile' or 'functional assessment questionnaire' or 'dartmouth coop functional health assessment*') #55 TS=('sickness impact profile') #56 TS=(health near/3 (utilit* or status)) #57 TS=(utilit* near/3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)) #58 TS=(preference* near/3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)) #59 TS=(disutilit*) #60 TS=(rosser or 'willingness to pay' or 'standard gamble*') #61 TS=('time trade off' or 'time tradeoff' or tto) #62 TS=(hui or hui1 or hui2 or hui3) #63 TS=(eq or euroqol or 'euro qol' or eq5d or 'eq 5d' or euroqual or 'euro qual') #64 #63 OR #62 OR #61 OR #60 OR #59 OR #58 OR #57 OR #56 OR #55 OR #54 OR #53 OR #52 OR #51 OR #50 OR #49 OR #48 OR #47 OR #46 OR #45 OR #44 OR #43 OR #42 OR #41 OR #40 OR #39 OR #38 #65 #64 AND #37 AND #1 #66 (#65) AND LANGUAGE: (English)	
Cochrane Library, Wiley Date of original search: 18 June 2021	#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees #2 (prostat* near/3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)):ti,ab,kw (Word variations have been searched) #3 #1 or #2 #4 (prostat* near/3 biops*):ti,ab,kw (Word variations have been searched) #5 MeSH descriptor: [Biopsy] this term only #6 MeSH descriptor: [Biopsy, Needle] explode all trees #7 ((needle or puncture or aspiration) near/3 biops*):ti,ab,kw (Word variations have been searched) #8 #4 or #5 or #6 or #7 #9 (transperineal or perineal or transrectal):ti,ab,kw (Word variations have been searched) #10 #8 and #9 #11 (precisionpoint):ti,ab,kw (Word variations have been searched) #12 (BXTAccelyon):ti,ab,kw (Word variations have been searched) #13 (UA1232):ti,ab,kw (Word variations have been searched) #14 ('BK Medical'):ti,ab,kw (Word variations have been searched) #15 ((Trinity or Perine) and prostat*):ti,ab,kw (Word variations have been searched) #16 (Koelis):ti,ab,kw (Word variations have been searched) #17 (CamPROBE):ti,ab,kw (Word variations have been searched) #18 ('cambridge prostate biopsy device'):ti,ab,kw (Word variations have been searched) #19 (JEB):ti,ab,kw (Word variations have been searched) #20 (SureFire):ti,ab,kw (Word variations have been searched) #21 (LeapMed*):ti,ab,kw (Word variations have been searched) #22 (EZU-PA3U):ti,ab,kw (Word variations have been searched) #23 (Hitachi and prostat*):ti,ab,kw (Word variations have been searched) #24 (needle near/1 (device or grid or guide or template)):ti,ab,kw (Word variations have been searched)	Original search: 35

continued

TABLE 48 Search strategies for 'HRQoL 1' (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	#25 (stepping near/1 (device or grid or guide or template)):ti,ab,kw (Word variations have been searched) #26 (device near/2 (grid or guide or stepping or template)):ti,ab,kw (Word variations have been searched) #27 ((freehand or free?hand) near/2 (device* or needle* or biops*)):ti,ab,kw (Word variations have been searched) #28 ('local an?esthetic transperineal'):ti,ab,kw (Word variations have been searched) #29 ('local an?esthesia transperineal'):ti,ab,kw (Word variations have been searched) #30 ('general an?esthetic transperineal'):ti,ab,kw (Word variations have been searched) #31 ('general an?esthesia transperineal'):ti,ab,kw (Word variations have been searched) #32 (LATP near/5 (biops* or prostat*)):ti,ab,kw (Word variations have been searched) #33 (transperineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')):ti,ab,kw (Word variations have been searched) #34 (transperineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic')):ti,ab,kw (Word variations have been searched) #35 (perineal near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')):ti,ab,kw (Word variations have been searched) #36 (perineal near/2 biops* near/12 ('general an?esthesia' or 'general an?esthetic')):ti,ab,kw (Word variations have been searched) #37 (('transrectal ultraso*' or TRUS) near/2 biops* near/12 ('local an?esthesia' or 'local an?esthetic')):ti,ab,kw (Word variations have been searched) #38 ('cognitive MRI-targeted biops*'):ti,ab,kw (Word variations have been searched) #39 ('cognitive fusion biops*'):ti,ab,kw (Word variations have been searched) #40 (cognitive* near/2 biops*):ti,ab,kw (Word variations have been searched) #41 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 #42 MeSH descriptor: [Value of Life] this term only #43 MeSH descriptor: [Quality of Life] this term only #44 ('quality of life'):ti OR ('quality of life'):kw (Word variations have been searched) #45 (((instrument or instruments) near/3 'quality of life')):ab (Word variations have been searched) #46 MeSH descriptor: [Quality-Adjusted Life Years] this term only #47 ('quality adjusted life' or qaly* or qald* or qale* or qtime* or 'life year' or 'life years'):ti,ab,kw (Word variations have been searched) #48 ('disability adjusted life' or daly*):ti,ab,kw (Word variations have been searched) #49 (sf36 or 'sf 36' or 'short form 36' or 'shortform 36' or 'short form36' or shortform36 or 'sf thirtysix' or sfthirtysix or 'sfthirty six' or 'sf thirty six' or 'shortform thirtysix' or 'shortform thirty six' or 'short form thirtysix' or 'short form thirty six'):ti,ab,kw (Word variations have been searched) #50 (sf6 or 'sf 6' or 'short form 6' or 'shortform 6' or 'sf six' or sfsix or 'shortform six' or 'short form six' or shortform6 or 'short form6'):ti,ab,kw (Word variations have been searched) #51 (sf8 or 'sf 8' or 'sf eight' or sfeight or 'shortform 8' or 'shortform 8' or shortform8 or 'short form8' or 'shortform eight' or 'short form eight'):ti,ab,kw (Word variations have been searched) #52 (sf12 or 'sf 12' or 'short form 12' or 'shortform 12' or 'short form12' or shortform12 or 'sf twelve' or sftwelve or 'shortform twelve' or 'short form twelve'):ti,ab,kw (Word variations have been searched) #53 (sf16 or 'sf 16' or 'short form 16' or 'shortform 16' or 'short form16' or shortform16 or 'sf sixteen' or sfsixteen or 'shortform sixteen' or 'short form sixteen'):ti,ab,kw (Word variations have been searched)	

TABLE 48 Search strategies for 'HRQoL 1' (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
	#54 (sf20 or 'sf 20' or 'short form 20' or 'shortform 20' or 'short form20' or shortform20 or 'sf twenty' or sftwenty or 'shortform twenty' or 'short form twenty'):ti,ab,kw (Word variations have been searched) #55 (hql or hqol or 'h qol' or hrqol or 'hr qol'):ti,ab,kw (Word variations have been searched) #56 (hye or hyes):ti,ab,kw (Word variations have been searched) #57 (health* near/2 year* near/2 equivalent*):ti,ab,kw (Word variations have been searched) #58 (pqol or qls):ti,ab,kw (Word variations have been searched) #59 ('quality of wellbeing' or 'quality of well being' or 'index of wellbeing' or 'index of well being' or qwb):ti,ab,kw (Word variations have been searched) #60 ('nottingham health profile*' or 'sickness impact profile' or 'duke health profile' or 'functional status questionnaire' or 'dartmouth coop functional health assessment'):ti,ab,kw (Word variations have been searched) #61 MeSH descriptor: [Health Status Indicators] explode all trees #62 (health near/3 (utilit* or status)):ti,ab,kw (Word variations have been searched) #63 (utilit* near/3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)):ti,ab,kw (Word variations have been searched) #64 (preference* near/3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)):ti,ab,kw (Word variations have been searched) #65 (disutilit*):ti,ab,kw (Word variations have been searched) #66 (rosser or 'willingness to pay' or 'standard gamble*'):ti,ab,kw (Word variations have been searched) #67 ('time trade off' or 'time tradeoff' or tto):ti,ab,kw (Word variations have been searched) #68 (hui or hui1 or hui2 or hui3):ti,ab,kw (Word variations have been searched) #69 (eq or euroqol or 'euro qol' or eq5d or 'eq 5d' or euroqual or 'euro qual'):ti,ab,kw (Word variations have been searched) #70 #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 #71 #3 and #41 and #70	

TABLE 49 Search strategies for 'HRQoL 2'

Database, host, years searched, date searched	Literature search strategy	Results
Ovid MEDLINE(R) and Epub Ahead of Print, In-process, In-data-review & Other Non-indexed Citations, Daily and Versions(R) 1946–14 September 2021 Date of original search: 15 September 2021 Date of update search: 29 January 2022	1 exp *Prostatic Neoplasms/ 2 (prostat* adj3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)).tw. 3 1 or 2 4 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf. 5 3 and 4 6 limit 5 to yr='2011 -Current' 7 limit 6 to english language	Original search: 89 Update search:
Ovid Embase Classic + Embase 1947–2021 Week 36 Date of original search: 15 September 2021 Date of update search: 29 January 2022	1 exp *prostate cancer/ 2 (prostat* adj3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)).tw. 3 1 or 2 4 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw. 5 3 and 4 6 limit 5 to yr='2011 -Current' 7 limit 6 to english language	Original search: 261 Update search:

continued

TABLE 49 Search strategies for 'HRQoL 2' (*continued*)

Database, host, years searched, date searched	Literature search strategy	Results
Web of Science – Science Citation Index Expanded (SCI-EXPANDED), Conference Proceedings Citation Index – Science (CPCI-S) Date of original search: 16 September 2021 Date of update search: 29 January 2022	(TS=(prostat* near/3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*))) AND TS=(eq or euroqol or 'euro qol' or eq5d or 'eq 5d' or euroqual or 'euro qual') Publication date: 1 January 2011–16 September 2021 Refine by English language	Original search: 133 Update search:
Cochrane Library, Wiley Date of original search: 16 September 2021 Date of update search:	#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees #2 (prostat* near/3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)):ti,ab,kw (Word variations have been searched) #3 #1 or #2 #4 (eq or euroqol or 'euro qol' or eq5d or 'eq 5d' or euroqual or 'euro qual'):ti,ab,kw #5 #3 and #4 with Cochrane Library publication date Between Jan 2011 and Sep 2021	Original search: 146 Update search:

Appendix 2 Further detail on inclusion/exclusion of studies

Extended inclusion/exclusion criteria for the systematic review of diagnostic test evaluation and clinical effectiveness

TABLE 50 Population, intervention, comparator, outcome (PICO) table for inclusion and exclusion criteria

Population (decision questions 1 and 2)
Population: People with suspected prostate cancer where prostate biopsy is indicated
Inclusion criteria • People with clinical suspicion of prostate cancer • People who have had a previous prostate biopsy that was negative for prostate cancer
Exclusion criteria • People who have already been diagnosed with prostate cancer (receiving treatment or monitoring by active surveillance or watchful waiting) • People already known to have metastatic prostate cancer
Interventions – relevant diagnostic procedures (decision question 1)
• LATP prostate biopsy by any of these methods: ◦ Grid and stepping device ◦ Coaxial needle (double freehand) ◦ Freehand TP device • The following freehand TP devices: ◦ PrecisionPoint (BXTAccelyon) ◦ UA1232 (BK Medical) ◦ Trinity Perine (KOELIS) ◦ CamPROBE (JEB) ◦ SureFire Guide (LeapMed) ◦ EZU-PA3U (Hitachi)
Comparators – relevant alternative diagnostic procedures (decision question 1)
• LATRUS prostate biopsy (LATRUS) • General anaesthetic transperineal prostate (GATP) biopsy using a grid and stepping device
Inclusion criteria • Systematic and/or targeted biopsies • Cognitive/visual registration fusion biopsy
Exclusion criteria • Software-based fusion biopsy • Sedation
Interventions – relevant diagnostic procedures (decision question 2)
• The following freehand TP devices: ◦ PrecisionPoint (BXTAccelyon) ◦ UA1232 (BK Medical) ◦ Trinity Perine (KOELIS) ◦ CamPROBE (JEB) ◦ SureFire Guide (LeapMed) ◦ EZU-PA3U (Hitachi)
Comparators – relevant alternative diagnostic procedures (decision question 2)
• LATRUS prostate biopsy (LATRUS) • General anaesthetic transperineal prostate (GATP) biopsy using a grid and stepping device • LATP prostate biopsy using a grid and stepping device

continued

TABLE 50 PICO table for inclusion and exclusion criteria (*continued*)

Population (decision questions 1 and 2)	
Inclusion criteria	*Exclusion criteria*
• Systematic and/or targeted biopsies • Cognitive/visual registration fusion biopsy	• Software-based fusion biopsy • Sedation
Outcomes (decision questions 1 and 2)	
• Intermediate outcomes: ◦ Measures of diagnostic accuracy ◦ Cancer detection rates ◦ CS cancer detection rates ◦ Clinically insignificant cancer detection rates ◦ Low-, medium-, high-risk cancer detection rates ◦ Biopsy sample suitability/quality ◦ Number of biopsy samples taken ◦ Procedure completion rates ◦ Re-biopsy events within 6 months • Clinical outcomes: ◦ Hospitalisation events after biopsy ◦ Rates of biopsy-related complications, including infection, sepsis and haematuria ◦ Rates of urinary retention ◦ Rates of erectile dysfunction ◦ Survival ◦ Progression-free survival ◦ Adverse events from treatment • Patient-reported outcomes ◦ Health-related quality of life ◦ Patient-reported tolerability	
Inclusion criteria	*Exclusion criteria*
• Any outcomes listed above • Procedure time	• Cost outcomes[a]
Study design (decision questions 1 and 2)	
Inclusion criteria	*Exclusion criteria*
• Any comparative study design	• Single-arm studies or studies where only one arm is relevant to this review[b]
Publication type (decision questions 1 and 2)	
Inclusion criteria	*Exclusion criteria*
• Peer-reviewed publications • Conference abstracts with sufficient information to assess methodology and outcomes	• Conference abstracts without sufficient information to assess methodology and outcomes • Case reports • Narrative reviews • Systematic reviews and meta-analyses[c]
Language (decision questions 1 and 2)	
Inclusion criteria	*Exclusion criteria*
English	Non-English language

a Relevant studies that reported cost outcomes were cross-referenced with the cost-effectiveness searches.
b Single-arm studies were tagged in the screening database to retrieve if insufficient comparative evidence was identified.
c Systematic reviews and meta-analyses were noted and the references were checked.

List of studies excluded from the systematic review of diagnostic test evaluation and clinical effectiveness

Studies that have not been included in this review were either excluded or their eligibility remains unclear:

- Excluded studies: studies excluded after full-text screening are listed in *Table 51*. Studies may have been excluded for not meeting more than one eligibility criteria, but only the first exclusion reason is recorded.
- Unclear studies: studies whose eligibility for inclusion remained unclear after full-text screening and after contacting the authors for further information are listed in *Table 52*.

TABLE 51 Studies excluded at full-text screening

Study	Publication type	Exclusion reason
ACTRN12620001145998/ LATProBE 2020[58]	Trial register record	Ongoing study (no results)
ISRCTN98159689/ TRANSLATE 2021[52]	Trial register record	Ongoing study (no results)
Adshead 2019[116]	Conference abstract	Intervention
Berry 2020[97]	Journal article	Population
Berry 2020[114]	Conference abstract	Population
Chae 2009[117]	Journal article	Language
Eldred-Evans 2018[118]	Conference abstract	Intervention
Han 2008[119]	Journal article	Intervention
Israel 2021[120]	Conference abstract	Comparator
Kasivisvanathan 2015[121]	Letter	Intervention
Kawakami 2007[122]	Journal article	Intervention
Lavoipierre 2008[123]	Letter	Outcomes
Lim 2018[124]	Conference abstract	Intervention
Lim 2020[125]	Journal article	Intervention
Lo 2019[126]	Journal article	Comparator
NCT03496142 2018[127]	Trial register record	Intervention
NCT04108871 2019[128]	Trial register record	Ongoing study (no results)
NCT04815876 2021[57]	Trial register record	Ongoing study (no results)
NCT04843566 2021[56]	Trial register record	Ongoing study (no results)
Neale 2020[129]	Journal article	Intervention
Pahwa 2017[130]	Journal article	Outcomes
Pal 2018[131]	Journal article	Intervention
Pepe 2017[132]	Journal article	Design

continued

TABLE 51 Studies excluded at full-text screening (*continued*)

Study	Publication type	Exclusion reason
Postema 2017[133]	Journal article	Intervention
Presti 2000[134]	Journal article	Design
Ristau 2018[135]	Journal article	Comparator
Roberts 2020[136]	Conference abstract	Intervention
Roberts 2021[137]	Journal article	Intervention
Rochester 2009[138]	Journal article	Comparator
Rodriguez Socarras 2020[139]	Journal article	Intervention
Roethke 2014[140]	Journal article	Intervention
Rojas Claros 2019[141]	Conference abstract	Intervention
Salagierski 2019[142]	Journal article	Intervention
Satoh 2005[143]	Journal article	Comparator
Self 2018[144]	Conference abstract	Design
Shigemura 2007[145]	Journal article	Intervention
Sivaraman 2015[146]	Journal article	Intervention
Song 2019[147]	Journal article	Intervention
Stabile 2018[148]	Journal article	Intervention
Suga 1999[149]	Journal article	Population
Sulaiman 2019[150]	Conference abstract	Design
Taira 2010[151]	Journal article	Intervention
Tamhankar 2020[152]	Conference abstract	Intervention
Taverna 2016[153]	Journal article	Intervention
Taverna 2016[154]	Conference abstract	Intervention
Teoh 2015[155]	Journal article	Intervention
Tilak 2015[156]	Journal article	Comparator
Tschirdewahn 2020[157]	Journal article	Intervention
Valerio 2015[158]	Journal article	Intervention
Vanni 2004[159]	Journal article	Intervention
Vezelis 2021[160]	Journal article	Intervention
Wang 2019[161]	Journal article	Comparator
Westhoff 2019[162]	Journal article	Intervention
Williams 2018[163]	Conference abstract	Comparator
Williams 2018[164]	Conference abstract	Comparator
Yamada 2020[165]	Journal article	Intervention
Yang 2019[166]	Conference abstract	Intervention
Yaxley 2017[167]	Journal article	Intervention
Yunkai 2010[168]	Journal article	Comparator
Zhang 2020[169]	Journal article	Intervention

TABLE 51 Studies excluded at full-text screening (*continued*)

Study	Publication type	Exclusion reason
Zhang 2019[170]	Conference abstract	Intervention
Zhang 2017[171]	Journal article	Intervention
Zhang 2015[172]	Journal article	Intervention
Zhao 2012[173]	Journal article	Intervention
Zhou 2020[174]	Journal article	Intervention

TABLE 52 Studies where eligibility for inclusion remains unclear (after full-text screening and contacting authors)

Study	Publication type	Reason unclear	Notes
Al-Dahir 2019[175]	Conference abstract	Unclear comparator	No author contact details; no response via ResearchGate
Chan 2020[176]	Conference abstract	Unclear population	No author response
Chan 2020[177]	Conference abstract	Unclear population	No author response
Cole 2019[178]	Conference abstract	Unclear population and comparator	Invalid author contact details
Cole 2020[179]	Conference abstract	Unclear intervention	Invalid author contact details
Demozzi 2018[180]	Conference abstract	Unclear comparator	No author response
Di Franco 2017[181]	Journal article	Unclear population	No author response
Elkhoury 2020[182]	Conference abstract	Unclear population	No author contact details
Ferrante 2020[183]	Conference abstract	Unclear comparator	No author response
Ferriero 2019[184]	Conference abstract	Unclear population	No author response
Islam 2020[185]	Conference abstract	Unclear population	No author response
Islam 2021[186]	Conference abstract	Unclear population	No author response
Lai 2021[187]	Conference abstract	Unclear intervention	No author response
Lovegrove 2019[188]	Conference abstract	Unstratified data	Not data owner[a]
Lovegrove 2019[189]	Conference abstract	Unstratified data	Not data owner[a]
Marra 2015[190]	Conference abstract	Unclear intervention and comparator	No author response
Maruf 2020[191]	Conference abstract	Unclear population	No author response
Newman 2020[192]	Conference abstract	Unclear population	No author response
Ng 2019[193]	Conference abstract	Unclear population, intervention and comparator	No author response
Sharma 2019[194]	Conference abstract	Unclear population	No author contact details
Stroman 2019[195]	Conference abstract	Unclear intervention	No author response
Stroman 2020[196]	Conference abstract	Unclear population	No author response
Stroman 2020[197]	Conference abstract	Unclear population	No author response
Ting 2016[198]	Journal article	Unclear intervention	No author response

continued

TABLE 52 Studies where eligibility for inclusion remains unclear (after full-text screening and contacting authors) (*continued*)

Study	Publication type	Reason unclear	Notes
Urkmez 2020[199]	Conference abstract	Unclear population, intervention and comparator	No author response
Urkmez 2021[200]	Conference abstract	Unclear population	No author response
Zattoni 2021[201]	Conference abstract	Unclear intervention	No author response

a Author clarification indicated that data stratified by anaesthetic type might be available for the TP arm of this study by contacting the authors of the PROMIS study. Due to time constraints, the EAG was unable to follow up on this and the intervention arm of this study remains ineligible for inclusion in this review.

Appendix 3 Data-extraction template used in the systematic review of diagnostic test evaluation and clinical effectiveness

1. Study overview.
2. Relevant subgroup analyses (as per NICE scope).
3. Participant baseline characteristics.
4. Biopsy characteristics.
5. Results: intermediate outcomes (repeat for each subgroup reported).
6. Results: other intermediate outcomes.
7. Results: clinical outcomes.
8. Results: patient-reported outcomes.
9. Results: costs and resources.
10. General reviewer comments (e.g. importance, methodological issues).

1. Study overview

Reviewer 1: **Date:**	**Reviewer 2:** **Date:**	**Version:**	
Reference and design	**Diagnostic tests**	**Participants**	**Outcome measures**
First author and ref ID:	**Condition being diagnosed/detected:**	**Number of participants:**	**Primary outcome of study:**
Publication year:	Prostate cancer		*Include definition where available.*
Linked papers:	*Emphasis here on describing the elements of the biopsy that define this DAR's intervention and comparators: transperineal or transrectal approach, anaesthetic type.*	**Sample attrition/ dropout:**	**Other relevant outcomes:**
Study name/trial identifier:		**Selection of participants:**	*List other (secondary) outcomes briefly. If there are many, list a couple of key outcomes and then cross refer to the results tables below* (see *table 5 onwards*)
Study design:		**Inclusion criteria for study entry:**	
Country:	*Further details are in the 'Biopsy characteristics' table below.*	**Exclusion criteria for study entry:**	**Definition of CS disease:**
Number of centres:	**Index test:**		*State any definition or threshold(s) used.*
Recruitment dates:	**Reference standard:**	**Sample size calculation:**	**Relevant subgroup analyses:**
Funding:	**Intervention:**		*If relevant to NICE scope.*
Competing interests:	**Comparator:**		*None/See table 3 below.*

2. Relevant subgroup analyses (as per NICE scope)

Subgroup in NICE scope	**Subgroup in study**
People with anterior lesions	
People with posterior lesions	
People with apical lesions	
People with basal lesions	
People with a Likert or PI-RADS score of 2 or less	
People with a Likert or PI-RADS score of 3, 4 or 5	
People with enlarged prostate	
People who have never had a prostate biopsy	
People who have had a previous negative prostate biopsy and are referred back	

3. Participant baseline characteristics

Characteristic, *units and variance measure*	Intervention: *(write short description), n =*	Comparator: *(write short description), n =*	*p-value/CI/other relevant statistic (e.g. ORs)*
Age, years, mean (SD)			
Ethnicity			
BMI/Height/Weight			
PSA level, ng/ml, mean (SD)			
Prostate volume, ml, mean (SD)			
DRE findings, (*n*, %)			
Imaging findings (ultrasound, CT or MRI), (*n*, %)			
Family history of prostate cancer, (*n*, %)			
Previous prostate biopsy experience, *n* (%) **First biopsy** **Repeat biopsy**			
MRI performed, *n* (%)			
Likert or PI-RADs score			
Lesion location (posterior, anterior, basal, apical) and number			
Previous prostate biopsy was abnormal (e.g. HGPIN, ASAP) but not cancer, *n* (%)			
Previous prostate biopsy was positive for cancer, *n* (%)			

4. Biopsy characteristics

Characteristics	Intervention:	Comparator:
Device(s)	E.g. *grid + stepper, or coaxial needle, or freehand device*, e.g. *PrecisionPoint*	
Targeted/systematic/saturation, and sequence		
Type of imaging used	E.g. *TRUS or MRI/TRUS-guided fusion*	
Number of cores		
Location of cores		
Anaesthetic used (type of anaesthesia – name of drug (strength), dose, method of admin., location of admin.)	*Example: Periprostatic nerve block – lidocaine (1%) 10 ml injected at five injections sites from base to apex of prostate*	
Antibiotic prophylaxis		
Other medications administered as standard protocol procedure		
Patient position		
Clinician's experience and training in prostate biopsy		

5. Results: intermediate outcomes (repeat for each subgroup reported)

	Prostate cancer on histopathology	No prostate cancer on histopathology	Total
Index test positive	a	b	a + b
Index test negative	c	d	c + d
Total	a + c	b + d	a + b + c + d

Accuracy

Calculate clinical sensitivity, specificity, PPV, NPV if possible and note whether these agree with any values that may be reported in the paper. Use www.medcalc.org/calc/diagnostic_test.php *to assist with calculations*

Diagnosis	Value	95% CI
Clinical sensitivity a/(a + c)		
Clinical specificity d/(b + d)		
PPV a/(a + b)		
NPV d/(c + d)		
Positive likelihood ratio [sensitivity/(1−specificity)]		
Negative likelihood ratio [(1−sensitivity)/specificity]		
Diagnostic odds ratio (a × d)/(b × c)		

NPV, negative predictive value; PPV, positive predictive value.

Notes
Comments: e.g. *Calculations agree with values reported in paper. Note if any cases where 0.5 added to values to avoid division by zero when calculating diagnostic odds ratio. Add an asterisk to denote where values have been calculated by the reviewer. Repeat for other tests/thresholds as appropriate or delete if not required.*

Outcome in NICE scope	Specific outcome(s) measured in study *Specify units and mean, median, range, SD, SE, % etc. as appropriate – for % report with (n/N). Add rows as necessary. When scope outcome was not measured, state 'Not reported'. Delete examples below.*	Intervention: *(write short description), n =*	Comparator: *(write short description), n =*	*p-value/CI/other relevant statistic (e.g. ORs)*
Cancer detection rates	*Examples:* *Positive detectable rate, n (%)* *Cancer core rate, n (%)*			
CS cancer detection rates				
Clinically insignificant cancer detection rates				
Low-, medium-, high-risk cancer detection rates	*Example:* *Gleason score, n (%)* *Gleason 6* *Gleason 7* *Gleason 8* *Gleason 9* *Gleason 10*			
Interpretability of test				
Interobserver agreement				
Intraobserver agreement				

SE, standard error.

6. Results: other intermediate outcomes

Outcome in NICE scope	Specific outcome(s) in the study	Intervention: *(write short description), n =*	Comparator: *(write short description), n =*
Biopsy sample suitability/quality			
Number of biopsy samples taken			
Procedure completion rates			
Re-biopsy events within 6 months			
Outcome(s) added by EAG			
Length of time to perform the biopsy			

7. Results: clinical outcomes

Outcome in NICE scope	Specific outcome(s) in the study	Intervention: *(write short description), n =*	Comparator: *(write short description), n =*
Hospitalisation events after biopsy			
Rates of biopsy-related complications			
Rates of urinary retention			
Rates of erectile dysfunction			
Survival			
Progression-free survival			
Adverse events from treatment			

8. Results: patient-reported outcomes

Outcome in NICE scope	Specific outcome(s) in the study	Intervention: *(write short description), n =*	Comparator: *(write short description), n =*
Health-related quality of life			
Patient-reported tolerability			

9. Results: costs and resources

Outcome in NICE scope	Specific outcome(s) in the study	Intervention: *(write short description), n =*	Comparator: *(write short description), n =*
e.g. cost of biopsy devices *(refer to the NICE scope for the full list of relevant costs)*			

10. General reviewer comments (e.g. importance, methodological issues)

Comments

Appendix 4 Further information on studies included in the systematic review of diagnostic test evaluation and clinical effectiveness

TABLE 53 Details of LATP biopsy procedures (LATP-any biopsy vs. LATRUS biopsy, decision question 1)

Study	LATP device/ approach	Sampling	Number of cores taken	Pre-biopsy imaging (MRI)	Prostate biopsy image guidance	Anaesthesia
RCTs						
Cerruto *et al.* 2014[24]	Coaxial needle	Systematic	14	Not reported	TRUS	Mepivacaine (1%) 2 ml at the level of the prostate apex
Guo *et al.* 2015[25]	Not reported[a]	Systematic	12 cores if PV > 50 ml; 8 cores if PV < 50 ml; 2 cores per suspicious area detected by TRUS/DRE	Not reported	TRUS	Periprostatic nerve block: lidocaine (2%) 2 ml; additional lidocaine (2%) 2 ml administered where participant could not tolerate pain
Hara *et al.* 2008[26]	Not reported[a]	Systematic	12	Not reported	TRUS	Spinal anaesthesia: bupivacaine (0.5%)
Lam *et al.* 2021 (AB)[27]	Freehand PrecisionPoint	Systematic	Not reported (modified Ginsburg protocol)	Not reported	Not reported	Local anaesthetic (details not reported)
Takenaka *et al.* 2008[28]	Attachment for needle guidance	Systematic	12	Not reported	TRUS	'Saddle blockade': bupivacaine (0.5%)
Other prospective studies						
Bojin 2019[29]	Freehand PrecisionPoint	Systematic and targeted	Not reported (up to 24 for participants needing the full template)	Unclear	TRUS	Peri-prostatic block: lignocaine (1%) 13–20 ml
Chen *et al.* 2021[30,31]	Freehand PrecisionPoint	Systematic	12	30% of participants had a pre-biopsy MRI	TRUS	Periprostatic nerve block: lignocaine (1%) at the perineal skin on both sides. Further, lignocaine (1%) 10 ml given on each side
Emiliozzi *et al.* 2003[32]	Not reported[a]	Targeted and systematic (Fan technique but any hypoechoic area was also included)	6	Not reported	TRUS	Mepivacaine (2%) two 10 ml transperineal injections, one in each lobe
Hung *et al.* 2020 (AB)[33]	Freehand PrecisionPoint	Not reported	Not reported	Not reported	Not reported	Local anaesthetic (details not reported)

TABLE 53 Details of LATP biopsy procedures (LATP-any biopsy vs. LATRUS biopsy, decision question 1) (*continued*)

Study	LATP device/ approach	Sampling	Number of cores taken	Pre-biopsy imaging (MRI)	Prostate biopsy image guidance	Anaesthesia
Kum (AB) 2018[34,35]	Freehand PrecisionPoint	Systematic (52%), targeted (25%), and systematic and targeted (23%)	Not reported	Not reported	TRUS	Lidocaine (1%) approximately 10–12 ml (up to 30 ml in total) injected on each side, around perineal body and to the apex of the prostate, then laterally to the neurovascular bundles
Starmer *et al.* 2021[36,37]	Freehand PrecisionPoint	Systematic, plus targeted biopsies if a PI-RADSv2 > 2 lesion on MRI	Not reported	Pre-biopsy MRI assisted in assigning participants to groups	Not reported	Lidocaine (1%) 10 ml[a] and chirocaine[b] (0.5%) 10 ml
Watanabe *et al.* 2005[38]	Not reported[a]	Systematic with additional targeted biopsies for any hypoechoic lesions or palpable nodules on DRE	6	Not reported	Ultrasound	Spinal anaesthesia (details not reported)
Retrospective studies						
Abdollah *et al.* 2011[39]	Coaxial needle	Saturation	24	Not reported	TRUS	Anaesthetic block of the periprostatic plexus: mepivacaine (1%) 2 ml at prostate apex
Jiang *et al.* 2019[40]	Not reported[a]	Systematic	12	Pre-biopsy MRI performed in some participants (proportion not reported)	TRUS	Subcutaneous infiltration plus periprostatic nerve block: lidocaine (1%)
Szabo *et al.* 2021[41]	Freehand PrecisionPoint	Systematic Participants with PI-RADS 4 or 5 had additional cognitive (42/242) or software-based (6/242) targeted biopsy	Varied with the size of the prostate (samples spaced 1 cm apart)	31% had pre-biopsy MRI	Ultrasound	Lidocaine gel (2%) 10 ml into the rectum and lidocaine (0.5%) 5 ml mixed with 8.4% sodium bicarbonate injected into the perineal skin; additional 10 ml anaesthetic solution infiltrated into the ischiorectal fat, pelvic diaphragm, and periapical triangle. Maximum dose: 4.5 mg/kg
Szabo *et al.* 2021[41]	Freehand co-axial needle (without PrecisionPoint)	Not reported	Not reported	Not reported	Not reported	Not reported

PV, prostate volume.
a Most likely freehand (EAG inference).
b Conference poster reports 20 ml of 1% lidocaine only (does not report chirocaine).

TABLE 54 Overview of participant characteristics (LATP-any biopsy vs. LATRUS biopsy, decision question 1)

Study	Age, years, mean (SD)	PSA ng/ml, mean (SD)	Prostate volume, cm^3, mean (SD)	Abnormal DRE findings, *n*/*N* (%)	Abnormal pre-biopsy imaging findings
RCTs					
Cerruto *et al.* 2014[24]					
LATP	66.50 (8.87)	15.95 (41.04)	56.29 (31.33)	11/54 (20.4)	10/54 (18.2)
LATRUS	67.30 (8.05)	12.36 (36.95)	61.49 (33.39)	10/54 (18.2)	10/54 (18.2)
Guo *et al.* 2015[25]					
LATP	67.18 (6.76)	8.81 (3.6–56.0)[a]	47.2 (12.9–97.7)	20/173 (11.6)	40/173 (23.1)[b]
LATRUS	67.35 (7.28)	10.48 (6.2–69.0)[a]	45.9 (20.0–98.0)	19/166 (11.5)	30/166 (20.1)[b]
Hara *et al.* 2008[26]					
LATP	71.0 (7.29)	8.34 (3.44)	33.2 (15.2)		23/126 (18)[b]
LATRUS	71.7 (7.55)	8.48 (3.90)	36.0 (17.1)	22/120 (18.0)	12/120 (10)[b]
Lam *et al.* 2021 (AB)[27]					
LATP	Not reported	Not reported	Not reported	Not reported	Not reported
LATRUS	Not reported	Not reported	Not reported	Not reported	Not reported
Takenaka *et al.* 2008[28]					
LATP	71.1 (7.53)	17.1 (30.1)	34.5 (18.9)[c]	16/100 (16.0)	28/100 (28)[b]
LATRUS	72.1 (7.42)	19.6 (43.2)	37.2 (19.7)[c]	28/100 (28.0)	22/100 (22)[b]
Other prospective studies					
Bojin 2019[29]					
LATP	65 (45–82)[e]	10.5 (3.6–89)[i]	57 (15–210)[e]	Not reported	Unclear
LATRUS	69 (43–88)[e]	32.44 (1–1581)[i]	51.6 (16–175)[e]	Not reported	Unclear
Chen *et al.* 2021[30,31]					
LATP	69.40 (7.75)	13.17 (6.82–47.13)[a]	45.08 (26.78)[c]	102/205	Unclear
LATRUS	68.24 (7.98)	10.76 (6.45–50.97)[a]	49.62 (27.76)[c]	77/177	Not reported
Emiliozzi *et al.* 2003[32]					
LATP and LATRUS[d]	68 (52–88)[e]	8.2 (4.1 to 240)[e]	Not reported	26/107 (24.0)	29/107 (27)[b]
Hung *et al.* 2020 (AB)[33]					
LATP and LATRUS[f]	Median 68	7.66 (3.23)	Not reported	Not reported	Not reported
Kum *et al.* 2018 (AB)[34,35]					
LATP	65 (36–83)[e]	7.9 (0.7–1374)[e]	45 (15–157)[e]	Not reported	Not reported
LATRUS	Not reported	Not reported	Not reported	Not reported	Not reported
Starmer *et al.* 2021[36,37]					
LATP	66.8 (53–80)[g]	10.7 (2.2–55.6)[g]	47.8 (20–100)[g,h]	Not reported	Not reported
LATRUS	66.5 (52–78)[g]	18.15 (1.2–160)[g]	48.0 (14–147)[g,h]	Not reported	Not reported
Watanabe *et al.* 2005[38]					
LATP and LATRUS[d]	72.5 (41 to 98)[e]	Median 10.3	Not reported	130 (32.3)	Not reported
Retrospective studies					
Abdollah *et al.* 2011[39]					
LATP	66.4 (52.0–79.0)[e]	10 (0.9 to 31.5)[e]	62.3 (17.0–98.0)[c]	15/140 (10.7)	Not reported
LATRUS	66.2 (47.6–82.1)[e]	9.7 (2.1 to 26.2)[e]	65.4 (15.0–93.0)[c]	16/140 (11.4)	Not reported
Jiang *et al.* 2019[40]					
LATP	69.72 (8.93)	38.02 (91.11)	51.75 (23.94)[c]	Not reported	Not reported
LATRUS	69.20 (8.03)	40.31 (130.08)	59.64 (33.44)[c]	Not reported	Not reported

TABLE 54 Overview of participant characteristics (LATP-any biopsy vs. LATRUS biopsy, decision question 1) (*continued*)

Study	Age, years, mean (SD)	PSA ng/ml, mean (SD)	Prostate volume, cm^3, mean (SD)	Abnormal DRE findings, *n*/*N* (%)	Abnormal pre-biopsy imaging findings
Szabo *et al.* 2021[41]					
LATP using PrecisonPoint	63 (9)	7.2 (7.7)	50 (35.7)[c]	Not reported	Not reported
LATP coaxial needle	Not reported	Not reported	Not reported	Not reported	Not reported
LATRUS	Not reported	Not reported	Not reported	Not reported	Not reported

a Paper reports median (IQR).
b Ultrasound imaging.
c Prostate volume measured in ml.
d Both biopsies performed in same participants.
e Paper reports mean (range).
f Study arms not reported separately.
g Unclear whether paper reports range or IQR.
h Prostate volume measured in cc.
i Paper reports median (range).

TABLE 55 Details of LATP biopsy procedures used (LATP-any biopsy vs. GATP biopsy studies, decision question 1)

Study	Device/ approach	Sampling	Number of cores taken	Pre-biopsy imaging (MRI)	Prostate biopsy image guidance	Anaesthesia
RCTs						
Lv *et al.* 2020[42]	Grid and stepper	Systematic and targeted	12 + X targeted cores as per suspicious areas on MRI	Pre-biopsy MRI was performed	TRUS for systematic cores; MRI/TRUS cognitive fusion for targeted cores.	Subcutaneous perineal anaesthesia: lidocaine (2%) 5 ml and 1 : 200,000 adrenaline. Followed by deep periprostatic anaesthesia on right then left side of prostate
Other prospective studies						
Takuma *et al.* 2012 (AB)[43]	Not reported	Systematic and targeted	10 + additional cores from suspicious lesions on DRE or ultrasound	Not reported	Not reported	Lumbar spinal anaesthesia (no details reported)
Walters *et al.* 2021 (AB)[44]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Retrospective studies						
Rij and Chapman 2020 (AB)[45]	Freehand PrecisionPoint	Systematic (Ginsburg consensus method); plus targeted for 88% participants with a MRI abnormality; targeted only for 43% of participants	Median of 20.6 for the systematic biopsies	Pre-biopsy MRI was performed	Not reported	Local anaesthesia without sedation (no details reported)

Note
(AB) denotes study only available as a conference abstract at the time of writing.

TABLE 56 Overview of participant characteristics (LATP-any biopsy vs. GATP with grid and stepping device, decision question 1)

Study	Age, years, mean (SD)	PSA ng/ml, mean (SD)	Prostate volume, ml, mean (SD)	Abnormal DRE findings, *n*/*N* (%)	Abnormal pre-biopsy imaging findings
RCTs					
Lv *et al.* 2020[42]					
LATP	66.50 (9.48)	22.00 (22.59)	53.05 (15.43)	90/108 (83.33)	105/108 (97.22)
GATP	67.06 (7.55)	22.97 (24.78)	54.00 (19.04)	81/108 (75.00)	102/108 (94.44)
Other studies (observational)					
No information reported by: Takuma *et al.* 2012 (AB)[43] Walters *et al.* 2021 (AB)[44] Rij and Chapman 2020 (AB)[45]					

Note
(AB) denotes study only available as a conference abstract at the time of writing.

TABLE 57 Overview of participant characteristics for LATP freehand device (PrecisionPoint) vs. LATRUS

Study	Age, years, mean (SD)	PSA ng/ml, mean (SD)	Prostate volume, cm^3, mean (SD)	Abnormal DRE findings, *n*/*N*	Abnormal pre-biopsy imaging findings
RCTs					
Lam *et al.* 2021 (AB)[27]					
LATP	Not reported	Not reported	Not reported	Not reported	Not reported
LATRUS	Not reported	Not reported	Not reported	Not reported	Not reported
Other prospective studies					
Bojin 2019[29]					
LATP	65 (45–82)[e]	10.5 (3.6–89)[i]	57 (15–210)[e]	Not reported	Unclear
LATRUS	69 (43–88)[e]	32.44 (1–1581)[i]	51.6 (16–175)[e]	Not reported	Unclear
Chen *et al.* 2021[30,31]					
LATP	69.40 (7.75)	13.17 (6.82–47.13)[a]	45.08 (26.78)[c]	102/205	Unclear
LATRUS	68.24 (7.98)	10.76 (6.45–50.97)[a]	49.62 (27.76)[c]	77/177	Not reported
Hung *et al.* 2020 (AB)[33]					
LATP and LATRUS[f]	Median 68	7.66 (3.23)	Not reported	Not reported	Not reported
Kum *et al.* 2018 (AB)[34,35]					
LATP using PrecisionPoint	65 (36–83)[a]	7.9 (0.7–1374)[a]	45 (15–157)[a]	Not reported	Not reported
LATRUS	Not reported	Not reported	Not reported	Not reported	Not reported
Starmer *et al.* 2021[36,37]					
LATP using PrecisionPoint	66.8 (53–80)[b]	10.7 (2.2–55.6)[b]	47.8 (20–100)[b,c]	Not reported	Not reported
LATRUS	66.5 (52–78)[b]	18.15 (1.2–160)[b]	48.0 (14–147)[b,c]	Not reported	Not reported
Retrospective studies					
Szabo *et al.* 2021[41]					
LATP using PrecisonPoint	63 (9)	7.2 (7.7)	50 (35.7)[d]	Not reported	Not reported

TABLE 57 Overview of participant characteristics for LATP freehand device (PrecisionPoint) vs. LATRUS (*continued*)

Study	Age, years, mean (SD)	PSA ng/ml, mean (SD)	Prostate volume, cm^3, mean (SD)	Abnormal DRE findings, *n/N*	Abnormal pre-biopsy imaging findings
LATRUS	Not reported	Not reported	Not reported	Not reported	Not reported

a Paper reports mean (range).
b Unclear whether paper reports range or IQR.
c Prostate volume measured in cc.
d Prostate volume measured in ml.

Note
(AB) denotes study only available as a conference abstract at the time of writing.

TABLE 58 Details of relevant ongoing studies

Study	Population	Intervention	Comparator	Outcomes
LATP vs. LATRUS				
Study: **TRANSLATE**[53,54] ISRCTN98159689[52] **Country:** UK (multicentre RCT) **Estimated completion date:** October 2023	Men undergoing investigation for suspected prostate cancer **Target recruitment:** *n* = 1042	LATP biopsy using the PrecisionPoint and UA1232 devices; pre-biopsy MRI will influence any additional targeted biopsies	LATRUS biopsy; pre-biopsy MRI will influence any additional targeted biopsies	Detection rates; infection rates; hospital readmissions; HRQoL; tolerability; complications, e.g. bleeding, pain, erectile function; number of subsequent biopsies; cost
Study: ProBE-PC[55] NCT04081636 **Country:** USA (single-centre RCT) **Estimated completion date:** December 2022	Men requiring prostate biopsy due to clinical suspicion of prostate cancer **Estimated recruitment:** *n* = 568	LATP biopsy (either with ultrasound-guided or with MRI-guided biopsy)	LATRUS biopsy (either with ultrasound-guided or with MRI-guided biopsy)	Rate of infectious complications; rate of bleeding complications; cancer detection rate; tolerability under local anaesthesia; urinary function; cost; sexual function
Study: [a]NCT04843566[56] **Country:** USA (multicentre RCT) **Estimated completion date:** June 2025	Men with elevated PSA or abnormal digital rectal exam **Estimated recruitment:** *n* = 400	MRI-targeted LATP biopsy	MRI-targeted LATRUS biopsy	Infection adverse events; pain and discomfort; anxiety; detection of CS disease; change in adverse events
Study: [a]NCT04815876[57] **Country:** USA (multicentre RCT) **Estimated completion date:** April 2025	Men on active surveillance, or with prior negative prostate biopsy and a clinical concern for the presence of prostate cancer **Estimated recruitment:** *n* = 1302	MRI-targeted LATP biopsy	MRI-targeted LATRUS biopsy	Infection adverse events; pain and discomfort; anxiety; detection of CS disease; change in adverse events
LATP vs. GATP				
Study: LATProBE[58] ACTRN12620001145998p **Country:** Australia (multicentre RCT) **Estimated completion date:** Not yet recruiting.	Men with suspected prostate cancer **Target recruitment:** *n* = 620	Freehand LATP biopsy (no device reported)	GATP biopsy using a template grid	Cancer detection rates; costs; patient experience; pain; 30-day complications; HRQoL

a These studies are run by the same institution and only the study population differs.

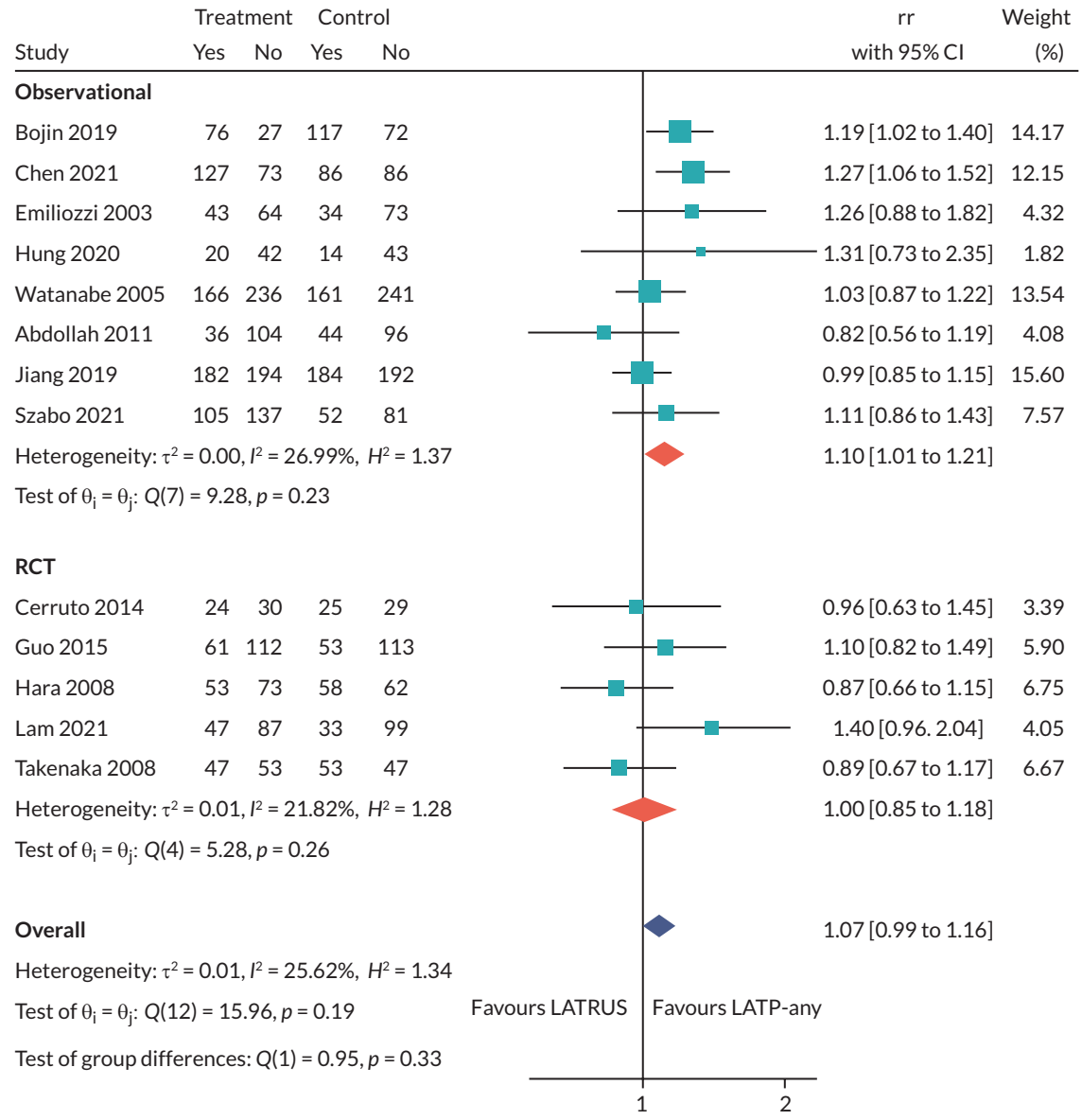

FIGURE 9 Meta-analysis forest plot of cancer detection rates for LATP-any vs. LATRUS (decision question 1). REML, random-effects maximum likelihood.

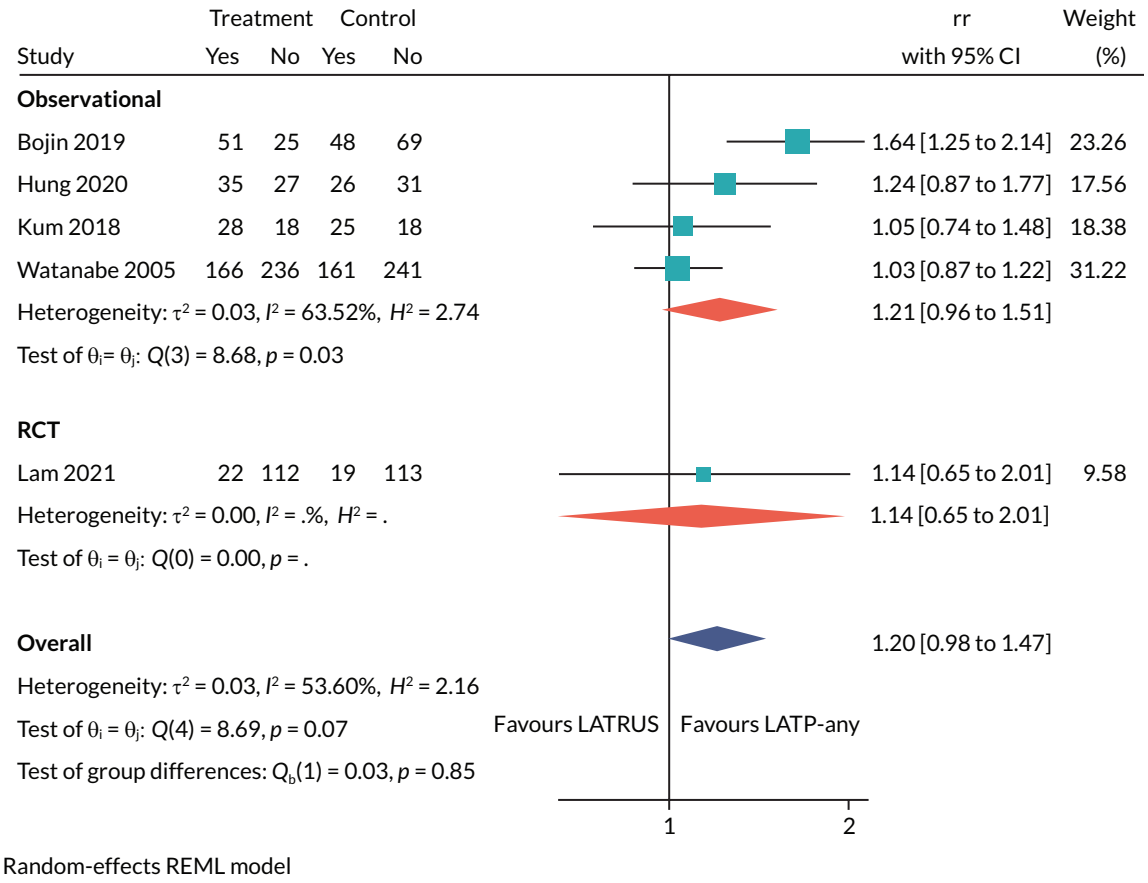

FIGURE 10 Meta-analysis forest plot of CS cancer detection rates for LATP-any vs. LATRUS (decision question 1). REML, random-effects maximum likelihood.

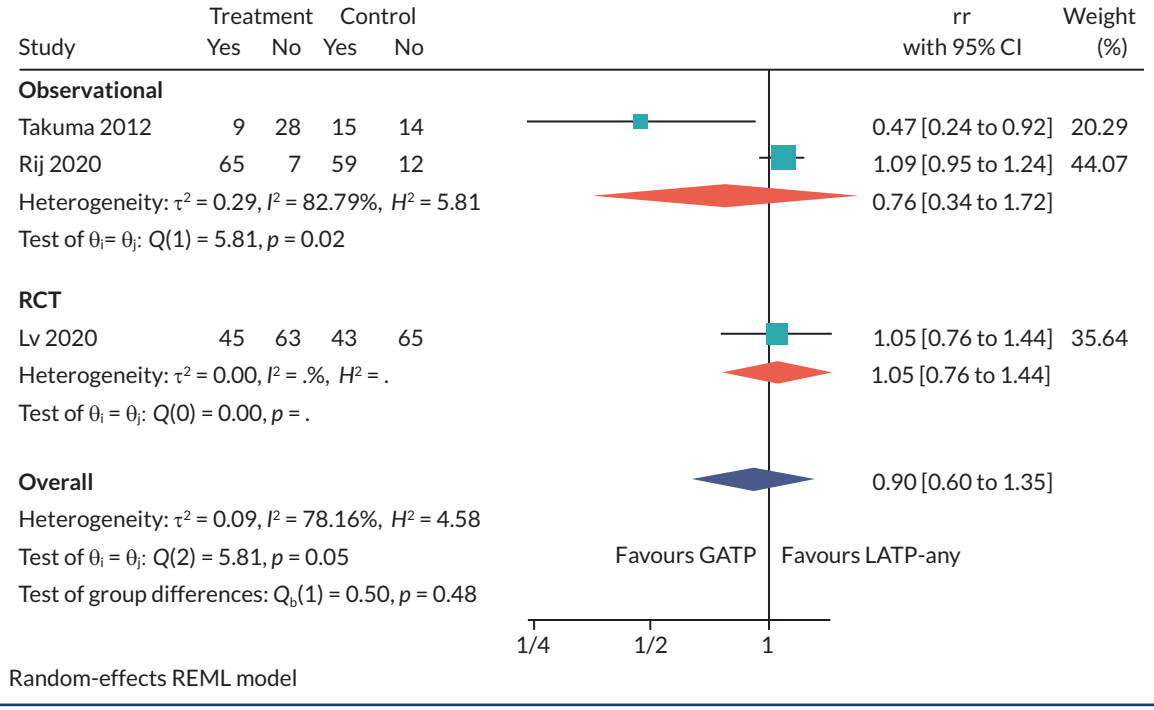

FIGURE 11 Meta-analysis forest plot of cancer detection rates for LATP-any vs. GATP grid and stepping device (decision question 1).

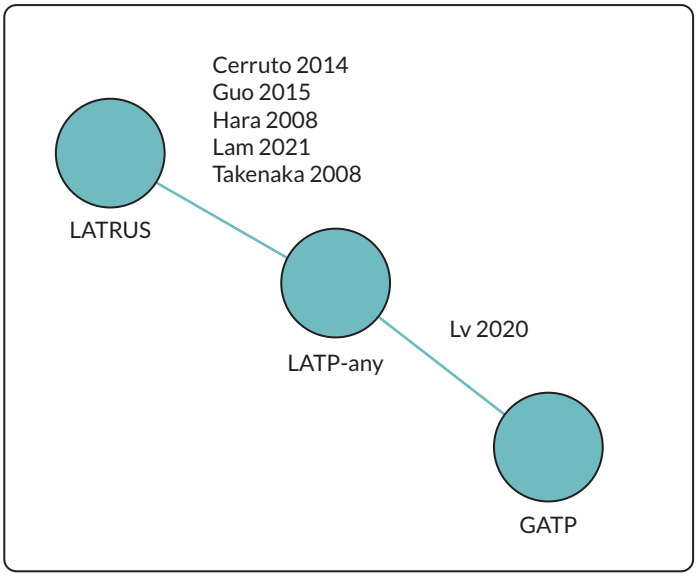

FIGURE 12 Evidence network for indirect comparison of LATP-any, LATRUS, and GATP grid and stepping device (decision question 1). NB: LATRUS is the reference treatment to which all other treatments are compared against.

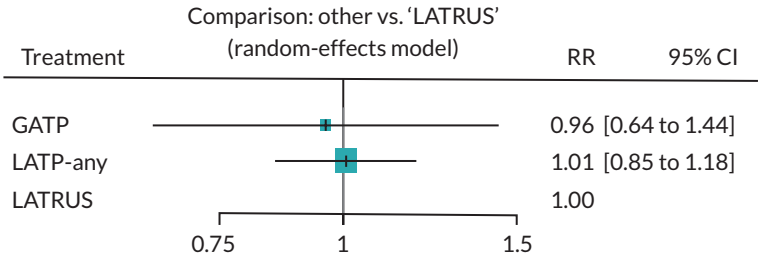

FIGURE 13 Network meta-analysis forest plot of cancer detection rates for LATP-any vs. LATRUS vs. GATP grid and stepping device (decision question 1).

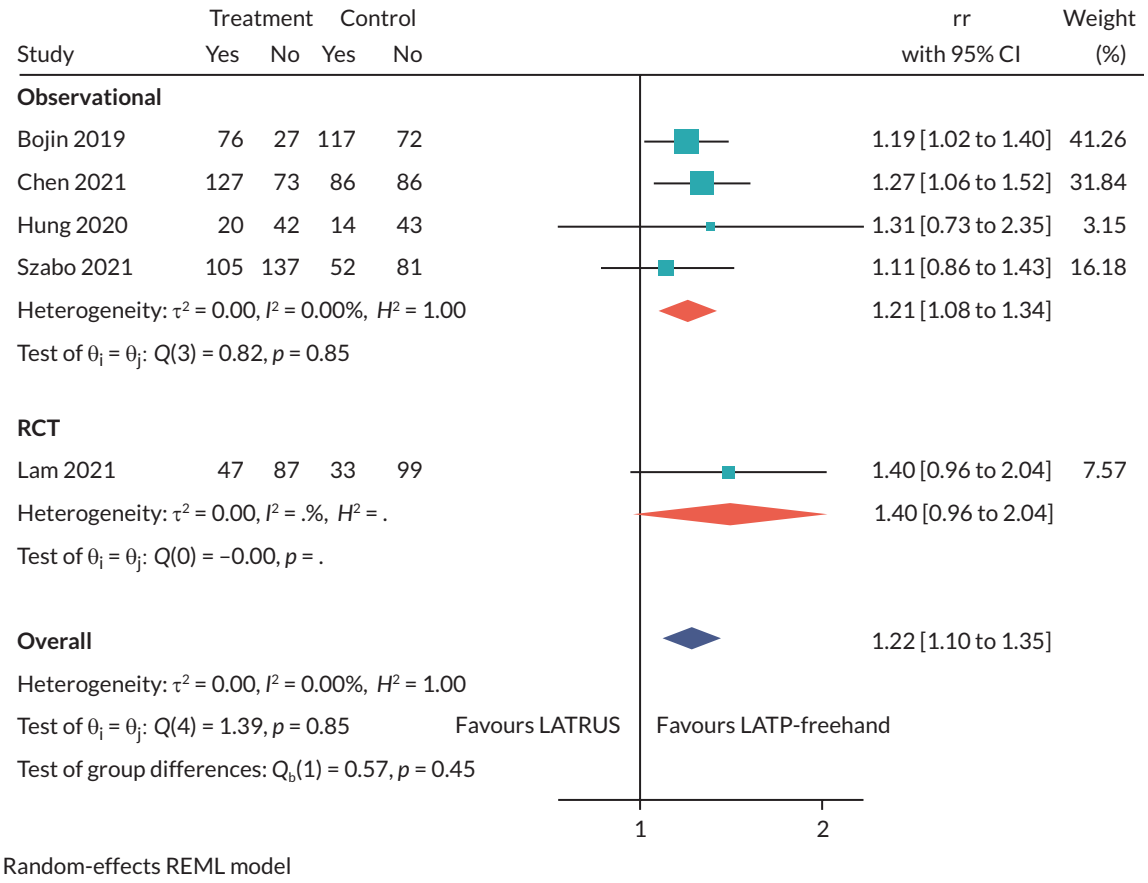

FIGURE 14 Meta-analysis forest plot of cancer detection rates for LATP-freehand vs. LATRUS (decision question 2).

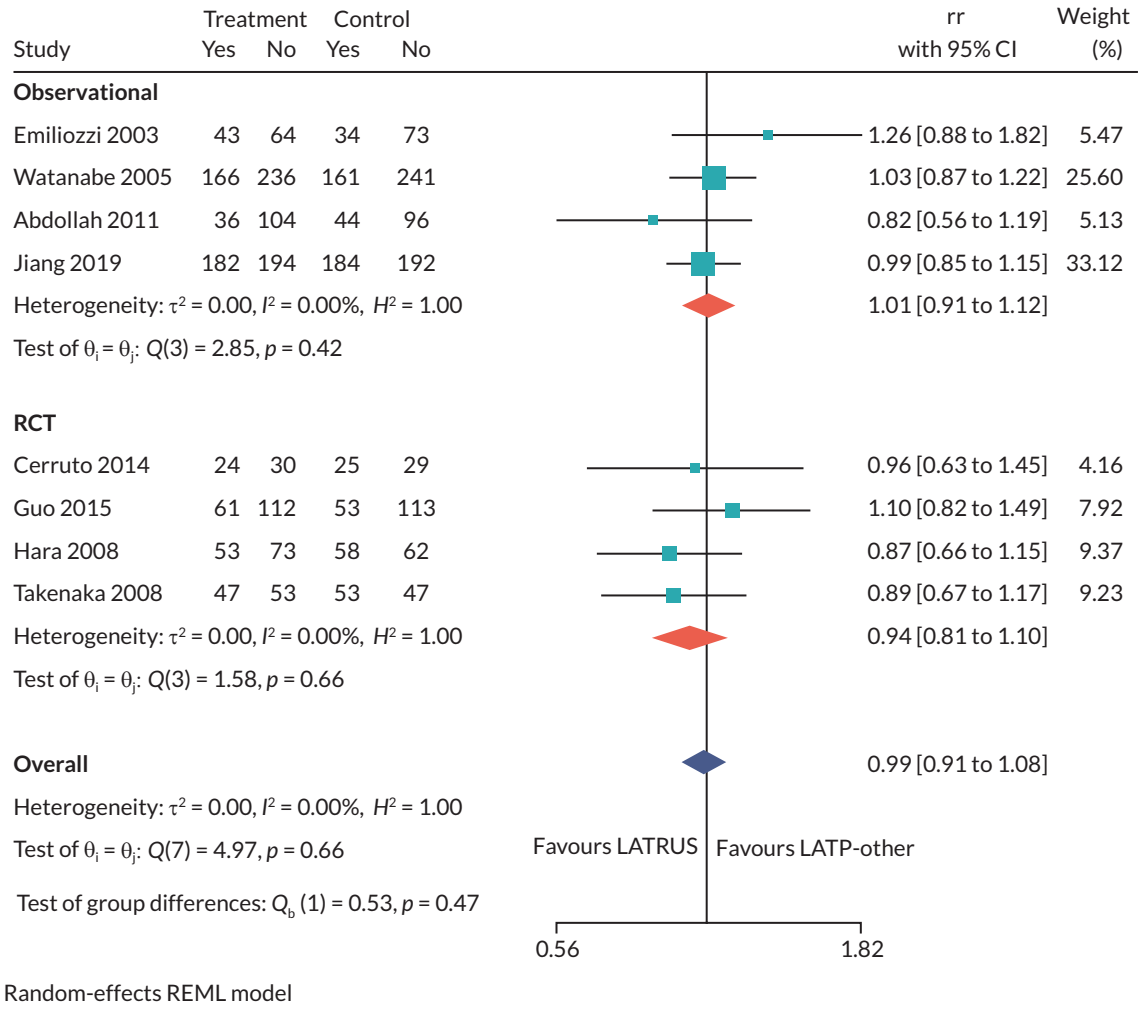

FIGURE 15 Meta-analysis forest plot of cancer detection rates for LATP-other vs. LATRUS (decision question 2).

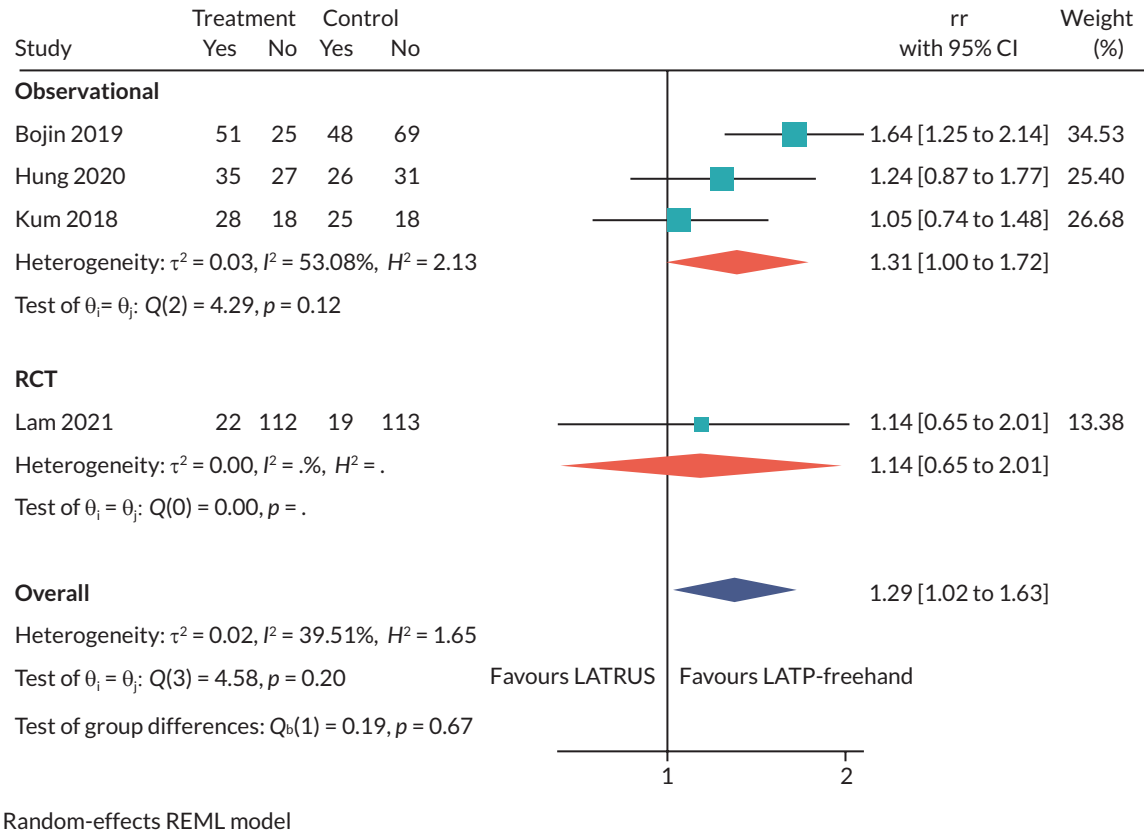

FIGURE 16 Meta-analysis forest plot of CS cancer detection rates for LATP-freehand vs. LATRUS (decision question 2).

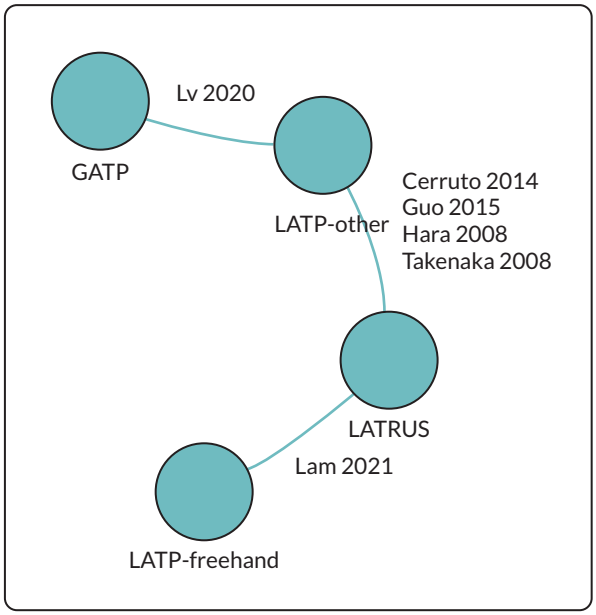

FIGURE 17 Evidence network for indirect comparison of LATP-freehand, LATP-other, LATRUS, and GATP grid and stepping device (decision question 2). NB: LATRUS is the reference treatment to which all other treatments are compared.

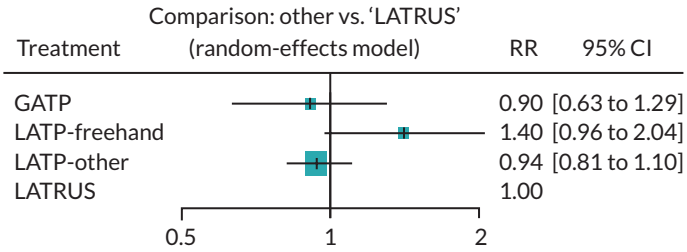

FIGURE 18 Forest plot of NMA results comparing cancer detection rates for LATP freehand, LATP other, GATP grid and stepping device and LATRUS.

Appendix 5 Critical appraisal assessments of studies included in the systematic review of diagnostic test evaluation and clinical effectiveness

TABLE 59 Summary risk-of-bias assessments of RCTs

Study	Random sequence generation	Allocation concealment	Blinding (participants; personnel)	Blinding (outcome assessors)	Incomplete outcome data	Selective reporting
Cerruto *et al.* 2014[24]	Unclear	Unclear	High	Unclear	Low	Unclear
Guo *et al.* 2015[25]	Low	Unclear	High	Low	Low	Low
Hara *et al.* 2008[26]	Unclear	Unclear	High	Unclear	Low	Unclear
Lam *et al.* 2021 (AB)[27]	Unclear	Unclear	High	Unclear	Low	Unclear
Lv *et al.* 2020[42]	Low	Unclear	High	Unclear	Low	Unclear
Takenaka *et al.* 2008[28]	Unclear	Unclear	High	Unclear	Low	Unclear

Individual risk-of-bias assessments of included RCTs using the Cochrane Risk of Bias tool (version 1)

Cerruto *et al.* 2014[24]

Domain	Type of bias	Assessment (low, high, unclear)
Random sequence generation	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	**UNCLEAR** States 'with a randomisation ratio of 1:1.' (p285). No further information provided.
Allocation concealment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment	**UNCLEAR** States 'with a randomisation ratio of 1:1.' (p285), but no further information provided.
Blinding of participants and personnel	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	**HIGH** No details reported but blinding highly unlikely due to nature of study. Unclear whether there was any protocol in place to reduce the risk of differential behaviours by patients and healthcare provider.
Blinding of outcome assessors	Detection bias due to knowledge of the allocated interventions by outcome assessment	**UNCLEAR** No information provided.
Incomplete outcome data	Attrition bias due to amount, nature, or handling of incomplete outcome data	**LOW** Not explicitly reported but number of people in analysis is equal to number of people randomised
Selective outcome reporting	Reporting bias due to selective outcome reporting.	**UNCLEAR** Insufficient information to permit judgement
Other sources of bias	Not applicable	Not applicable

Guo *et al.* 2015[25]

Domain	Type of bias	Assessment (low, high, unclear)
Random sequence generation	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	**LOW** 'The randomization procedure was carried out before biopsy using a computer-generated random-number sequence to assign patients to two groups' (p. 2)
Allocation concealment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment	**UNCLEAR** 'two independent investigators were in charge of the randomization procedure, data recording, and follow-up' (p. 2)
Blinding of participants and personnel	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	**HIGH** 'All patients and investigators were aware of study group assignments except for the pathologist' (p. 2). Unclear whether there was any protocol in place to reduce the risk of differential behaviours by patients and healthcare provider.
Blinding of outcome assessors	Detection bias due to knowledge of the allocated interventions by outcome assessment	**LOW** 'One pathologist with 20 years' experience made all the pathological diagnoses. Besides, two independent investigators were in charge of the randomization procedure, data recording, and follow-up. All patients and investigators were aware of study group assignments except for the pathologist'
Incomplete outcome data	Attrition bias due to amount, nature, or handling of incomplete outcome data	**LOW** All participants analysed on intention-to-treat basis, except for post-biopsy complications where 6 from TP were lost to follow-up and 5 from transrectal biopsy were lost to follow-up
Selective outcome reporting	Reporting bias due to selective outcome reporting.	**UNCLEAR** Insufficient information to permit judgement
Other sources of bias	Not applicable	Not applicable

Hara *et al.* 2008[26]

Domain	Type of bias	Assessment (low, high, unclear)
Random sequence generation	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	**UNCLEAR** 'a prospective randomized study of transperineal vs. transrectal 12-core biopsy', 'we performed a prospective randomized Study'. No further information provided.
Allocation concealment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment	**UNCLEAR** 'a prospective randomized study of transperineal vs. transrectal 12-core biopsy', 'we performed a prospective randomized study'. No further information provided
Blinding of participants and personnel	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	**HIGH** No details reported but blinding highly unlikely due to nature of study. Unclear whether there was any protocol in place to reduce the risk of differential behaviours by patients and healthcare provider
Blinding of outcome assessors	Detection bias due to knowledge of the allocated interventions by outcome assessment	**UNCLEAR** No information provided
Incomplete outcome data	Attrition bias due to amount, nature, or handling of incomplete outcome data	**LOW** Not explicitly reported but denominator for overall cancer detection rate is the same as that randomised

Domain	Type of bias	Assessment (low, high, unclear)
Selective outcome reporting	Reporting bias due to selective outcome reporting.	**UNCLEAR** Insufficient information to permit judgement
Other sources of bias	Not applicable	Not applicable

Lam *et al.* 2021[27]

Domain	Type of bias	Assessment (low, high, unclear)
Random sequence generation	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	**UNCLEAR** 'A parallel group randomized study of men suspected with Pca were allocated in a 1 : 1 ratio.' No further information provided
Allocation concealment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment	**UNCLEAR** 'A parallel group randomized study of men suspected with Pca were allocated in a 1 : 1 ratio.' No further information provided
Blinding of participants and personnel	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	**HIGH** No details reported but blinding highly unlikely due to nature of study. Unclear whether there was any protocol in place to reduce the risk of differential behaviours by patients and healthcare provider
Blinding of outcome assessors	Detection bias due to knowledge of the allocated interventions by outcome assessment	**UNCLEAR** No information provided
Incomplete outcome data	Attrition bias due to amount, nature, or handling of incomplete outcome data	**LOW** Not explicitly reported but denominator for overall cancer detection rate is the same as that randomised reported
Selective outcome reporting	Reporting bias due to selective outcome reporting.	**UNCLEAR** Insufficient information to permit judgement
Other sources of bias	Not applicable	Not applicable

Lv *et al.* 2020[42]

Domain	Type of bias	Assessment (low, high, unclear)
Random sequence generation	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	**LOW** 'All patients were randomly assigned to the control group or the experimental group at a ratio of 1 : 1. The randomisation was implemented with SPSS 19.0 for Windows, which randomly generated a series of numbers. The randomisation was conducted by an independent doctor to ensure that membership in each group could not be predicted'
Allocation concealment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment	**UNCLEAR** 'All patients were randomly assigned to the control group or the experimental group at a ratio of 1 : 1. The randomisation was implemented with SPSS 19.0 for Windows, which randomly generated a series of numbers. The randomisation was conducted by an independent doctor to ensure that membership in each group could not be predicted'

Domain	Type of bias	Assessment (low, high, unclear)
Blinding of participants and personnel	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	**HIGH** 'it was not possible to blind the groups and the operator. The lack of blinding may have affected the operator's perceptions and led to measurement bias in the questionnaire results'
Blinding of outcome assessors	Detection bias due to knowledge of the allocated interventions by outcome assessment	**UNCLEAR** 'The secondary outcomes included changes in vital signs during the procedure, the operative time, the volume of blood loss, the duration of hospitalisation and the incidence of postoperative complications. The operative time was the combined anaesthetic time and puncture time. The postoperative complications were infection, perineal haematoma, urethral bleeding, haematospermia, retention of urine and dysuresia. All the observed indexes mentioned above were recorded by an independent urologist'
Incomplete outcome data	Attrition bias due to amount, nature, or handling of incomplete outcome data	**LOW** Figure 1. Consort diagram of patient enrolment shows that no patients were lost to follow-up or excluded from the analyses
Selective outcome reporting	Reporting bias due to selective outcome reporting.	**UNCLEAR** Insufficient information to permit judgement
Other sources of bias	Not applicable	Not applicable

Takenaka *et al.* 2008[28]

Domain	Type of bias	Assessment (low, high, unclear)
Random sequence generation	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	**UNCLEAR** 'We prospectively randomized'; 'The randomly assigned groups of 100 patients underwent TP 12-core biopsy or TR 12-core biopsy'
Allocation concealment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment	**UNCLEAR** 'We prospectively randomized'; 'The randomly assigned groups of 100 patients underwent TP 12-core biopsy or TR 12-core biopsy'
Blinding of participants and personnel	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	**HIGH** No details reported but blinding highly unlikely due to nature of study. Unclear whether there was any protocol in place to reduce the risk of differential behaviours by patients and healthcare provider
Blinding of outcome assessors	Detection bias due to knowledge of the allocated interventions by outcome assessment	**UNCLEAR** No information provided
Incomplete outcome data	Attrition bias due to amount, nature, or handling of incomplete outcome data	**LOW** Not explicitly reported but number of people in analysis is equal to number of people randomised
Selective outcome reporting	Reporting bias due to selective outcome reporting.	**UNCLEAR** Insufficient information to permit judgement
Other sources of bias	Not applicable	Not applicable

Summary of risk-of-bias assessments of included non-randomised observational studies using The Joanna Briggs Institute Critical Appraisal Checklists

The tables below show reviewer responses to the JBI checklist questions for critical appraisal of included cohort studies (see *Table 60*) and included case series (see *Table 61*) The reasons for the responses are documented in a spreadsheet available from the review authors on request.

TABLE 60 Summary of risk-of-bias assessments for included observational cohort studies

	Study										
JBI Checklist for cohort studies[50]	**Abdollah *et al.* 2011[39]**	**Bojin 2019[29]**	**Chen *et al.* 2021[30]**	**Emiliozzi *et al.* 2003[32]**	**Hung *et al.* 2020[33]**	**Jiang *et al.* 2019[40]**	**Kum *et al.* 2018[34]**	**Rij *et al.* 2020[45]**	**Starmer *et al.* 2021[36]**	**Takuma *et al.* 2012[43]**	**Watanabe *et al.* 2005[38]**
1. Were the two groups similar and recruited from the same population?	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes, and No	Yes	Yes
2. Was each biopsy method clearly defined and described to enable reviewers to assess whether or not the participants received the biopsies of interest?[a]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes
3. Were the biopsies carried out in a valid and reliable way? E.g. use of a protocol or schema for sampling of cores, other protocols, staff carrying out the procedure[a]	Yes	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Unclear	Unclear
4. Were confounding factors identified?	Yes	No	Yes	NA	Unclear	Yes	No	No	Yes	No	NA
5. Were strategies to deal with confounding factors stated?	Yes	No	Yes	NA	No	Yes	No	No	Yes	No	NA
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes
7. Were the outcomes measured in a valid and reliable way?	Unclear	Yes for CDR; Unclear for other outcomes	Yes	Yes	Unclear for CDR; Yes for other outcomes	Yes	Yes for CDR; Unclear for pain and complications	Yes for CDR; Unclear for complica-tions	Yes for tolerability and CDR; Unclear for complication	Unclear	Yes
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	NA	Unclear/ NA	Unclear	Yes	Unclear	NA	Unclear	Unclear	Yes	Unclear	Unclear

TABLE 60 Summary of risk of bias assessments for included observational cohort studies (*continued*)

	Study										
JBI Checklist for cohort studies[50]	**Abdollah *et al.* 2011[39]**	**Bojin 2019[29]**	**Chen *et al.* 2021[30]**	**Emiliozzi *et al.* 2003[32]**	**Hung *et al.* 2020[33]**	**Jiang *et al.* 2019[40]**	**Kum *et al.* 2018[34]**	**Rij *et al.* 2020[45]**	**Starmer *et al.* 2021[36]**	**Takuma *et al.* 2012[43]**	**Watanabe *et al.* 2005[38]**
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?	NA	Unclear	Unclear	Yes	Unclear	NA	Unclear	Unclear	Yes/Unclear	Unclear	Unclear
10. Were strategies to address incomplete follow-up utilised?	NA	Unclear	Unclear	Unclear	Unclear	NA	Unclear	Unclear	Unclear	Unclear	Unclear
11. Was appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes

CDR, cancer detection rate; NA not applicable;
a Question edited by EAG to accommodate biopsy methods as an exposure.

TABLE 61 Summary of risk-of-bias assessments for included observational case series studies

JBI Checklist for case series[51]	Study	
	Szabo *et al.* 2021[41]	Walters *et al.* 2021[44]
1. Were there clear criteria for inclusion in the case series?	No	No
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes	Unclear
3. Were valid methods used for identification of the condition for all participants included in the case series?	Unclear	Unclear
4. Did the case series have consecutive inclusion of participants?	Yes	Yes
5. Did the case series have complete inclusion of participants?	Yes	Yes
6. Was there clear reporting of the demographics of the participants in the study?	Unclear	No
7. Was there clear reporting of clinical information of the participants?	Unclear	No
8. Were the outcomes or follow-up results of cases clearly reported?	Yes	Unclear
9. Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	Unclear	Unclear
10. Was statistical analysis appropriate?	Yes	Unclear

Appendix 6 Systematic review of cost-effectiveness studies

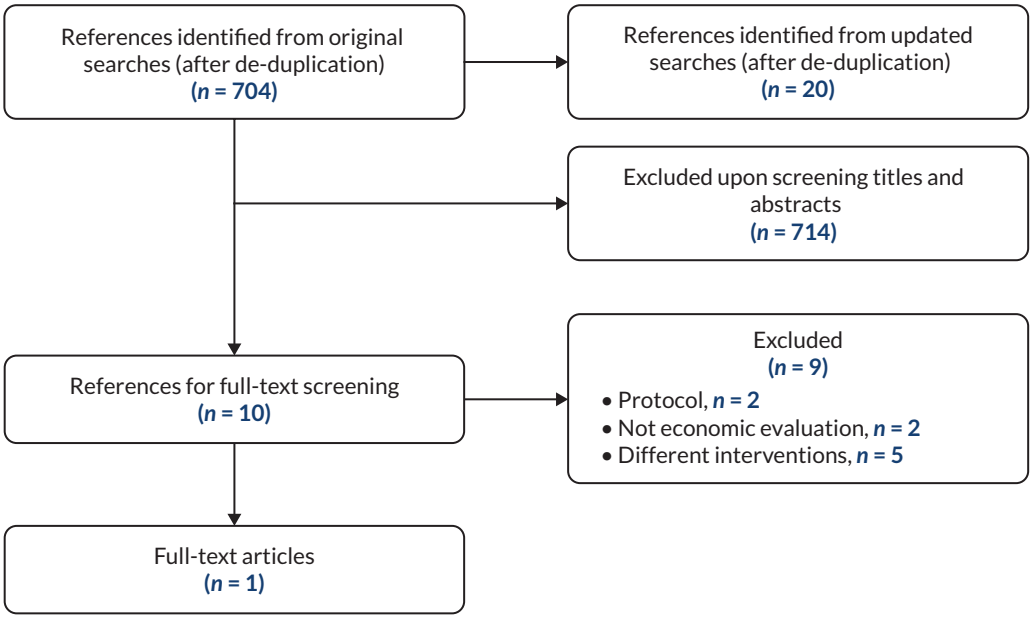

FIGURE 19 Flow chart for the identification of economic studies.

TABLE 62 Cost-effectiveness review: excluded references and reason for exclusion

Study	Reasons for exclusion
Actrn 2020[58]	Only protocol/No results posted
NCT 2020[202]	Only protocol/No results posted
Altok 2018[203]	Does not include the interventions of interest
Brown 2018[64]	Does not include the interventions of interest
Faria 2018[65]	Does not include the interventions of interest
Cheng 2021[204]	Does not include the interventions of interest
Cricco-Lizza 2021[205]	Does not include the interventions of interest
Jimenez 2021[113]	Not an economic evaluation
Popert 2020[206]	Not an economic evaluation

TABLE 63 Wilson *et al.* 2021: study characteristics

Study	Wilson *et al.*[63]	
Year	2021	
Country	UK	
Research question	What is the cost effectiveness of transperineal vs. TRUS-guided local anaesthesia procedures for prostate biopsy in the diagnosis of prostate cancer in a secondary care setting?	
Perspective of analysis	UK NHS	
Population	Men with suspected localised prostate cancer	
Interventions	TP biopsy (CamPROBE) vs. TRUS biopsy	
Type of model	Decision tree (diagnostic and short-term treatment pathway) Markov model (long-term consequences; composed by three health states: PF, metastatic and death)	
Time horizon	Lifetime	
Cycle length	1 year	
Discount rate	3.5%	
Diagnostic pathway	Based on NICE guideline and on strategy 'M7' of the Faria *et al.* decision model, men referred to secondary care are offered a mpMRI: • Men with a positive mpMRI (CS) are recommended a mpMRI-targeted biopsy, with an associated risk of complications (fever, urinary-tract infection, sepsis, sepsis death, or no infection) ◦ Men with a positive biopsy (CS) enter the treatment pathway ◦ Men with a negative biopsy (CNS or NC) have a repeat biopsy, with an associated risk of complications (as above) - Men with a second negative biopsy are discharged to routine follow-up and exit the model - Men with a second positive biopsy enter the treatment pathway • Men with a negative mpMRI (CNS or NC) are discharged to routine follow-up and exit the model	
Model inputs		
Prevalence of PC	No cancer: 27.9% Non-clinically significant cancer: 16.0% Intermediate-risk cancer: 52.9% High-risk cancer: 3.2%	Source: PROMIS
Diagnostic accuracy	mpMRI mpMRI (NC)|NC: 0.33 (0.26–0.4) mpMRI (CNS)|NC: 0.17 (0.11–0.23) mpMRI (CS)|NC: 0.50 (0.43–0.58) mpMRI (NC)|CNS: 0.28 (0.19–0.38) mpMRI (CNS)|CNS: 0.16 (0.08–0.24) mpMRI (CS)|CNS: 0.56 (0.46–0.67) mpMRI (NC)|IR: 0.08 (0.05–0.11) mpMRI (CNS)|IR: 0.05 (0.02–0.07) mpMRI (CS)|IR: 0.87 (0.83–0.91) mpMRI (NC)|HR: 0.00 mpMRI (CNS)|HR: 0.00 mpMRI (CS)|HR: 1.00	Source: PROMIS, as reported in Faria *et al.*,[65] definition 2, cutoff 3. Assumption, as per Faria *et al.* PROMIS, Schoots *et al.*, as reported in Faria *et al.*,[65] test 4, definition 2. Assumption, as per Faria *et al.*[65] PROMIS, Schoots *et al.*, as reported in Faria *et al.*,[65] test 5, definition 2. Assumption, as per Faria *et al.*[65] Assumption, as per NC findings above (see Faria *et al.*[65])

TABLE 63 Wilson et al. 2021: study characteristics (*continued*)

Study	Wilson *et al.*[63]	
	First mpMRI-targeted TRUS/TPUS biopsy (if mpMRI = CS) Biopsy1 (NC)|NC: 1.00 Biopsy1 (CNS)|NC: 0.00 Biopsy1 (CS)|NC: 0.00 Biopsy1 (NC)|CNS: 0.79 (0.66–0.89) Biopsy1 (CNS)|CNS: 0.21 (0.11–0.34) Biopsy1 (CS)|CNS: 0.00 Biopsy1 (NC)|IR: 0.15 (0.09–0.21) Biopsy1 (CNS)|IR: 0.11 (0.06–0.16) Biopsy1 (CS)|IR: 0.74 (0.65–0.84) Biopsy1 (NC)|HR: 0.00 Biopsy1 (CNS)|HR: 0.00 Biopsy1 (CS)|HR: 1.00 Second mpMRI-targeted TRUS/TPUS biopsy **If first biopsy = NC and mpMRI = CS** Biopsy2 (NC)|NC: 1.00 Biopsy2 (CNS)|NC: 0.00 Biopsy2 (CS)|NC: 0.00 Biopsy2 (NC)|CNS: 0.68 (0.02–1.00) Biopsy2 (CNS)|CNS: 0.32 (0.02–0.91) Biopsy2 (CS)|CNS: 0.00 Biopsy2 (NC)|IR: 0.05 (0.02–0.11) Biopsy2 (CNS)|IR: 0.08 (0.03–0.18) Biopsy2 (CS)|IR: 0.87 (0.71–0.95) Biopsy2 (NC)|HR: 0.05 (0.02–0.11) Biopsy2 (CNS)|HR: 0.08 (0.03–0.18) Biopsy2 (CS)|HR: 0.87 (0.71–0.95) **If first biopsy = CNS and mpMRI = CS** Biopsy2 (NC)|NC: 1.00 Biopsy2 (CNS)|NC: 0.00 Biopsy2 (CS)|NC: 0.00 Biopsy2 (NC)|CNS: 0.68 (0.02–1) Biopsy2 (CNS)|CNS: 0.32 (0.02–0.91) Biopsy2 (CS)|CNS: 0.00 Biopsy2 (NC)|IR: 0.05 (0.02–0.11) Biopsy2 (CNS)|IR: 0.08 (0.03–0.18) Biopsy2 (CS)|IR: 0.87 (0.71–0.95) Biopsy2 (NC)|HR: 0.05 (0.02–0.11) Biopsy2 (CNS)|HR: 0.08 (0.03–0.18) Biopsy2 (CS)|HR: 0.87 (0.71–0.95)	
Biopsy complications	TRUS biopsy No infection: 0.92 Mild infection: 0.04 (0.03–0.07) UTI: 0.033 (0.02–0.06) Sepsis: 0.00 (0.00–0.02) TP biopsy No infection: 1.00 Mild infection: 0.00 UTI: 0.00 Sepsis: 0.00 Mortality from sepsis: 0.04 (0.03–0.05)	Source: Zani *et al.*[66] Assumption Lee *et al.*[108]

continued

TABLE 63 Wilson et al. 2021: study characteristics (*continued*)

Study	Wilson *et al.*[63]	
Long-term transition probabilities	CNS cancer PF to metastatic: 0.01 (0.00–0.01) PF to dead: 0.05 (0.04–0.06) Metastatic to dead: 0.14 (0.06–0.23) Intermediate-risk cancer **Active surveillance** PF to metastatic: 0.02 (0.01–0.03) PF to dead: 0.06 (0.05–0.08) Metastatic to dead: 0.15 (0.07–0.22) **Radical prostatectomy** PF to metastatic: 0.01 (0.00–0.01) PF to dead: 0.05 (0.05–0.06) Metastatic to dead: 0.14 (0.06–0.23) High-risk cancer **Active surveillance** PF to metastatic: 0.02 (0.01–0.03) PF to dead: 0.08 (0.06–0.10) Metastatic to dead: 0.16 (0.09–0.23) **Radical prostatectomy** PF to metastatic: 0.01 (0.00–0.01) PF to dead: 0.07 (0.05–0.09) Metastatic to dead: 0.15 (0.07–0.23)	Source: Fit from figures reported in Faria *et al.*[65]
Treatment complications	Following radical prostatectomy Sexual dysfunction: 34.6% Urinary incontinence: 8.2% Bowel dysfunction: 5.9% Following active surveillance Sexual dysfunction: 20.1% Urinary incontinence: 3.1% Bowel dysfunction: 5.5%	Source: Will *et al.*, converted to 1-year probabilities as per Faria *et al.*[65]
Unit costs	Diagnosis mpMRI: £217 TRUS biopsy: £17 TP biopsy: £0 Complications Fever: £40 UTI: £46 Sepsis: £2206 Treatments Watchful waiting (per year): £123 Radical prostatectomy: £6667 Radical prostatectomy AEs (per year): £207 MD (per year): £1990 Components for compound costs Radical prostatectomy surgery: £6330 Surgical consultation pre surgery: £127 Surgical consultation follow-up: £105 Primary care PSA test: £6 Sexual dysfunction management: £217 Urinary incontinence management: £296 Bowel dysfunction management: £1810 GP visit: £39 Trimethoprim, 3 days: £0.40 Trimethoprim, 7 days: £0.93 Urinalysis: £6	Source: NHS Ref Costs 2018/19, Imaging: Outpatient, RD03Z Difference in cost between TP and TR. GP + 3-day trimethoprim GP + urinalysis + 7-day trimethoprim NHS Ref Costs 2018/19, Total HRGs, weighted average WJ06A to WJ06J 1 × follow-up visit + 3 × PSA test Surgery + 1 × first visit + 2 × follow-up visits Weighted average of 1-year probabilities As calculated by Faria *et al.*[65] NHS Ref Costs 2018/19, EL, weighted average LB21A, LB21B, LB22Z NHS Ref Costs 2018/19, CL, WF01B, 101, urology. NHS Ref Costs 2018/19, CL, WF01A, 101, urology. NHS Ref Costs 2018/19, DAPS, DAPS09. NHS Ref Costs 2018/19, Total HRGs, LB43Z. Inflated to 2018/19 from Faria *et al.*[65] Inflated to 2018/19 from Faria *et al.*[65] PSSRU 2019, p. 120 Drug Tariff, March 2019, trimethoprim 200 mg × 6 Drug Tariff, March 2019, trimethoprim 200 mg × 14 Assumption (same as PSA test)

TABLE 63 Wilson et al. 2021: study characteristics (*continued*)

Study	**Wilson *et al.*[63]**	
Utilities	QALY loss Fever: 0.001 UTI: 0.006 Sepsis: 0.040 Utility of progression free: age-dependent Disutility of MD: 0.137	Source: Assumption Barry *et al.*[109] Faria *et al.*[65] Faria *et al.*[65]
Key assumptions	1. No further monitoring was assumed for men with no cancer. 2. Active surveillance was assumed for men with CNS cancer (comprising one urology follow-up appointment and 3 PSA tests per year). 3. Active surveillance was the treatment strategy assumed for patients misdiagnosed as CNS or no cancer. 4. Radical prostatectomy was the treatment strategy assumed for patients with correctly diagnosed IR or HR disease. 5. Perfect specificity of TRUS biopsy was assumed. 6. No difference on average in diagnostic accuracy between TP and TRUS biopsies was assumed. 7. Zero risk of infection associated with TP biopsy (explored in sensitivity analyses) was assumed. 8. Equal procedure time between TP and TRUS biopsies and zero price for TP device (explored in sensitivity analyses) was assumed.	
Results		
Base-case results	TRUS biopsy Cost: £5052, QALYs: 10.291 TP biopsy Cost: £5022, QALYs: 10.292 Increment Cost: −£30, QALYs: 0.002, ICER: TPUS biopsy dominates TRUS biopsy	
Sensitivity-analysis results	1. One-way sensitivity analysis on the price of TP biopsy device, identifying the price associated with an ICER of £20,000. Increment results: Cost: £29, QALYs: 0.002, ICER: £19,999 2. One-way sensitivity analysis on risk of infection with TPUS biopsy, varying the risk between 0.0% and 100.0% of that of TRUS biopsy (base-case assumes zero risk of infection). Results: not reported 3. Two-way sensitivity analysis showing the maximum cost-effective per-procedure price of the TPUS biopsy device as a function of the infection risk. Results: maximum per-procedure cost-effective price of £15.	
Conflicts of interest	Vincent J. Gnanapragasam is the inventor and patent holder of the CamPROBE device. All other authors confirm they have no conflicts of interest to declare.	
Funding	NIHR i4i Product Development Award (II-LB-0716-20001).	

AE, adverse event; CS, clinically significant cancer; HR, high risk; HRG, Healthcare Resource Group; IR, intermediate risk; PC, prostate cancer; PF, progression free; UTI, urinary-tract infection.

TABLE 64 Wilson *et al.* 2021: relevance and credibility checklist

Item		Wilson *et al.* 2021[63]	Comments
RELEVANCE			
1	Is the population relevant? E.g. *demographics, risk factors, medical condition …*	Yes	
2	Are any critical interventions missing?	No	
3	Are any relevant outcomes missing?	No	
4	Is the context (settings and circumstances) applicable? E.g. *geographic location, health care system, time horizon, perspective of analysis, discount rate …*	Yes	
CREDIBILITY			
Design			
1	Is the modelling methodology appropriate? Is the model structure described and does it reflect the disease process? Are its assumptions listed and justified?	Yes	
Data inputs			
2	Are the data inputs for the model described and justified?	Yes	
Uncertainty			
3	Has uncertainty been assessed?	Yes	
Validation			
4	Has the model been validated?	Yes	

Note
Each question is answered with *Yes*, *No* or *Can't Answer*. *Can't Answer* is subdivided into four other answers: *not applicable*, *not reported*, *not enough information* or *not enough training*.

TABLE 65 Characteristics of economic studies of interest

Study	Decision problem	Model			Parameters of interest		
		type	Time horizon	Cycle length	Epidemiology, clinical, diagnostic	Utilities	Resource use/costs
Brown, 2018 (UK)[64]	Cost-effectiveness of diagnostic strategies using mpMRI, TRUS-guided biopsy and TPM biopsy (under general/spinal anaesthesia) in men with suspected localised prostate cancer	Decision tree + Markov model	–	–	Tables 26, 35	Tables 28, 35	Tables 29, 35
Faria, 2018 (UK)[65]	Cost-effectiveness of diagnostic strategies using mpMRI, TRUS-guided biopsy and TPM biopsy (under general/spinal anaesthesia) in men with suspected localised prostate cancer	Decision tree + Markov model	Lifetime	–	Tables 2, S9 and S11	Table S10	Tables S11, S12
Mowatt, 2013 (UK)[99]	Cost-effectiveness of using alternative MRS/MRI sequences to direct TRUS-guided biopsies compared to systematic TRUS-guided biopsy alone in patients with suspected prostate cancer and a prior negative/inconclusive biopsy	Decision tree + Markov model	30 years	3 months	Tables 16, 17, 18, 19	Table 25	Tables 18, 22, 23, 24
Nicholson, 2015 (UK)[207]	Cost-effectiveness of PCA3 assay or phi, in combination with existing tests, scans and clinical judgement, in the diagnosis of prostate cancer in men suspected of having malignant disease in whom the results of an initial prostate biopsy were negative or equivocal	Decision tree	3 years	–	Table 32	Page 81–82	Tables 32, 34, 35
Cerantola, 2016 (Canada)[208]	Cost-effectiveness of MRI-cognitive targeted biopsy compared to TRUS-guided biopsy in diagnosing patients with suspected prostate cancer	Markov model	5, 10, 15 and 20 years	1 year	Table 1	Section 2.4	Tables 1, 2
de Rooij, 2014 (The Netherlands)[209]	Cost-effectiveness of mpMRI followed by MRI-guided biopsy compared to TRUS-guided biopsy in diagnosing prostate cancer in patients with an elevated PSA	Decision tree + Markov model	10 years	1 year	Table 1	Table 3	Tables 1, 2
Dijkstra, 2017 (The Netherlands)[210]	Cost-effectiveness of SelectMDx to identify patients for TRUS-guided biopsy compared to the use of PSA only to select for TRUS-guided biopsy in patients with an elevated PSA	Decision tree + Markov model	18 years	1 year	Table 1	Table 2	Tables 1, 3

continued

TABLE 65 Characteristics of economic studies of interest (*continued*)

Study	Decision problem	Model			Parameters of interest		
		type	Time horizon	Cycle length	Epidemiology, clinical, diagnostic	Utilities	Resource use/costs
Hao, 2021 (Sweden)[211]	Cost-effectiveness of MRI with combinations of targeted biopsy and systematic biopsy (at outpatient care) for early detection of prostate cancer within the context of organised quadrennial PSA screening among men aged 55–69 years	Microsimulation model	Lifetime	–	Table 1	Table 1, S4	Table S2
Pahwa, 2017 (USA)[130]	Cost-effectiveness of mpMRI followed by MRI-guided biopsy compared to TRUS-guided biopsy to detect prostate cancer in biopsy-naïve men presenting with clinical suspicion of cancer	Decision tree	Lifetime	–	Table 1	Table E2	Table 2, E1
Patel, 2018 (The Netherlands)[212]	Cost-effectiveness of three active surveillance strategies (TRUS-guided biopsy, mpMRI followed by MRI-guided biopsy, mpMRI alone) for patients with LR prostate cancer	Markov model	Lifetime	1 year	Table 1	Table 2	Table 2
Sathianathen, 2018 (USA)[213]	Cost-effectiveness of four biomarker tests (PHI, 4Kscore, SelectMDx and the EPI) to determine which individuals require biopsy compared to TRUS-guided biopsy alone in men with elevated PSA	Decision tree + Markov model	Lifetime	–	Supplementary table, appendix 2	Supplementary table	Supplementary table
Venderink, 2017 (The Netherlands)[214]	Cost-effectiveness of three prostate biopsy approaches (TRUS-guided biopsy, direct in-bore MRI-guided biopsy and image fusion guided biopsy) for biopsy-naïve patients in whom CS prostate cancer was suspected	Decision tree + Markov model	18 years	1 year	Tables 1, 3	Table 3	Tables 1, 2
NG131 model, 2019 (UK)[67]	Cost-effectiveness of different follow-up strategies (including screening test, based on PSA and its derivatives at given intervals, and diagnostic procedures) for people who have a raised PSA, negative MRI and/or negative biopsy	Decision tree + Markov model	Lifetime	3 months	Tables HE02, HE05, HE07, HE09, HE11	Table HE14	Tables HE08, HE12, HE13

EPI, ExoDx™ Prostate [Intelli-Score]; PCA3, prostate cancer antigen 3; PHI, Prostate Health Index; MRS, magnetic resonance spectroscopy.

Appendix 7 Systematic review of health-related quality of life

Inclusion/exclusion criteria for health-related quality of life review

TABLE 66 Inclusion/exclusion criteria for the review of HRQoL studies

Inclusion criteria	***Searches 'HRQoL 1'***	***Searches 'HRQoL 2'***
Research type	Primary research studies	Primary research studies
Population	People undergoing screening/diagnostic tests for prostate cancer People diagnosed with prostate cancer	People undergoing screening/diagnostic tests for prostate cancer People diagnosed with prostate cancer
Outcomes	SF-36, SF-12, SF-6D, EQ-5D, HUI-1, -2 and -3 and 15D	EQ-5D
Value set	–	UK
Exclusion criteria	***Searches 'HRQoL 1'***	***Searches 'HRQoL 2'***
Reference type	Conference abstracts, letters, protocols, case reports	Conference abstracts, letters, protocols, case reports
Language	Studies not in English language	Studies not in English
Others	–	Studies assessing the quality of life of specific treatments

HUI, health utilities index, SF-6D, short form questionnaire-6 items; SF-12, short form questionnaire-12 items; SF-36, short form questionnaire-36 items.

Results of the systematic searches 'HRQoL 1'

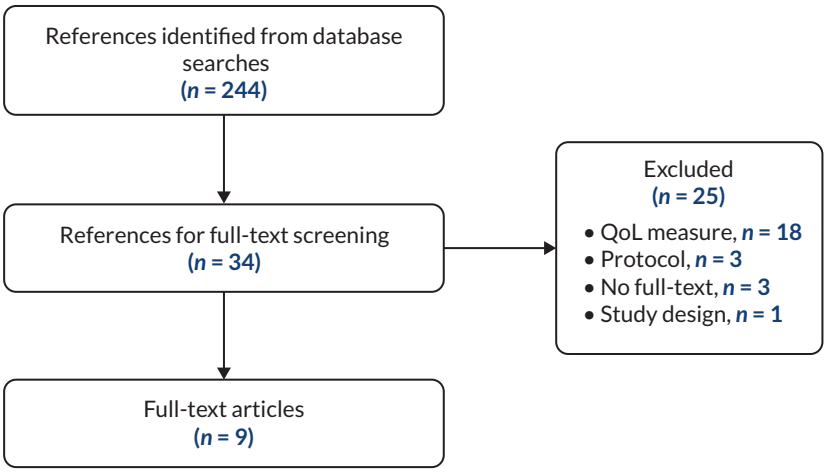

FIGURE 20 Flow chart for the identification of HRQoL studies (searches 'HRQoL 1').

TABLE 67 Health-related quality of life review: excluded references (searches 'HRQoL 1')

Study	Reasons for exclusion
Ahmed *et al.* 2011[215]	Different HRQoL outcome
Aktas *et al.* 2014[216]	Different HRQoL outcome
Awsare *et al.* 2008[217]	Different HRQoL outcome
Azzouzi *et al.* 2013[218]	Different HRQoL outcome
Burns *et al.* 2019[219]	Can't find full text
Cantor *et al.* 1995[220]	Can't find full text
Chaussy and Thüroff 2001[221]	HRQoL outcome not specified
Dickinson *et al.* 2013[222]	Protocol
Donovan *et al.* 2003[223]	Can't find full text
Egan *et al.* 2021[224]	Different HRQoL outcome
Ganzer *et al.* 2018[225]	Different HRQoL outcome
Ghai *et al.* 2015[226]	Can't find SF-12 results
Gu *et al.* 2015[227]	HRQoL outcome not specified
Koch *et al.* 2007[228]	Can't find results
Kok *et al.* 2006[229]	Different HRQoL outcome
Mettlin *et al.* 1997[230]	No HRQoL outcomes
Miki *et al.* 2010[231]	Different HRQoL outcome
Natarajan *et al.* 2016[232]	Different HRQoL outcome
Naughton *et al.* 2001[233]	Different HRQoL outcome
Pane-Alemany *et al.* 2021[234]	Protocol
Pisters *et al.* 1997[235]	Different HRQoL outcome
Soloway *et al.* 2010[236]	Different HRQoL outcome
Uchida *et al.* 2005[237]	Different HRQoL outcome
Valerio *et al.* 2014[238]	Protocol
Van de Ven *et al.* 2013[239]	Different study design

SF-12, short form questionnaire-12 items.

TABLE 68 Characteristics of included HRQoL studies (searches 'HRQoL 1')

First author, year	N[a]	Country	Instrument	Health state(s) described
Blazevski *et al.* 2020[69]	84	Australia	SF-12	At baseline, 6 weeks, 3, 6, 12 and 24 months after treating patients with localised prostate cancer with irreversible electroporation
Essink-Bot, 1998[70]	1126	Netherlands	SF-36, EQ-5D	3 weeks before the screening for prostate cancer, waiting room preceding the screening, 1 week after receiving the unsuspicious results of the initial screening tests, during the 2-week waiting period for the biopsy result, and 1 week after receiving the negative results of the biopsy
Hamdy, 2020[71]	1413	UK	SF-12, EQ-5D	At the recruitment phase to test for prostate cancer, at the moment of confirmatory biopsy, 6 and 12 months following randomisation to treatment strategy and yearly thereafter for at least 10 years

TABLE 68 Characteristics of included HRQoL studies (searches 'HRQoL 1') (*continued*)

First author, year	N[a]	Country	Instrument	Health state(s) described
Hamid, 2019[72]	110	UK	EQ-5D-5L	Before repeat biopsy, at 1 and 6 weeks after repeat biopsy
Kasivisvanathan, 2018[73]	483	Several[b]	EQ-5D-5L	At baseline, 24 hours and 30 days after the interventions (MRI-targeted biopsy or TRUS biopsy)
Peters, 2014[74]	14	Netherlands	SF-36	At baseline, 1 and 6 months and then annually after focal salvage treatment for prostate cancer
Sefik, 2020[75]	114	Turkey	SF-36	Before and 1 month after TRUS biopsy
Shankar, 2019[76]	110	USA	SF-12	1 to 3 days after the diagnostic test (mpMRI or TRUS biopsy) as part of active surveillance
Vasarainen, 2013[77]	386	Finland	SF-36	At invitation to participate in the trial, after PSA blood sample collection, after DRE (unaware of its result but aware of PSA result), after TRUS biopsy (unaware of its results but aware of PSA result)

SF-12, short form questionnaire-12 items; SF-36, short form questionnaire-36 items.
a Corresponds to the total number of participants who completed the HRQoL questionnaires.
b Argentina, Belgium, Canada, Finland, France, Germany, Italy, Switzerland, the Netherlands, UK, USA.

TABLE 69 Included HRQoL studies: summary of utility values (searches 'HRQoL 1')

Health states	Utility[a]	Source
Pre-screening		
3 weeks before	0.86785	Essink-Bot *et al.* 1998[70]
Before screening	0.9387	Vasarainen *et al.* 2013[77]
Screening		
Right after collecting blood for PSA analysis	0.936	Vasarainen *et al.* 2013[77]
PSA result known (positive or negative)	0.920	Vasarainen *et al.* 2013[77]
Right after DRE (result unknown)	0.906	Vasarainen *et al.* 2013[77]
Screening negative result	0.88215	Essink-Bot *et al.* 1998[70]
Screening positive result	0.908	Kasivisvanathan *et al.* 2018[73]
	0.692	Sefik *et al.* 2020[75]
Diagnostic		
24 hours after MRI-targeted biopsy	0.907	Kasivisvanathan *et al.* 2018[73]
30 days after MRI-targeted biopsy	0.917	Kasivisvanathan *et al.* 2018[73]
After TRUS biopsy (result unknown)	0.936	Vasarainen *et al.* 2013[77]
24 hours after TRUS biopsy	0.894	Kasivisvanathan *et al.* 2018[73]
30 days after TRUS biopsy	0.921	Kasivisvanathan *et al.* 2018[73]
	0.790	Sefik *et al.* 2020[75]
30 days after TRUS biopsy (with tamsulosine)	0.791	Sefik *et al.* 2020[75]
Repeat biopsy	0.879	Hamid *et al.* 2019[72]

continued

TABLE 69 Included HRQoL studies: summary of utility values (searches 'HRQoL 1') (*continued*)

Health states	Utility[a]	Source
Biopsy negative result	1.14889	Essink-Bot *et al.* 1998[70]
Biopsy positive result	0.883	Hamdy *et al.* 2020[71]
Treatment		
Active surveillance		
Before procedure (mpMRI or TRUS biopsy)	0.961	Shankar *et al.* 2019[76]
Before mpMRI	0.965	Shankar *et al.* 2019[76]
Before TRUS biopsy	0.956	Shankar *et al.* 2019[76]
Irreversible electroporation		
Before treatment	0.979	Blazevski *et al.* 2020[69]
Between 6 weeks and 24 months after	0.979	Blazevski *et al.* 2020[69]
Focal salvage treatment		
Before treatment	1.015	Peters *et al.* 2014[74]
1 month	0.967	Peters *et al.* 2014[74]
6 months	0.937	Peters *et al.* 2014[74]
3 years	0.977	Peters *et al.* 2014[74]

SF-12, short form questionnaire-12 items; SF-36, short form questionnaire-36 items.
a SF-12 and SF-36 scores mapped to EQ-5D, using the equations from Sullivan *et al.*[240] and Ara and Brazier,[241] respectively.

Results of the systematic searches 'HRQoL 2'

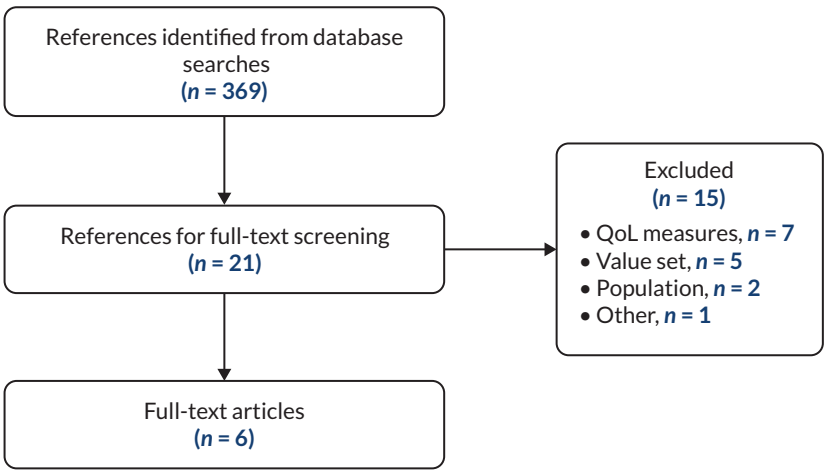

FIGURE 21 Flow chart for the identification of HRQoL studies (searches 'HRQoL 2'). QoL, quality of life.

TABLE 70 Health-related quality of life review: excluded references and reason for exclusion (searches 'HRQoL 2')

Study	Reasons for exclusion
Donnelly *et al.* 2018[242]	No prostate cancer
Downing *et al.* 2019[243]	No relevant results
Glaser *et al.* 2013[244]	No relevant results
Kuppen *et al.* 2020[245]	Non-UK value set
Lemanska *et al.* 2021[246]	Different population
Lloyd *et al.* 2015[247]	Assess specific interventions
Loeb *et al.* 2018[248]	Non-UK value set
Lopez-Calderero *et al.* 2017[249]	Unclear value set
Maguire *et al.* 2019[250]	No relevant results
Murasawa *et al.* 2019[251]	Non-UK value set
Smith *et al.* 2020[252]	No relevant results
Uemura *et al.* 2020[253]	Unclear value set
Venderbos *et al.* 2020[254]	No relevant results
Wilding *et al.* 2020[255]	No relevant results
Yao *et al.* 2020[256]	No relevant results

TABLE 71 Study characteristics for included HRQoL studies ('HRQoL 2')

Study	*Drummond et al.*[79]
Year	2015
Country	Republic of Ireland and Northern Ireland
Type of study	Cross-sectional study
Study objective	To perform an international population-based PROMs study form among short-term (<5 years), long-term (5–9.9 years) and very long-term (≥10 years postdiagnosis) prostate cancer survivors
Population	Men registered with invasive prostate cancer diagnosed between 1 January 1995 and 31 March 2010, and alive in November 2011
Sample size	3348 responders (1010 from Northern Ireland)
HRQoL instrument	EORTC QLQ-C30 and QLQ-PR25, EQ-5D-5L (UK value set)
Mapping	Mean utility scores were calculated using a crosswalk algorithm to convert EQ-5D-5L to the three-level version (Herdman *et al. Qual Life Res* 2011;20:1727–36)
Health states	Invasive prostate cancer (alive at least 20 months after diagnosis)
Results	Utility: 0.82
Conclusions/Limitations	Overall HRQoL of prostate cancer survivors in Ireland, measured by EQ-5D-5L, was similar to that of short-term prostate cancer survivors in the UK Limitations: no baseline (prediagnosis) HRQoL data
Study	*Booth et al.*[78]
Year	2014
Country	Finland

continued

TABLE 71 Study characteristics for included HRQoL studies ('HRQoL 2') (*continued*)

Type of study	Surveys conducted among men in the Finnish trial of screening for prostate cancer		
Study objective	To quantify the long-term HRQoL impact associated with screening for prostate cancer		
Population	Men born in from 1929 to 1944 who resided in the Helsinki or Tampere region during recruitment period (1996–9) without a diagnosis of prostate cancer before date of randomisation. Two groups of men from the trial received the questionnaires concerning HRQoL: - Men diagnosed with prostate cancer (both from the screening and control arms of the trial) - Men randomly sampled from the trial in 1998 (trial subsample) – all free of prostate cancer at baseline but some, in both the screening and control arm, were subsequently diagnosed with the disease		
Sample size	5516		
HRQoL instrument	15D, EQ-5D (UK value set) and SF-6D.		
Health states	Surveys completed by men diagnosed with prostate cancer, organ-confined prostate cancer and advanced prostate cancer and men from the trial subsample (without prostate cancer) in four different time points (1998, 1999, 2003 and 2011)		
Results	Utilities	EQ-5D results from 2011	
		Screening arm	Control arm
	Men free of PC from trial subsample	0.830	0.857
	Men with PC (vs. no PC)	+0.005	−0.031
	Men with organ-confined PC (vs. no PC)	+0.01	−0.031
	Men with advanced PC (vs. no PC)	−0.039	−0.051
Conclusions/limitations	Small advantage in mean HRQoL scores for the screening arm over the control arm for men diagnosed with prostate cancer in the 13-year follow-up. Lower HRQoL associated with more advanced age and lower socioeconomic status		
Study	***Farkkila et al.***[80]		
Year	2014		
Country	Finland		
Type of study	Cross-sectional study		
Study objective	To explore end-stage breast, prostate and colorectal cancer patients' HRQoL. To compare results obtained by different HRQoL instruments and to explore factors related to impaired HRQoL		
Population	Patients with metastatic breast, prostate and colorectal cancer and receiving palliative treatments only (no chemotherapy or radiotherapy) and patients who died due to cancer within 6 months of responding to the questionnaire (irrespective of treatment given)		
Sample size	114 (30 with prostate cancer)		
HRQoL instrument	15D, EQ-5D-3L (UK value set), EORTC QLQ-C30		
Health states	End-stage prostate cancer		
Results	EQ-5D utility for prostate cancer patients: 0.551 (0.405–0.664)		
Conclusions/limitations	With patients closer to death, HRQoL scores were lower and symptom burden increased. Symptoms, especially fatigue, leading to the impairment of both activities of daily living and psychological functioning seemed to be the most significant deteriorating factors		

TABLE 71 Study characteristics for included HRQoL studies ('HRQoL 2') (*continued*)

Study	***Gavin et al.*[81]**					
Year	2016					
Country	Republic of Ireland and Northern Ireland					
Type of study	Cross-sectional study					
Study objective	To investigate effects on men's health and well-being of higher prostate cancer investigation and treatment levels in similar populations					
Population	Prostate cancer survivors in Ireland, where Republic of Ireland has a 50% higher prostate cancer incidence than Northern Ireland					
Sample size	3348 responders (781 from Northern Ireland)					
HRQoL instrument	EORTC QLQ-C30, EQ-5D-5L (UK value set)					
Mapping	EQ-5D-5L were converted to EQ-5D-3L					
Health states	Early (stage I/II and Gleason grade 2–7) and late disease prostate cancer (stage III/IV and any Gleason grade at diagnosis) – 2–18 years post treatment					
Results	Utilities	Early disease	Late disease			
	Northern Ireland	*N* = 269 0.8	*N* = 282 0.7			
	Republic of Ireland	*N* = 1431 0.9	*N* = 407 0.8			
Conclusions/limitations	Patient-reported outcomes are very similar between Republic of Ireland and Northern Ireland despite different levels of PSA testing and diagnosed prostate cancer					
Study	***Torvinen et al.*[82]**					
Year	2013					
Country	Finland					
Type of study	Cross-sectional study					
Study objective	To assess HRQoL scores in different health states of prostate cancer, compare the results obtained by different HRQoL instruments, compare the HRQoL of prostate cancer patients with that of the Finnish general population, and explore the factors associated with the resultant HRQoL scores					
Population	Patients over 18 years of age diagnosed with prostate cancer					
Sample size	621					
HRQoL instrument	15D, EQ-5D-3L (UK value set), EORTC QLQ-C30					
Health states	1. < 6 months after diagnosis (Loc1) 2. Following 12 months (Loc2) 3. Subsequent years of remission (Loc3) 4. MD (Metastatic) 5. Palliative care (Palliative)					
Results	**EQ-5D**	***N***	**Mean**	**SD**	**95% CI**	**Δ vs. general population**
	Loc1	46	0.90	0.19	0.84 to 0.96	+0.103
	Loc2	91	0.89	0.14	0.86 to 0.92	+0.089
	Loc3	309	0.87	0.19	0.85 to 0.89	+0.043
	Metastatic	85	0.74	0.27	0.69 to 0.80	−0.054
	Palliative	17	0.59	0.22	0.48 to 0.70	−0.157
	All patients	621	0.85	0.03	0.83 to 0.86	-

continued

TABLE 71 Study characteristics for included HRQoL studies ('HRQoL 2') (*continued*)

Study	*Watson et al.*[83]			
Year	2016			
Country	UK			
Type of study	Cross-sectional study			
Study objective	To explore ongoing symptoms, unmet needs, psychological well-being, self-efficacy and overall health status in prostate cancer survivors			
Population	Men diagnosed 9–24 months previously, regardless of treatment modality, whose condition was considered stable as judged by the most recent PSA test result			
Sample size	316			
HRQoL instrument	EPIC-26, EQ-5D-5L			
Mapping	Conversion to EQ-5D-3L using a crosswalk algorithm (van Hout *et al. Value Healt*h 2012;15:708–715)			
Health states	Adverse events after treatment for prostate cancer: 1. Urine function (no/mild problems; moderate/big problems) 2. Bowel function (no/mild problems; moderate/big problems) 3. Sexual function (no/mild problems; moderate/big problems)			
Results	**Utilities**	**No/mild problems**	**Moderate/big problems**	***p*-value**
	Urine function	0.868 (0.160)	0.773 (0.222)	0.001
	Bowel function	0.862 (0.166)	0.653 (0.195)	0.000
	Sexual function	0.861 (0.176)	0.838 (0.170)	0.261
Conclusions/limitations	Treatment ongoing symptoms have an impact on the quality of life of patients Limitations: volunteer bias cannot be excluded, those with the greatest need may be less or more likely to participate in such a study (although no significant differences were found between respondents and non-respondents); two areas included may not be representative of the wider UK population; cross-sectional design HRQoL of prostate cancer patients appears to be surprisingly good prior to metastatic progression of the disease. Both generic instruments produced higher scores in the Loc1 and Loc2 groups – and the EQ-5D also in the Loc3 group – than those found among the general population standardised for gender and age. A significant proportion of patients entering prostate cancer treatment because of elevated PSA levels found in opportunistic testing can explain this finding. As PSA testing has not been recommended at the national level, such opportunistic testing in Finland is currently limited mainly to occupational health services Limitation: cross-sectional design (different patients in groups representing different states); response rate of 61.5% (it is possible that non-respondents may have had more severe disease, although there's no reason to expect significant differences regarding disease severity between respondents and non-respondents based on previous experiences with similar surveys)			

SF-6D, short form questionnaire-6 items.

Appendix 8 Resource use and cost estimates

Details of micro-costing of biopsy procedures

The component costs included in the base case are explained in further detail below.

Cost of devices

- LATP biopsies
    - CamPROBE: cost of £35 (provided by JEB), with each biopsy requiring two devices – resulting in a cost per biopsy of £70.
    - PrecisionPoint: cost of £200 (provided by BXTAccelyon), with each biopsy requiring one device – resulting in a cost per biopsy of £200.
    - EZU-PA3U: cost of £1826 for orders with quantity > 5 and £2000 for orders with quantity < 5 (provided by Hitachi). We assumed that half of EZU-PA3U orders is for a quantity > 5. Each device is reusable, and we assumed that it can be reprocessed 100 times (as for Trinity Perine, see below) – resulting in a cost per biopsy of £19.
    - UA1232: cost of £1400 (provided by BK Medical). Each device is reusable, and we assumed that it can be reprocessed 100 times (as for Trinity Perine, see below) – resulting in a cost per biopsy of £14.
    - Trinity Perine: cost of £754 for a Perine Mini Grid (provided by KOELIS). Each device is reusable and can be reprocessed 100 times, as advised by the company – resulting in a cost per biopsy of £8.
    - SureFire Guide: cost of £120 (provided by Delta Surgical), with each biopsy requiring one device – resulting in a cost per biopsy of £120.
    - Grid and stepping device:
        - Grid: cost of £78 per biopsy (obtained from YHEC study).
        - Stepper: cost of £22,000 (obtained from YHEC study) apportioned by the number of procedures carried out per stepper per year (18 procedures per week, of which 15 are biopsies) for a lifetime of 10 years (informed by our clinical expert) – resulting in a cost per biopsy of £2.
    - Double freehand device: not applicable.
- GATP biopsy: we assumed the same cost of the grid and stepping device as for the LATP biopsy – resulting in a cost per biopsy of £78 for grid and £2 for stepper.
- LATRUS biopsy: not applicable.

Cost of consumables

General consumables

- See below for the cost and quantity of each consumable per type of biopsy.
- LATP biopsies
    - LATP biopsies using freehand devices (except EZU-PA3U) and using grid and stepping device: we summed up the costs of the consumables that are common to all biopsies (£62) with the costs for the consumables that are used for TP biopsies (£3), for biopsies carried out under local anaesthesia (£18) – resulting in a cost per biopsy of £83.
    - LATP biopsies using double freehand devices and EZU-PA3U: we assumed the same costs as above (£83) plus the cost of the co-axial needle (£21) – resulting in a cost per biopsy of £104.

- GATP biopsy: we summed up the costs of the consumables that are common to all biopsies (£62) with the costs for the consumables that are used for TP biopsies (£3) and the cost of general anaesthesia (£100) – resulting in a cost per biopsy of £165.
- LATRUS biopsy: we summed up the costs of the consumables that are common to all biopsies (£62) with the costs for the consumables that are used for TRUS biopsies (£2) and for biopsies carried out under local anaesthesia (£18) – resulting in a cost per biopsy of £81.

Lithotomy bed

- The cost of a lithotomy bed was applied in the EAG revised base case after an expert has commented that it would be required for all types of TP but not for LATRUS. This expert informed us that the estimated cost of a lithotomy bed was £10,000 and we have apportioned this cost over an estimated lifetime of 10 years and an assumed 1000 biopsies per year – resulting in a cost per biopsy of £3.

Ultrasound

- Hitachi, BK Medical and KOELIS provided the cost of the ultrasound machine required to perform a biopsy using EZU-PA3U, UA1232 and Trinity Perine, respectively. For the remaining devices and methods, we assumed that the cost of the ultrasound machine and transducer is the average cost of the ultrasound machine costs of EZU-PA3U, UA1232 and Trinity Perine. We assumed the same lifetime (10 years) as for stepper and an estimated number of biopsies per year of 1000.
- EZU-PA3U: cost of £38,000 for a FUJIFILM transperineal transducer and FUJIFILM ultrasound system – resulting in a cost per biopsy of £3.
- UA1232: cost of £40,050 for a BK ultrasound system, urology software with 9048 transducer – resulting in a cost per biopsy of £3.
- Trinity Perine: cost of £68,509 for a Trinity 3D Prostate Suite (£45,000) plus Koelis Sidefire ultrasound probe (£23,509) – resulting in a cost per biopsy of £5.
- Remaining devices and methods: cost of £48,853 as the average of the abovementioned machines – resulting in a cost per biopsy of £3.

Cost of staff time spent on training

- We considered that five urologists have a given amount of training each year regardless of the biopsy method. The cost per working hour of a urologist (£119) was based on the cost per working hour of a consultant (medical) hospital-based doctor reported by Curtis and Burns.[89] We assumed that 1000 biopsies are carried out per year on average (as advised by our experts). The amount of time spent on training was provided by some companies, as follows:
- LATP biopsies:
    - CamPROBE: half day (4 hours) spent on training per person – resulting in a cost per biopsy of £2.
    - PrecisionPoint: 1 day (8 hours) spent on training per person – resulting in a cost per biopsy of £5.
    - EZU-PA3U: 1 hour spent on training per person – resulting in a cost per biopsy of £0.60.
    - UA1232: 2 hours spent on training per person – resulting in a cost per biopsy of £1.
    - Trinity Perine: 1 hour spent on training per person – resulting in a cost per biopsy of £0.60.
    - For the remaining LATP biopsies (SureFire Guide, LATP using grid and stepping device and LATP using double freehand devices), as no data are available, we assumed that a whole day (8 hours) of training would be required per person – resulting in a cost per biopsy of £5.
- GATP biopsy: again, as no data are available, we assumed that a whole day (8 hours) of training would be required per person – resulting in a cost per biopsy of £5.

- LATRUS biopsy: we assumed that this would only require 1 hour of training per person since we believe this is a well-known and also easy to use method – resulting in a cost per biopsy of £0.60.

Cost of staff time spent on performing the biopsy

- We assumed that all biopsies are carried out by one urologist and that there are two nurses in the room for assistance. For GATP biopsies, we considered the cost of one anaesthetist as well. The cost per working hour of the urologist and anaesthetist (£119) was informed by Curtis and Burns[89] as explained above. The cost per working hour of each nurse was based on the cost per working hour of a Band 4 hospital-based nurse (£31) reported by Curtis and Burns.[89]

- LATP biopsies:

    - CamPROBE: a procedure time of 0.41 hour was based on the study by Wilson *et al.*[63] – resulting in a cost per biopsy of £49 for the urologist and £25 for the two nurses.
    - PrecisionPoint: a procedure time of 0.33 hour was based on the study by Szabo[41] – resulting in a cost per biopsy of £40 for the urologist and £21 for the two nurses.
    - For the remaining LATP biopsies, due to lack of data on procedure time, we assumed the average between CamPROBE and PrecisionPoint (0.37 hour) – resulting in a cost per biopsy of £44 for the urologist and £23 for the two nurses.

- GATP biopsy: a procedure time of 1.00 hour was assumed – resulting in a cost per biopsy of £119 for the urologist and anaesthetist and £62 for the two nurses.
- LATRUS biopsy: a procedure time of 0.31 hour was assumed. This was obtained by multiplying the average procedure time of LATP biopsies (0.37 hour) by the LATRUS/LATP procedure time ratio (0.84) derived from Guo *et al.*[25] This study reported a procedure time of 14.73 minutes for LATRUS and 17.51 minutes for LATP – resulting in a cost per biopsy of £37 for the urologist and £19 for the two nurses.

Cost of place of biopsy

- The YHEC study reported a cost per biopsy for an outpatient room of £43 and for a theatre session of £194. We assumed that the cost of the outpatient room corresponds to a procedure time of 0.33 hour (based on Szabo 2021), being the cost per hour of £129. The cost of the theatre session was assumed for a procedure time of 1.00 hour.
- LATP biopsies.

    - CamPROBE: assuming the use of an outpatient room and a procedure time of 0.41 hour results in a cost per biopsy of £53.
    - PrecisionPoint: assuming the use of an outpatient room and a procedure time of 0.33 hour results in a cost per biopsy of £43.
    - For the remaining LATP biopsies, assuming the use of an outpatient room and a procedure time of 0.37 hour results in a cost per biopsy of £48.

- GATP biopsy: assuming the use of a theatre session and a procedure time of 1.00 hour results in a cost per biopsy of £194.
- LATRUS biopsy: assuming the use of an outpatient room and a procedure time of 0.31 hours results in a cost per biopsy of £40.

Cost of reprocessing

- The cost of reprocessing was applied to reusable devices only – the LATP devices EZU-PA3U, UA1232 and Trinity Perine and the LATP and GATP using a grid and stepping device.

- The cost of reprocessing was assumed to be £5 per biopsy as advised by a Specialist Committee Member. This might include the cost of use of an autoclave, the blood cleaning, the item packaging in sterile cloth or paper and the technician time.

Cost of histopathology

- The cost of histopathological analysis was applied to all biopsy methods. We used the cost of £37 per sample from NHS Cost Data 2019–20 (diagnostic code DAPSO2).[90] For the base case, we assumed that 12 samples were taken from a prostate biopsy – resulting in a cost per biopsy of £439.

Costing for diagnosis, monitoring and treatment

Base-case estimates of the quantities of healthcare resources used for diagnosis, monitoring and treatment of prostate cancer and adverse events are listed in *Table 73*. Unit costs are listed in *Table 74*.

TABLE 72 Cost of consumables for each biopsy method

Consumables	Cost per biopsy	Unit cost	Source	Pack	Source	Quantity	Source	Notes
All biopsies								
Biopsy gun	£26.00	£26	YHEC 2020[257]	1	Assumption	1	Assumption	YHEC study reported the cost per biopsy directly
Biopsy needle	£27.00	£135	Wilson 2021[63]	5	Wilson 2021[63]	1	Wilson 2021[63]	
Condoms	£0.06	£28	Wilson 2021[63]	500	Wilson 2021[63]	1	Wilson 2021[63]	
Ultrasound lubricant gel	£0.01	£4	Wilson 2021[63]	5000	Wilson 2021[63]	10	Wilson 2021[63]	ml
Sterile gloves	£3.00	£79	Wilson 2021[63]	50	Wilson 2021[63]	2	Wilson 2021[63]	
Dressing towel	£0.20	£0.20	Wilson 2021[63]	1	Wilson 2021[63]	1	Wilson 2021[63]	
Syringe	£0.07	£4	Wilson 2021[63]	100	Wilson 2021[63]	2	Wilson 2021[63]	
Antiseptic wash	£0.04	£3	Wilson 2021[63]	600	Wilson 2021[63]	10	Wilson 2021[63]	ml
Sterile saline	£0.04	£4	Wilson 2021[63]	1000	Wilson 2021[63]	10	Wilson 2021[63]	ml
Sponges/ cassettes	£0.68	£0.10	Wilson 2021[63]	1	Wilson 2021[63]	12	Wilson 2021[63]	Average between cost reported by Wilson 2021 and YHEC; YHEC reported the cost per biopsy directly
		£0.16	YHEC 2020[257]	1	Assumption	1	Assumption	
Balloon/probe cover	£5.00	£5	YHEC 2020[257]	1	Assumption	1	Assumption	YHEC study reported the cost per biopsy directly
TP biopsies								
Orange needles	£0.06	£3	JEB/ Wilson 2021[63]	100	JEB/ Wilson 2021[63]	2	JEB/ Wilson 2021[63]	
Green needles	£0.04	£2	JEB/ Wilson 2021[63]	100	JEB/ Wilson 2021[63]	2	JEB/ Wilson 2021[63]	
Marker skin pen with ruler	£0.33	£2	JEB	5	JEB	1	JEB	
Cotton gauze	£0.09	£0.90	JEB/ Wilson 2021[63]	100	JEB/ Wilson 2021[63]	10	JEB/ Wilson 2021[63]	
Steri-Strips	£0.31	£8	JEB/ Wilson 2021[63]	50	JEB/ Wilson 2021[63]	2	JEB/ Wilson 2021[63]	

continued

TABLE 72 Cost of consumables for each biopsy method (*continued*)

Consumables	Cost per biopsy	Unit cost	Source	Pack	Source	Quantity	Source	Notes
Sterile drapes/ gowns	£2.00	£111	JEB/ Wilson 2021[63]	50	JEB/ Wilson 2021[63]	1	JEB/ Wilson 2021[63]	Average between cost reported by Wilson 2021 and YHEC; YHEC reported the cost per biopsy directly
		£2	YHEC 2020[257]	1	Assumption	1	Assumption	
Shallow sterile plastic tray	£0.36	£18	JEB/ Wilson 2021[63]	50	JEB/Wilson 2021[63]	1	JEB/ Wilson 2021[63]	
Antibiotics prophylaxis	£0.31	£3	emiT 2020[101]	10	emiT 2020[101]	1	Expert opinion	Assumed as one prophy-lactic dose of ciprofloxacin (500 mg), as advised by EAG expert
TP biopsies using double freehand devices and EZU-PA3U device								
Co-axial needles	£21.00	£107	Hitachi	5	Hitachi	1	Hitachi	
TRUS biopsies								
Antibiotics course	£2.00	£3	emiT 2020[101]	10	emiT 2020[101]	6	SmPC/ Assumption	Assumed as a course of ciprofloxacin 500 mg twice a day for 3 days, according to SmPC and as advised by EAG expert
LA biopsies								
Spinal needles	£6	£6	YHEC 2020[257]	1	Assumption	1	Assumption	YHEC study reported the cost per biopsy directly
Local anaesthetic	£12	£11	Wilson 2021[63]	20	Wilson 2021[63]	20	Wilson 2021[63]	ml; Average between cost reported by Wilson 2021 and YHEC study; YHEC study reported the cost per biopsy directly
		£13	YHEC 2020[257]	20	Assumption	20	Assumption	
GA biopsies								
General anaesthetic	£100	£100	YHEC 2020[257]	1	Assumption	1	Assumption	YHEC study reported the cost per biopsy directly

GA, general anaesthetics; LA, local anaesthetics; SmPC, summary of product characteristics; TP, transperineal.

TABLE 73 Base-case resource use inputs in the economic model

Parameter	Input	Source	Notes
Distribution of LATP biopsy methods			
CamPROBE	12.5%	Assumption	
PrecisionPoint	12.5%	Assumption	
EZU-PA3U	12.5%	Assumption	
UA1232	12.5%	Assumption	
Trinity Perine	12.5%	Assumption	
SureFire Guide	12.5%	Assumption	
Grid and stepping device	12.5%	Assumption	
Double freehand	12.5%	Assumption	
BSA	1.91	Sacco *et al.* 2010 (from NG131 model)[67]	
Proportion of patients that repeat biopsy after a first biopsy result NC or CNS			
MRI Likert score 3+			
Result first biopsy: CNS	15.5%	Jimenez *et al.* 2021[113]	
Result first biopsy: NC	5.0%	Assumption	Fewer patients with NC than CNS result repeat biopsy
MRI Likert score 1 or 2			
Result first biopsy: CNS	5.0%	Assumption	Fewer patients with MRI score 1 or 2 than 3 + repeat biopsy
Result first biopsy: NC	1.3%	Assumption	Fewer patients with NC than CNS result repeat biopsy
Frequency of follow-up (per year)			
FN LR, IR, HR or metastatic that did not repeat biopsy or after repeat biopsy			
PSA	1	NG131 economic model[67]	
Nurse appointment	1	NG131 economic model[67]	
TRUS	1	NG131 economic model[67]	
% having TRUS	69.0%	NG131 economic model[67]	Sensitivity of PSA test
True positive LR (receiving active surveillance)			
PSA (1st year)	4	NG131[67]	
PSA (subs years)	2	NG131[67]	
Nurse appointment (1st year)	4	NG131[67]	
Nurse appointment (subs years)	2	NG131[67]	
DRE	1	NG131[67]	
mpMRI (1st year)	1	NG131[67]	
True positive LR (receiving radical treatment)			
PSA (1st and 2nd year)	4	NG131[67]	

continued

TABLE 73 Base-case resource use inputs in the economic model (*continued*)

Parameter	Input	Source	Notes
PSA (subs years)	1	NG131[67]	
Nurse appointment (1st year)	4	NG131[67]	
Nurse appointment (subs years)	1	NG131[67]	
True positive IR (receiving active surveillance)			
PSA (1st year)	4	NG131[67]	
PSA (subs years)	2	NG131[67]	
Nurse appointment (1st year)	4	NG131[67]	
Nurse appointment (subs years)	2	NG131[67]	
DRE	1	NG131[67]	
mpMRI (1st year)	1	NG131[67]	
CT scan (1st year)	1	Clinical expert advice	
Bone scan (1st year)	1	Clinical expert advice	
% having CT and bone scan	50.0%	Clinical expert advice	
True positive IR (receiving radical treatment)			
PSA (1st and 2nd year)	4	NG131[67]	
PSA (subs years)	1	NG131[67]	
Nurse appointment (1st year)	4	NG131[67]	
Nurse appointment (subs years)	1	NG131[67]	
CT scan (1st year)	1	Clinical expert advice	
Bone scan (1st year)	1	Clinical expert advice	
% having CT and bone scan	50.0%	Clinical expert advice	
True positive IR (receiving watchful waiting)			
PSA	1	NG131[67]	
Nurse appointment	1	NG131[67]	
CT scan (1st year)	1	Clinical expert advice	
Bone scan (1st year)	1	Clinical expert advice	
% having CT and bone scan	50.0%	Clinical expert advice	
True positive HR (receiving radical treatment)			
PSA (1st and 2nd year)	4	NG131[67]	
PSA (subs years)	1	NG131[67]	
Nurse appointment (1st year)	4	NG131[67]	

TABLE 73 Base-case resource use inputs in the economic model (*continued*)

Parameter	Input	Source	Notes
Nurse appointment (subs years)	1	NG131[67]	
CT scan (1st year)	1	Clinical expert advice	
Bone scan (1st year)	1	Clinical expert advice	
% having CT and bone scan	70.0%	Assumption	
True positive HR (receiving watchful waiting)			
PSA	1	NG131[67]	
Nurse appointment	1	NG131[67]	
CT scan (1st year)	1	Clinical expert advice	
Bone scan (1st year)	1	Clinical expert advice	
% having CT and bone scan	70.0%	Assumption	
True positive metastatic			
CT scan (1st year)	1	Clinical expert advice	
Bone scan (1st year)	1	Clinical expert advice	
% having CT and bone scan	100.0%	Assumption	
Treatment distribution			
Localised disease (LR)			
Active surveillance	95.0%	NPCA Annual Report 2020[92]	
Radical treatment	5.0%	NPCA Annual Report 2020[92]	
Radical prostatectomy	2.0%	Gnanapragasam *et al.* 2016[98]	Weighted proportions based on Gnanapragasam *et al.* 2016
External radiotherapy	2.3%	Gnanapragasam *et al.* 2016[98]	
Brachytherapy	0.7%	Gnanapragasam *et al.* 2016[98]	
Watchful waiting	0.0%	Assumption	Assume that no patients with LR have watchful waiting
ADT therapies	3.0%	Assumption	All patients on radical radiotherapy receive ADT
Localised disease (IR)			
Active surveillance	12.7%	Gnanapragasam *et al.* 2016[98]	Assumed that half of patients not receiving radical treatment are on active surveillance and the other half on watchful waiting
Radical prostatectomy	21.9%	Gnanapragasam *et al.* 2016[98]	
External radiotherapy	48.7%	Gnanapragasam *et al.* 2016[98]	
Brachytherapy	4.1%	Gnanapragasam *et al.* 2016[98]	
Watchful waiting	12.7%	Gnanapragasam *et al.* 2016[98]	
ADT therapies	52.8%	Assumption	All patients on radical radiotherapy receive ADT
Localised disease (HR)			
Active surveillance	0.0%	Assumption	Assume that no patients with HR have active surveillance

continued

TABLE 73 Base-case resource use inputs in the economic model (*continued*)

Parameter	Input	Source	Notes
Radical treatment	71.0%	NPCA Annual Report 2020[92]	
Radical prostatectomy	17.6%	Gnanapragasam *et al.* 2016[98]	Weighted proportions based on Gnanapragasam *et al.* 2016
External radiotherapy	52.5%	Gnanapragasam *et al.* 2016[98]	
Brachytherapy	0.9%	Gnanapragasam *et al.* 2016[98]	
Watchful waiting	29.0%	NPCA Annual Report 2020[92]	
ADT therapies	53.4%	Assumption	All patients on radical radiotherapy receive ADT
ADT market share (localised disease)			
Leuprorelin	33.3%	Assumption	Assumed that LHRH therapies are used at the same rate
Triptorelin	33.3%	Assumption	
Goserelin	33.3%	Assumption	
Bicalutamide	100.0%	Assumption	
Metastatic hormone-sensitive disease			
ADT alone	50.0%	Assumption	
Docetaxel + ADT	36.0%	NPCA Annual Report 2020[92]	
Apalutamide + ADT	7.0%	Assumption	
Enzalutamide + ADT	7.0%	Assumption	
ADT market share (mHSPC)			
Leuprorelin	33.3%	Assumption	Assumed that LHRH therapies are used at the same rate
Triptorelin	33.3%	Assumption	
Goserelin	33.3%	Assumption	
Bicalutamide	50.0%	Assumption	
Metastatic hormone-relapsed disease			
Abiraterone	28.3%	NICE TA712[87]	Weighted proportions according to treatment for metastatic hormone-sensitive prostate cancer
Docetaxel	22.4%	NICE TA712[87]	
Enzalutamide	30.1%	NICE TA712[87]	
Best supportive care	19.2%		
Duration of drug therapies			
Localised disease			
LHRH drugs			
Low risk	3 months	NG131 model, Mowatt *et al.* 2013[67,99]	
Intermediate risk	6 months	NG131 model, Mowatt *et al.* 2013[67,99]	
High risk	2 years	NG131 model, Mowatt *et al.* 2013[67,99]	
Bicalutamide	21 days	NG131 model, Mowatt *et al.* 2013[67,99]	
Metastatic hormone-sensitive disease			
ADT alone	2 years	Assumption	
Docetaxel + ADT	6 cycles	STAMPEDE (from NG131 model)[67,103]	Cycles of 3 weeks

TABLE 73 Base-case resource use inputs in the economic model (*continued*)

Parameter	Input	Source	Notes
Apalutamide + ADT	2 years	Assumption	Same as ADT
Enzalutamide + ADT	2 years	Assumption	Same as ADT
Metastatic hormone-relapsed disease			
Abiraterone	8 months	COU-AA-301 (from NG131 model)[67]	
Docetaxel	9.5 cycles	TAX327 (from NG131 model)[67]	Cycles of 3 weeks
Enzalutamide	14 months	Pilon *et al.* 2017[258]	
Adverse events			
Incidence of biopsy adverse events (TRUS)			
Mild AEs	10.4%	Rosario *et al.* 2012[95]	
AEs requiring admission	3.7%	Tamhankar *et al.* 2020[94]	
Mortality	0.1%	Tamhankar *et al.* 2020[94]	
Incidence of biopsy adverse events (TP)			
Mild AEs	9.1%	Pepe and Aragona 2013[96]	
AEs requiring admission	3.5%	Tamhankar *et al.* 2020[94]	
Mortality	0.1%	Tamhankar *et al.* 2020[94]	
Incidence of radical treatment adverse events			
Active surveillance/watchful waiting			
Erectile dysfunction	50.9%	ProtecT study[71]	1-year FUP (table 2; table S2B, erect not firm f/intercourse)
Urinary incontinence	4.2%	ProtecT study[71]	1-year FUP (table 2; table S2A, one/more pads per day)
Bowel dysfunction	1.7%	ProtecT study[71]	1-year FUP (table S2C, mod/sev impact on QoL)
Radical prostatectomy			
Erectile dysfunction	85.4%	ProtecT study[71]	1-year FUP (table 2; table S2B, erect not firm f/intercourse)
Urinary incontinence	26.2%	ProtecT study[71]	1-year FUP (table 2; table S2A, one/more pads per day)
Bowel dysfunction	2.5%	ProtecT study[71]	1-year FUP (table S2C, mod/sev impact on QoL)
Radical radiotherapy			
Erectile dysfunction	62.4%	ProtecT study[71]	1-year FUP (table 2; table S2B, erect not firm f/intercourse)
Urinary incontinence	3.6%	ProtecT study[71]	1-year FUP (table 2; table S2A, one/more pads per day)
Bowel dysfunction	5.8%	ProtecT study[71]	1-year FUP (table S2C, mod/sev impact on QoL)
Incidence of metastatic treatment adverse events			
ADT			
Cardiac disorder	3.0%	STAMPEDE (from NG131 model)[67,103]	

continued

TABLE 73 Base-case resource use inputs in the economic model (*continued*)

Parameter	Input	Source	Notes
Endocrine disorder	12.2%	STAMPEDE (from NG131 model)[67,103]	
Gastrointestinal disorder	3.0%	STAMPEDE (from NG131 model)[67,103]	
General disorder	3.9%	STAMPEDE (from NG131 model)[67,103]	
Musculoskeletal disorder	5.8%	STAMPEDE (from NG131 model)[67,103]	
Nervous system disorder	1.7%	STAMPEDE (from NG131 model)[67,103]	
Neutropenia	1.8%	STAMPEDE (from NG131 model)[67,103]	
Renal disorder	6.0%	STAMPEDE (from NG131 model)[67,103]	
Respiratory disorders	2.3%	STAMPEDE (from NG131 model)[67,103]	
Docetaxel + ADT			
Cardiac disorder	2.9%	STAMPEDE (from NG131 model)[67,103]	
Endocrine disorder	10.4%	STAMPEDE (from NG131 model)[67,103]	
Gastrointestinal disorder	8.2%	STAMPEDE (from NG131 model)[67,103]	
General disorder	6.2%	STAMPEDE (from NG131 model)[67,103]	
Musculoskeletal disorder	5.8%	STAMPEDE (from NG131 model)[67,103]	
Nervous system disorder	3.5%	STAMPEDE (from NG131 model)[67,103]	
Neutropenia	27.3%	STAMPEDE (from NG131 model)[67,103]	
Renal disorder	4.2%	STAMPEDE (from NG131 model)[67,103]	
Respiratory disorder	5.3%	STAMPEDE (from NG131 model)[67,103]	
Apalutamide + ADT			
Blood disorder	2.1%	TITAN study (Kim *et al.* 2019)[104]	table 4
Cardiac disorder	8.4%	TITAN study (Kim *et al.* 2019)[104]	table 4
Gastrointestinal disorder	1.1%	TITAN study (Kim *et al.* 2019)[104]	table 4
General disorder	3.4%	TITAN study (Kim *et al.* 2019)[104]	table 4
Musculoskeletal disorder	6.5%	TITAN study (Kim *et al.* 2019)[104]	table 4
Nervous system disorder	0.2%	TITAN study (Kim *et al.* 2019)[104]	table 4
Renal disorder	0.8%	TITAN study (Kim *et al.* 2019)[104]	table 4
Skin disorder	6.5%	TITAN study (Kim *et al.* 2019)[104]	table 4
Enzalutamide + ADT			
Cardiac disorder	4.9%	ARCHES study (Armstrong 2019)[105]	table 3
Endocrine disorder	0.3%	ARCHES study (Armstrong 2019)[105]	table 3
Gastrointestinal disorder	0.5%	ARCHES study (Armstrong 2019)[105]	table 3

TABLE 73 Base-case resource use inputs in the economic model (*continued*)

Parameter	Input	Source	Notes
General disorder	2.8%	ARCHES study (Armstrong 2019)[105]	table 3
Musculoskeletal disorder	4.4%	ARCHES study (Armstrong 2019)[105]	table 3
Nervous system disorder	2.1%	ARCHES study (Armstrong 2019)[105]	table 3
Neutropenia	0.3%	ARCHES study (Armstrong 2019)[105]	table 3
Skin disorder	0.3%	ARCHES study (Armstrong 2019)[105]	table 3

AEs, adverse events; BSA, body surface area; CT, computerised tomography; FUP, follow-up; LHRH, luteinizing hormone-releasing hormone; mHSPC, metastatic hormone-sensitive prostate cancer, QoL, quality of life.

TABLE 74 Unit costs used in the economic model

Parameter	Cost	Source	Notes
Follow-up costs			
PSA	£1	NHS Cost Data 2019/20[90]	DAPS: DAPS04
Primary care nurse	£10	PSSRU 2020[89]	10-minute appointment with a Band 7 community-based nurse (p.129)
DRE	£78	PSSRU 2020[89]	Assumed as a 20-minute GP appointment
mpMRI	£211	NHS Cost Data 2019/20[90]	IMAG: RD03Z (outpatient)
CT scan	£126	NHS Cost Data 2019/20[90]	IMAG: RD21A
Bone scan	£331	NHS Cost Data 2019/20[90]	NM: RN15A
Treatment costs			
Localised disease			
Radical prostatectomy			
Surgery	£8331	NHS Cost Data 2019/20[90]	EL: LB69Z
First appointment	£247	NHS Cost Data 2019/20[90]	OPROC: WF01B
Follow-up appointment	£214	NHS Cost Data 2019/20[90]	OPROC: WF01A
Number of follow-up appointments	2	Wilson *et al.* 2021[63]	
External radiotherapy	£3114	NHS Cost Data 2019/20[90]	RAD: weighted average of SC40Z and SC41Z (outpatient) plus SC21Z (outpatient) multiplied by 20 fractions
Brachytherapy	£3106	NHS Cost Data 2019/20[90]	RAD: SC55Z + SC30Z (weighted average of inpatient, day case and outpatient)
ADT therapies			
Low risk	£246	BNF 2021, eMIT 2020[100,101]	21-day course of bicalutamide + 1 injection of LHRH + admin costs
Intermediate risk	£489	BNF 2021, eMIT 2020[100,101]	21-day course of bicalutamide + 2 injections of LHRH + admin costs
High risk	£1947	BNF 2021, eMIT 2020[100,101]	21-day course of bicalutamide + 8 injections of LHRH + admin costs

continued

TABLE 74 Unit costs used in the economic model (*continued*)

Parameter	Cost	Source	Notes
Metastatic hormone-sensitive disease			
ADT alone	£1946	BNF 2021, eMIT 2020	28-day course of bicalutamide + 2-year LHRH drugs
Docetaxel + ADT	£4076	eMIT 2020[101]	Cost of ADT alone + 6 cycles of 75 mg/m^2 docetaxel + admin costs
Apalutamide + ADT	£73,300	BNF 2021[100]	Cost of ADT alone + 2-year apalutamide
Enzalutamide + ADT	£73,291	BNF 2021[100]	Cost of ADT alone + 2-year enzalutamide
Metastatic hormone-relapsed disease			
Abiraterone	£23,785	BNF 2021[100]	8 months (from NG131 model)
Docetaxel	£3411	eMIT 2020[101]	9.5 cycles of 75 mg/m^2 docetaxel + admin costs
Enzalutamide	£41,618	BNF 2021[100]	14 months
Best supportive care	£0	Assumption	Assumed no costs as they are negligible
Administration costs			
LHRH drugs	£13	PSSRU 2020[89]	15.5 minutes with a Band 6 hospital-based nurse (p.155)
Docetaxel (IV, 1st attendance)	£300	NHS Cost Data 2019/20[90]	CHEM: SB12Z
Docetaxel (IV, subs attendances)	£366	NHS Cost Data 2019/20[90]	CHEM: SB15Z
Adverse event costs			
Biopsy adverse events			
Mild AEs (urinary infection)	£48	Wilson *et al.* 2021[63]	GP visit + urinalysis + 7-day trimethoprim
GP visit	£39	PSSRU 2020[89]	10.3b GP (unit costs per patient contact lasting 9.22 minutes)
Urinalysis	£8	NHS Cost Data 2019/20[90]	DAPS: DAPS07
7-day trimethoprim	£0.23	eMIT 2020[101]	200 mg × 14 tablets
Non-elective admission (TRUS)	£2503	Tamhankar *et al.* 2020[94]	Inflated to 2019/20
Non-elective admission (TP)	£1895	Tamhankar *et al.* 2020[94]	Inflated to 2019/20
Overnight stay	£602	PSSRU 2020[89]	7.1 NHS reference costs for hospital services – average cost per episode of non-elective short stay (<2 days)
Mortality	£9740	NHS Cost Data 2019/20[90]	NE: WJ06A (weighted average of short and long stay)
Radical treatment adverse events			
Erectile dysfunction	£174	NHS Cost Data 2019/20[90]	OPROC: LB43Z (weighted average)
Urinary incontinence	£308	NG131 model[67]	Managed by containment pads. Inflated to 2019/20
Bowel dysfunction	£1883	NG131 model[67]	Mean weighted cost including costs associated with sigmoidoscopy, laser therapy, enemas and blood transfusion. Inflated to 2019/20

TABLE 74 Unit costs used in the economic model (*continued*)

Parameter	Cost	Source	Notes
Metastatic treatment adverse events			
Blood disorder	£1831	NHS Cost Data 2019/20[90]	NE: SA03G-SA03H, SA08G-SA08J, SA12G-SA12K (weighted average of short and long stay)
Cardiac disorder	£1592	NHS Cost Data 2019/20[90]	NE: EB10 (weighted average of short and long stay)
Endocrine disorder	£174	Assumption	Same as erectile dysfunction
Gastrointestinal disorder	£1492	NHS Cost Data 2019/20[90]	NE: FD10 (weighted average of short and long stay)
General disorder	£40	Assumption	Same as fever
Musculoskeletal disorder	£1061	NHS Cost Data 2019/20[90]	NE: HD26 (weighted average of short and long stay)
Nervous system disorder	£1513	NHS Cost Data 2019/20[90]	NE: AA26 (weighted average of short and long stay)
Neutropenia	£6605	NHS Cost Data 2019/20[90]	NE: PM45 (weighted average of short and long stay)
Renal disorder	£48	Assumption	Same as urinary infection
Respiratory disorders	£657	NHS Cost Data 2019/20[90]	NE: DZ19 (weighted average of short and long stay)
Skin disorder	£1615	NHS Cost Data 2019/20[90]	NE: JD07 (weighted average of short and long stay)
Other costs			
End of life	£16,052	Round *et al.* 2015[106]	From initiation of strong opioids until death (expected survival 243 days); inflated to 2019/20

AEs, adverse events; IV, intravenous, LHRH, luteinising hormone-releasing hormone.

Appendix 9 Additional cost-effectiveness results

Probabilistic sensitivity analyses: decision question 1

Results for the probabilistic sensitivity analysis for decision question 1 are shown in *Table 75*. These results are illustrated for subgroup A in the scatterplot and CEAC in *Figures 22* and *23*, respectively.

TABLE 75 Base-case cost-effectiveness (probabilistic): decision question 1

	Total		Incremental		INHB (QALYs)		ICERs
Biopsy method	cost	QALYs	cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3 + first biopsy							
LATRUS	£19,938	9.296					
LATP-any	£19,982	9.303	£44	0.007	0.004	0.005	£6710
GATP	£20,479	9.300	£497	−0.003	−0.023	−0.014	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,825	9.474					
LATP-any	£15,880	9.479	£55	0.004	0.002	0.003	£12,544
GATP	£16,362	9.477	£482	−0.002	−0.024	−0.015	Dominated
Subgroup C: MRI Likert 3 + previous negative biopsy							
LATRUS	£16,679	9.452					
LATP-any	£16,730	9.456	£51	0.004	0.001	0.002	£14,141
GATP	£17,207	9.454	£477	−0.002	−0.024	−0.015	Dominated
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	£14,109	9.543					
LATP-any	£14,168	9.546	£58	0.003	0.000	0.001	£19,126
GATP	£14,639	9.546	£530	−0.001	−0.024	−0.015	Dominated

INHB, incremental net health benefit.

Notes
ICER (fully incremental).
INHB vs. LATRUS, at thresholds £20,000–30,000/QALY gained.

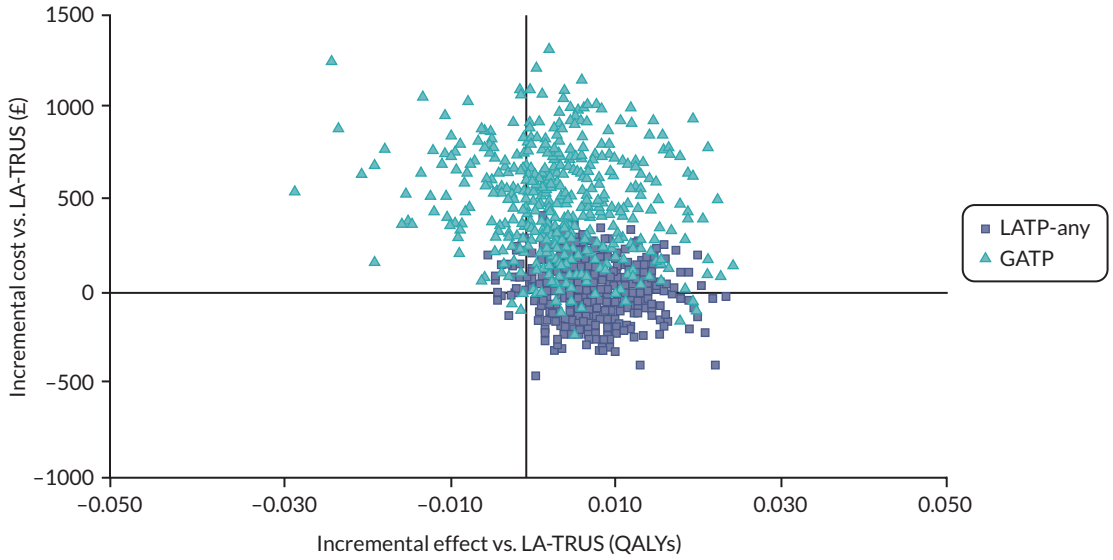

FIGURE 22 Cost-effectiveness scatterplot: subgroup A (decision question 1).

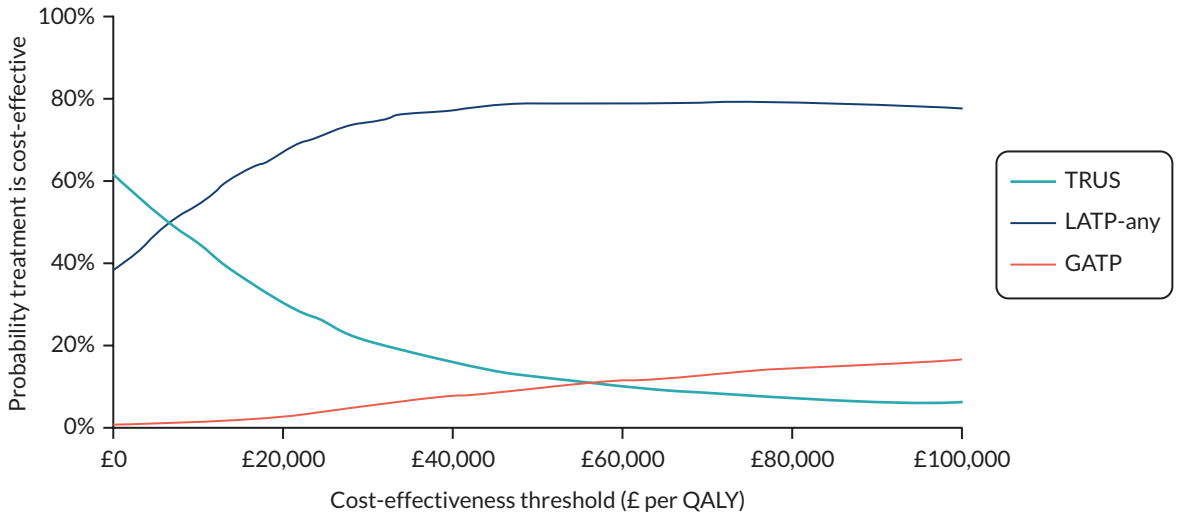

FIGURE 23 Cost-effectiveness acceptability curve: subgroup A (decision question 1).

Probabilistic sensitivity analyses: decision question 2

Table 76 shows probabilistic results for decision question 2. The probabilistic results for subgroup A are illustrated in the scatterplot and CEACs in *Figures 24* and *25*, respectively.

TABLE 76 Base-case cost-effectiveness (probabilistic): decision question 2

	Total		Incremental		INHB (QALYs)		ICERs
Biopsy method	**cost**	**QALYs**	**cost**	**QALYs**	**£20k**	**£30k**	**£/QALY**
Subgroup A: MRI Likert 3 + first biopsy							
LATRUS	£19,859	9.299					
LATP-freehand	£19,882	9.309	£23	0.010	0.009	0.010	£2184
LATP-other	£19,932	9.302	£50	−0.007	−0.000	0.001	Dominated
GATP	£20,414	9.300	£482	−0.002	−0.027	−0.017	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,740	9.473					
LATP-freehand	£15,784	9.480	£45	0.007	0.004	0.005	£6846
LATP-other	£15,818	9.476	£34	−0.004	−0.001	0.000	Dominated
GATP	£16,291	9.475	£473	−0.001	−0.026	−0.017	Dominated
Subgroup C: MRI Likert 3 + previous negative biopsy							
LATRUS	£16,756	9.452					
LATP-freehand	£16,806	9.456	£50	0.004	0.002	0.003	£11,330
LATP-other	£16,836	9.454	£30	−0.002	−0.002	−0.000	Dominated
GATP	£17,298	9.453	£462	−0.001	−0.026	−0.017	Dominated
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	£14,076	9.543					
LATP-freehand	£14,121	9.547	£45	0.004	0.002	0.003	£11,022
LATP-other	£14,153	9.545	£32	−0.002	−0.002	−0.000	Dominated
GATP	£14,612	9.544	£459	−0.001	−0.025	−0.016	Dominated

INHB, incremental net health benefit.

Notes
ICER (fully incremental).
INHB vs. LATRUS, at thresholds £20,000–30,000/QALY gained.

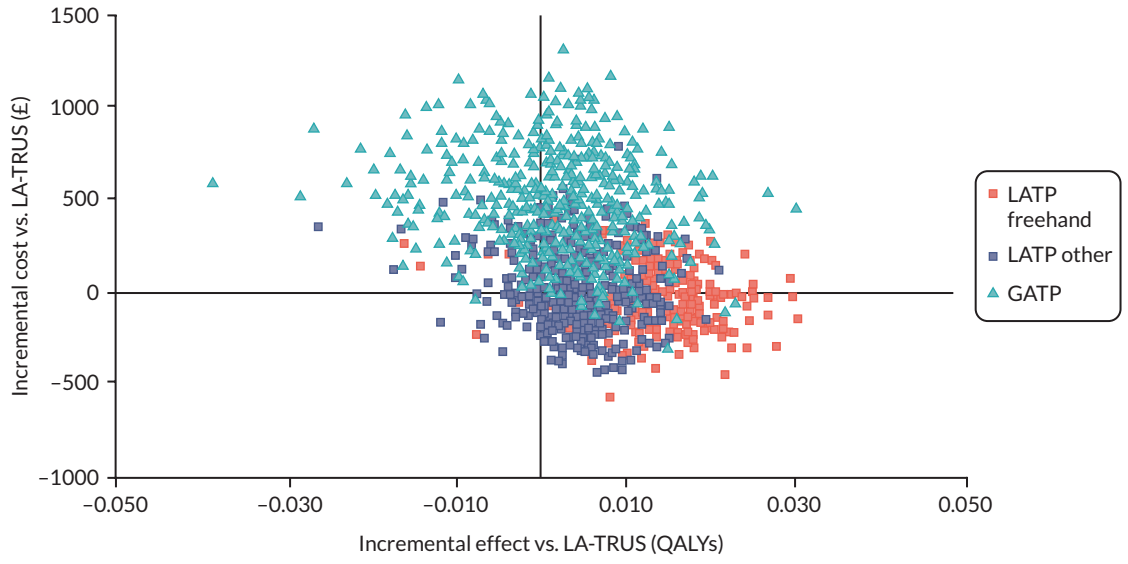

FIGURE 24 Cost-effectiveness scatterplot: subgroup A (decision question 2).

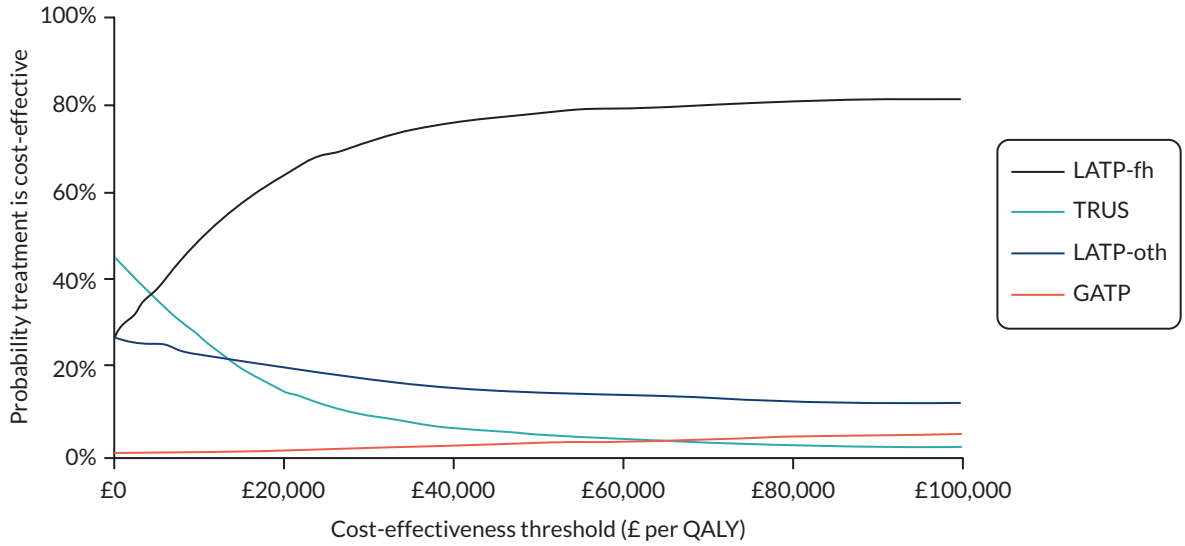

FIGURE 25 Cost-effectiveness acceptability curve: subgroup A (decision question 2).

Intermediate outcomes: decision question 1

Intermediate outcomes related to the decision-tree biopsy pathway are shown in *Table 77*. Outcomes from the Markov model are summarised in *Table 78*. *Table 79* summarises costs estimated from the decision-tree and Markov models.

TABLE 77 Base-case decision-tree outcomes: decision question 1

		Undiagnosed		Biopsy-related AE			
Biopsy method	Mean biopsies	CNS (%)	CS (%)	Mild (%)	Admissions (%)	Deaths (%)	AE QALY loss
Subgroup A: MRI Likert 3 + first biopsy							
LATRUS	1.034	9.92	15.22	10.7	3.9	0.07	−0.0018
LATP-any	1.034	9.62	12.23	9.5	3.7	0.05	−0.0017
GATP	1.034	9.74	13.36	9.5	3.7	0.05	−0.0017
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	1.013	20.40	6.73	10.5	3.8	0.07	−0.0018
LATP-any	1.013	19.72	5.47	9.3	3.6	0.05	−0.0017
GATP	1.013	19.99	5.95	9.3	3.6	0.05	−0.0017
Subgroup C: MRI Likert 3 + previous negative biopsy							
LATRUS	1.000	17.44	4.45	10.4	3.7	0.07	−0.0018
LATP-any	1.000	16.46	3.28	9.1	3.5	0.05	−0.0017
GATP	1.000	16.85	3.71	9.1	3.5	0.05	−0.0017
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	1.000	21.74	1.12	10.4	3.7	0.07	−0.0018
LATP-any	1.000	20.53	0.82	9.1	3.5	0.05	−0.0017
GATP	1.000	21.01	0.93	9.1	3.5	0.05	−0.0017

AE, adverse events; CNS, clinically non-significant prostate cancer (low-risk localised); CS, clinically significant prostate cancer (IR or HR localised disease).

TABLE 78 Base-case Markov model outcomes: decision question 1

	Deaths (% of whole cohort)			Undiscounted		Discounted	
Biopsy method	Prostate cancer	Other cause	All	LYs	QALYs	LY	QALY
Subgroup A: MRI Likert 3 + first biopsy							
LATRUS	19.60	80.31	99.90	16.010	12.578	11.717	9.301
LATP-any	19.52	80.41	99.92	16.024	12.589	11.726	9.307
GATP	19.55	80.38	99.92	16.020	12.586	11.723	9.306
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	10.86	89.03	99.89	16.780	12.960	12.138	9.480
LATP-any	10.82	89.09	99.91	16.789	12.967	12.143	9.484
GATP	10.84	89.08	99.91	16.787	12.965	12.142	9.483
Subgroup C: MRI Likert 3 + previous negative biopsy							
LATRUS	12.64	87.26	99.90	16.638	12.903	12.063	9.458
LATP-any	12.60	87.32	99.92	16.647	12.910	12.069	9.462
GATP	12.61	87.31	99.92	16.645	12.908	12.067	9.462
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	7.32	92.57	99.89	17.087	13.111	12.304	9.549
LATP-any	7.30	92.61	99.91	17.093	13.115	12.308	9.552
GATP	7.31	92.60	99.91	17.092	13.114	12.308	9.552

Intermediate outcomes: decision question 2

Intermediate outcomes and costs for decision question 2 are shown in *Tables 80*, *81* and *82*.

Scenario analysis: relative risk of cancer detection from observational data

The base-case analysis uses cancer detection rates from network meta-analyses of RCT data only. We tested the effect of using estimates from observational studies, based on pairwise meta-analysis comparisons reported in *Intermediate outcomes* above (see *Appendix 4*, *Figures 9*, *14* and *15*). Observational data for GATP are only available in comparison with LATP (method not specified). Therefore, the RR for GATP versus LATRUS has to be adjusted by the RR for LATP versus LATRUS for use in the model. This yields different estimates for the effectiveness of GATP in decision questions 1 and 2: 1.45 (1.31 × 1.10) or 1.33 (1.31 × 1.01) respectively in the base case.

Following questions raised by NICE specialist committee members for this assessment, we conducted additional scenario analysis to investigate the impact of uncertainty over which observational studies should be included. These include scenarios excluding the Bojin study or excluding the Watanabe study, a scenario including a study by Walters *et al.* and a scenario including Walters but excluding the Takuma study.[29,38,43,44]

TABLE 79 Base-case intermediate costs: decision question 1

Biopsy method	Decision-tree costs			Markov model, undiscounted costs					Discounted total costs
	Biopsies	AE	Total cost	Treatment	AE	Follow-up	End of life	Total	
Subgroup A: MRI Likert 3 + first biopsy									
LATRUS	£704	£109	£813	£8965	£2709	£662	£16,042	£28,378	£19,065
LATP-any	£799	£80	£879	£8942	£2715	£651	£16,043	£28,351	£19,040
GATP	£1274	£80	£1354	£8951	£2713	£655	£16,043	£28,363	£19,050
Subgroup B: MRI Likert 1 or 2 first biopsy									
LATRUS	£690	£107	£796	£5118	£1715	£639	£16,040	£23,513	£14,957
LATP-any	£785	£78	£863	£5107	£1718	£630	£16,042	£23,498	£14,942
GATP	£1260	£78	£1338	£5112	£1717	£634	£16,042	£23,505	£14,948
Subgroup C: MRI Likert 3 + previous negative biopsy									
LATRUS	£681	£105	£786	£5953	£1987	£654	£16,041	£24,634	£15,867
LATP-any	£776	£76	£852	£5942	£1990	£643	£16,042	£24,617	£15,851
GATP	£1251	£76	£1328	£5947	£1989	£647	£16,042	£24,625	£15,857
Subgroup D: MRI Likert 1 or 2 previous negative biopsy									
LATRUS	£681	£105	£786	£3568	£1303	£607	£16,039	£21,516	£13,280
LATP-any	£776	£76	£852	£3563	£1304	£597	£16,041	£21,505	£13,269
GATP	£1251	£76	£1328	£3565	£1304	£601	£16,041	£21,510	£13,273

AE, adverse events.

TABLE 80 Base-case decision-tree outcomes: decision question 2

Biopsy method	Mean biopsies	Undiagnosed (%)		Biopsy-related AE (%)			AE QALY loss
		CNS		Mild	Admission	Death	
Subgroup A: MRI Likert 3 + first biopsy							
LATRUS	1.0342	9.92	15.22	10.7	3.9	0.07	−0.0018
LATP-freehand	1.0344	9.15	8.38	9.5	3.7	0.05	−0.0017
LATP-other	1.0342	9.82	14.16	9.5	3.7	0.05	−0.0017
GATP	1.0342	9.90	15.01	9.5	3.7	0.05	−0.0017
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	1.0132	20.40	6.73	10.5	3.8	0.07	−0.0018
LATP-freehand	1.0139	18.64	3.85	9.3	3.6	0.05	−0.0017
LATP-other	1.0132	20.17	6.29	9.3	3.6	0.05	−0.0017
GATP	1.0132	20.35	6.64	9.3	3.6	0.05	−0.0017
Subgroup C: MRI Likert 3 + previous negative biopsy							
LATRUS	1.0000	17.44	4.45	10.4	3.7	0.07	−0.0018
LATP-freehand	1.0000	14.95	3.59	9.1	3.5	0.05	−0.0017

TABLE 80 Base-case decision-tree outcomes: decision question 2 (*continued*)

Biopsy method	Mean biopsies	Undiagnosed (%) CNS		Biopsy-related AE (%) Mild	Admission	Death	AE QALY loss
LATP-other	1.0000	17.11	4.02	9.1	3.5	0.05	−0.0017
GATP	1.0000	17.38	4.37	9.1	3.5	0.05	−0.0017
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	1.0000	21.74	1.12	10.4	3.7	0.07	−0.0018
LATP-freehand	1.0000	18.64	0.90	9.1	3.5	0.05	−0.0017
LATP-other	1.0000	21.33	1.01	9.1	3.5	0.05	−0.0017
GATP	1.0000	21.66	1.09	9.1	3.5	0.05	−0.0017

AE, adverse events; CNS, clinically non-significant prostate cancer (low-risk localised); CS, clinically significant prostate cancer (IR or HR localised disease).

TABLE 81 Base-case Markov outcomes: decision question 2

Biopsy method	Deaths (% of whole cohort) Prostate cancer	Other cause	All	Undiscounted LYs	QALYs	Discounted LY	QALY
Subgroup A: MRI Likert 3 + first biopsy							
LATRUS	19.60	80.31	99.90	16.010	12.578	11.717	9.301
LATP-freehand	19.41	80.51	99.92	16.037	12.599	11.734	9.314
LATP-other	19.57	80.35	99.92	16.017	12.584	11.722	9.304
GATP	19.59	80.33	99.92	16.014	12.581	11.720	9.303
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	10.86	89.03	99.89	16.780	12.960	12.138	9.480
LATP-freehand	10.77	89.15	99.91	16.795	12.972	12.147	9.487
LATP-other	10.85	89.06	99.91	16.785	12.964	12.141	9.483
GATP	10.86	89.05	99.91	16.784	12.963	12.140	9.482
Subgroup C: MRI Likert 3 + previous negative biopsy							
LATRUS	12.64	87.26	99.90	16.638	12.903	12.063	9.458
LATP-freehand	12.58	87.33	99.92	16.648	12.911	12.069	9.463
LATP-other	12.62	87.29	99.92	16.643	12.907	12.067	9.461
GATP	12.64	87.28	99.92	16.642	12.906	12.066	9.460
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	7.32	92.57	99.89	17.087	13.111	12.304	9.549
LATP-freehand	7.28	92.63	99.91	17.096	13.117	12.310	9.553
LATP-other	7.32	92.60	99.91	17.092	13.114	12.307	9.551
GATP	7.32	92.59	99.91	17.091	13.113	12.307	9.551

TABLE 82 Base-case intermediate costs: decision question 2

Biopsy method	Decision-tree costs			Markov model, undiscounted costs					Discounted total costs
	Biopsies	AE	Total	Treatment	AE	Follow-up	End of life	Total	
Subgroup A: MRI Likert 3 + first biopsy									
LATRUS	£704	£109	£813	£8965	£2709	£662	£16,042	£28,378	£19,065
LATP-freehand	£805	£80	£885	£8909	£2721	£637	£16,043	£28,309	£19,004
LATP-other	£814	£80	£894	£8958	£2711	£658	£16,043	£28,371	£19,058
GATP	£1275	£80	£1355	£8965	£2710	£661	£16,043	£28,380	£19,066
Subgroup B: MRI Likert 1 or 2 first biopsy									
LATRUS	£690	£107	£796	£5118	£1715	£639	£16,040	£23,513	£14,957
LATP-freehand	£791	£78	£868	£5092	£1721	£618	£16,042	£23,472	£14,920
LATP-other	£800	£78	£877	£5115	£1717	£636	£16,042	£23,510	£14,952
GATP	£1260	£78	£1338	£5119	£1716	£638	£16,042	£23,515	£14,957
Subgroup C: MRI Likert 3 + previous negative biopsy									
LATRUS	£681	£105	£786	£5953	£1987	£654	£16,041	£24,634	£15,867
LATP-freehand	£781	£76	£858	£5942	£1990	£633	£16,042	£24,607	£15,841
LATP-other	£791	£76	£867	£5950	£1988	£650	£16,042	£24,630	£15,862
GATP	£1251	£76	£1328	£5953	£1987	£653	£16,042	£24,636	£15,867
Subgroup D: MRI Likert 1 or 2 previous negative biopsy									
LATRUS	£681	£105	£786	£3568	£1303	£607	£16,039	£21,516	£13,280
LATP-freehand	£781	£76	£858	£3560	£1305	£583	£16,041	£21,489	£13,254
LATP-other	£791	£76	£867	£3566	£1303	£603	£16,041	£21,514	£13,277
GATP	£1251	£76	£1328	£3568	£1303	£606	£16,041	£21,518	£13,280

AE, adverse events.

Table 83 shows the results for decision question 1 subgroup A. The ICERs for LATP-any compared with LATRUS are higher in the observational scenarios (from £7609 to £11,175 per QALY) than in the base case analysis with RCT data (£5859 per QALY). The ICERs for LATP-any remain below £20,000 per QALY for all observational scenarios and subgroups, with the exception of scenario 2 in subgroup D, for which the ICER is £22,260 per QALY. GATP has a high ICER (above £30,000 per QALY) or is dominated in all observational scenarios and subgroups.

Table 84 shows the observational scenario results for decision question 2 subgroup A. The ICERs for LATP-freehand versus LATRUS are higher when based on observational data than in the base case (£743 per QALY), but they remain below £20,000 per QALY in all observational scenarios and subgroups. LATP-other and GATP are dominated or have high ICERs in all observational scenarios and subgroups. This remains the case if we use the same RR for GATP versus TRUS as in decision question 1.

TABLE 83 Observational scenarios: RR of cancer detection from observational studies – decision question 1, subgroup A (deterministic)

		Total		Incremental		ICERs
Biopsy method	RR[a]	Cost	QALYs	Cost	QALYs	£/QALY
Observational scenario 1: original pairwise meta-analysis						
LATRUS	1.00	£19,878	9.299			
LATP-any	1.10	£19,927	9.304	£49	0.005	£9159
GATP	1.45	£20,359	9.312	£431	0.008	£54,953
Observational scenario 2: excluding Bojin[29]						
LATRUS	1.00	£19,878	9.299			
LATP-any	1.08	£19,931	9.304	£53	0.005	£11,175
GATP	1.42	£20,358	9.312	£427	0.009	£49,771
Observational scenario 3: excluding Watanabe[38]						
LATRUS	1.00	£19,878	9.299			
LATP-any	1.12	£19,924	9.305	£46	0.006	£7609
GATP	1.47	£20,359	9.312	£435	0.007	£61,058
Observational scenario 4: including Walters[44]						
LATRUS	1.00	£19,878	9.299			
LATP-any	1.10	£19,927	9.304	£49	0.005	£9159
GATP	1.16	£20,393	9.306	£466	0.002	£263,212
Observational scenario 5: including Walters and excluding Takuma[43,44]						
LATRUS	1.00	£19,878	9.299			
LATP-any	1.10	£19,927	9.304	£49	0.005	£9159
GATP	0.97	£20,428	9.300	£500	−0.004	Dominated

a Relative risk for cancer detection.

TABLE 84 Observational scenarios: RR of cancer detection from observational studies – decision question 2, subgroup A (deterministic)

		Total		Incremental		ICERs
Biopsy method	RR[a]	Cost	QALYs	Cost	QALYs	£/QALY
Observational scenario 1: original pairwise meta-analysis						
LATRUS	1.00	£19,878	9.299			
LATP-freehand	1.21	£19,915	9.308	£36	0.009	£4209
LATP-other	1.01	£19,960	9.301	£45	−0.006	Dominated
GATP	1.33	£20,367	9.311	£408	0.009	£148,623
Observational scenario 2: excluding Bojin[29]						
LATRUS	1.00	£19,878	9.299			

continued

TABLE 84 Observational scenarios: RR of cancer detection from observational studies – decision question 2, subgroup A (deterministic) (*continued*)

		Total		Incremental		ICERs
Biopsy method	RR[a]	Cost	QALYs	Cost	QALYs	£/QALY
LATP-freehand	1.22	£19,913	9.308	£35	0.009	£3904
LATP-other	1.01	£19,960	9.301	£46	−0.007	Dominated
GATP	1.33	£20,367	9.311	£408	0.009	£163,869
***Observational scenario 3: excluding Watanabe*[38]**						
LATRUS	1.00	£19,878	9.299			
LATP-freehand	1.21	£19,915	9.308	£36	0.009	£4209
LATP-other	1.00	£19,962	9.301	£47	−0.007	Dominated
GATP	1.32	£20,369	9.310	£408	0.009	£166,422
***Observational scenario 4: including Walters*[44]**						
LATRUS	1.00	£19,878	9.299			
LATP-freehand	1.21	£19,915	9.308	£36	0.009	£4209
LATP-other	1.01	£19,960	9.301	£45	−0.006	Dominated
GATP	1.06	£20,410	9.303	£450	0.002	Dominated
***Observational scenario 5: including Walters and excluding Takuma*[43,44]**						
LATRUS	1.00	£19,878	9.299			
LATP-freehand	1.21	£19,915	9.308	£36	0.009	£4209
LATP-other	1.01	£19,960	9.301	£45	−0.006	Dominated
GATP	0.89	£20,445	9.297	£486	−0.005	Dominated

a Relative risk for cancer detection.

TABLE 85 Core scenarios with Surrey costs: decision question 1, subgroup A (deterministic)

		Total		Incremental		ICERs
Biopsy method	Biopsy samples	Cost	QALYs	Cost	QALYs	£/QALY
Core scenario 1: 24 core samples for all transperineal methods						
LATRUS	12	£19,467	9.299			
LATP-any	24	£19,597	9.306	£130	0.007	£18,852
GATP	24	£20,081	9.304	£484	−0.002	Dominated

Scenario analysis: cost of histopathology

We reported results for three scenarios with alternative assumptions on the numbers of core samples for the different biopsy methods in *Tables 42* and *43*. These analyses used the base-case histopathology cost of £36.58 per core sample. *Tables 85* and *86* report results for the core scenarios with alternative unit costs for histopathology from an online report by the University of Surrey: £37.50 for 'standard histology' (1–2 sites/lesions) and £7 per additional site/lesion.[112]

TABLE 86 Core scenarios with Surrey costs: for decision question 2, subgroup A (deterministic)

		Total		Incremental		ICERs
Biopsy method	Biopsy samples	Cost	QALYs	Cost	QALYs	£/QALY
Core scenario 1: 24 cores for all transperineal methods						
LATRUS	12	£19,467	9.299			
LATP-freehand	24	£19,574	9.312	£107	0.013	£8052
LATP-other	24	£19,626	9.303	£52	−0.010	Dominated
GATP	24	£20,093	9.301	£467	−0.001	Dominated
Core scenario 2: 24 cores for LATP-freehand only						
LATRUS	12	£19,467	9.299			
LATP-other	12	£19,542	9.303	£75	0.004	Dominated[a]
LATP-freehand	24	£19,574	9.312	£32	0.010	£8052
GATP	12	£20,009	9.301	£435	−0.011	Dominated
Core scenario 3: 24 cores for LATP-freehand and 16 for LATP-other and GATP						
LATRUS	12	£19,467	9.299			
LATP-other	16	£19,570	9.303	£103	0.004	Dominated[a]
LATP-freehand	24	£19,574	9.312	£4	0.010	£8052
GATP	16	£20,037	9.301	£463	−0.011	Dominated

a Extendedly dominated by LATRUS and LATP-freehand.

Scenario analysis: probability of repeat biopsy

The base-case value for the probability of repeat biopsy for MRI Likert score 3 + after first biopsy result CNS was 15.45% for LATRUS, LATP and GATP, informed by the rate after a first LATRUS biopsy reported by Jimenez *et al.* (see *Probability of a repeat biopsy*).[85] Jimenez *et al.* also reported the rate of re-biopsy after a first GATP biopsy (5.36%), which we have not used in the base case because it is associated with some uncertainty – a much lower sample size and prostates with higher volume than for LATRUS.

Jimenez *et al.* do not report the probability of repeat biopsy after a first LATP biopsy. It is unclear whether this is closer to the rate after LATRUS or after GATP: whether the likelihood of repeat biopsy is more related to the route of biopsy or the type of anaesthesia. The route of biopsy may affect accessibility of different areas of the prostate, which could influence the proportion of unexpected negative biopsy results when there is a high suspicion of prostate cancer. On the otherhand, we understand that it can be possible to take more and better samples of the prostate under general anaesthetic, when patients cannot tolerate a prolonged procedure under local anaesthetics.

Experts advising NICE stated that they would expect rates of repeat biopsy to be lower for GATP than for LATP and LATRUS. They stated a preference for an analysis with the rate for LATP assumed equal to that for LATRUS (15.45%), but with a lower rate for GATP (5.36%). The view that the likelihood of repeat biopsy is similar for LATRUS and LATP was supported by a stakeholder comment. This attributed the lower rate of repeat biopsy for GATP compared with LATRUS in the Jimenez study to the greater number of biopsy core samples taken for GATP (reported as 12–18 for LATRUS and 30 for GATP).

We therefore report results for two repeat biopsy scenarios:

1. In the first scenario we use the lower repeat biopsy rate from Jimenez (5.36%) for LATP and GATP.
2. In the second scenario, we retain the high repeat biopsy rate for LATP (assumed equal to LATRUS) but use the lower rate for GATP. Note that these scenarios are not relevant for the other subgroups because we assume lower rates of repeat biopsy for patients with a MRI Likert score of 1 or 2, and no repeat biopsy after a second biopsy.

Table 87 shows that the ICER for LATP-any versus LATRUS is lower when the lower rate of repeat biopsy (5.36%) observed after TP in the Jimenez *et al.* study[85] is used for LATP (rather than 15.45% as observed after LATRUS). LATP-freehand dominates all other comparators when the lower rate of repeat biopsy is assumed. These scenarios do not change overall conclusions in subgroup A: the ICER for LATP-any or LATP-freehand versus LATRUS remains below the £20,000 per QALY threshold.

We also tested the impact of changing the probability of repeat biopsy after a 'no cancer' biopsy result (assumed to be 5% for all biopsy methods in the base case). This did not change the cost-effectiveness conclusions, even when we increased this probability to 15.45% for LATP (the same as if the biopsy had detected CNS disease) but left the probability at 5% for other comparators.

TABLE 87 Scenario: probability of repeat biopsy 5.36% for LATP and GATP, and 15.45% for LATRUS (subgroup A, deterministic)

	Total		Incremental		ICERs
Biopsy method	**Cost**	**QALYs**	**Cost**	**QALYs**	**£/QALY**
Decision question 1: lower rate for LATP and GATP					
LATRUS	£19,878	9.299			
LATP all	£19,908	9.305	£29	0.006	£5094
GATP	£20,394	9.303	£486	−0.002	Dominated
Decision question 1: lower rate for GATP only					
LATRUS	£19,878	9.299			
LATP all	£19,919	9.306	£40	0.007	£5859
GATP	£20,394	9.303	£475	−0.003	Dominated
Decision question 2: lower rate for LATP and GATP					
LATP-freehand	£19,877	9.311			
LATRUS	£19,878	9.299	£2	−0.012	Dominated
LATP-other	£19,941	9.301	£63	0.003	Dominated
GATP	£20,410	9.300	£469	−0.001	Dominated
Decision question 2: lower rate for GATP only					
LATRUS	£19,878	9.299			
LATP-freehand	£19,888	9.312	£10	0.013	£743
LATP-other	£19,952	9.303	£63	−0.010	Dominated
GATP	£20,410	9.300	£458	−0.003	Dominated

TABLE 88 Other scenario analyses: subgroup A (first biopsy with MRI Likert score 3+)

					ICER (£ per QALY gained)				
					Decision question 1		Decision question 2		
	Element	Base case	Scenario analysis	Justification	LATP vs. LATRUS	LATP vs. GATP	LATP-fh vs. LATRUS	LATP-fh vs. LATP-other	LATP-fh vs. GATP
Base-case results					£5859	Dominant	£743	Dominant	Dominant
1	Time horizon	40 years	20 years	Test the impact of an alternative time horizon	£5913	Dominant	£68	Dominant	Dominant
2	Discount rate	3.5%	0.0%	Test the impact of alternative discount rates as recommended by NICE	£3591	Dominant	£66	Dominant	Dominant
3			1.5% QALYs 1.5% costs		£4404	Dominant	£228	Dominant	Dominant
4			1.5% QALYs 3.5% costs		£4641	Dominant	£580	Dominant	Dominant
5	Initial age of the cohort	66 years	55 years	Test the impact of a younger cohort	£4586	Dominant	£231	Dominant	Dominant
6			63 years	Mean age at referral for a first prostate biopsy in PROMIS trial	£5290	Dominant	£493	Dominant	Dominant
7			75 years	Test the impact of an older cohort	£9859	Dominant	£2987	Dominant	Dominant
8	Proportion of initial cohort with MD	0.0%	5.0%	It is likely that a small proportion of patients with MD undergo biopsy	£5859	Dominant	£743	Dominant	Dominant
9	Probability of CS result for LR disease (at first/second LATRUS)	0.0%	5.0%	As advised by SCM it's unlikely that there are no false positive results of CS for patients with LR disease	£5701	Dominant	£585	Dominant	Dominant
10	Probability of CNS/NC result for HR disease (first/second LATRUS)	0.0%	CNS: 8.0% NC: 5.0%	Test the impact of FN results by using the probabilities of CNS and NC from second biopsy	£5689	Dominant	£734	Dominant	Dominant

TABLE 88 Other scenario analyses: subgroup A (first biopsy with MRI Likert score 3+) (*continued*)

					ICER (£ per QALY gained)				
					Decision question 1		Decision question 2		
	Element	Base case	Scenario analysis	Justification	LATP vs. LATRUS	LATP vs. GATP	LATP-fh vs. LATRUS	LATP-fh vs. LATP-other	LATP-fh vs. GATP
11	Incidence of prostate cancer	0.0%	0.8% per 3 month Markov model cycle	Assume some incident cases as in practice	£5871	Dominant	£749	Dominant	Dominant
12	Proportion of patients in primary care follow-up having PSA	100.0% per year	50.0% per year	It is unlikely that all patients comply and measure their PSA every year	£3401	Dominant	£587	Dominant	Dominant
14	Radical treatment: probability of erectile dysfunction	AS/WW: 50.9% RP: 85.4% RT: 62.4%	AS/WW: 70.0% RP: 90.0% RT: 80.0%	As suggested by expert the probability of erectile dysfunction is likely to be higher	£5862	Dominant	£751	Dominant	Dominant
15	Distribution of treatments for mHSPC	ADT: 50.0% DOX + ADT: 36.0% APA + ADT: 7.0% ENZA + ADT: 7.0%	ADT: 25.0% ENZA + ADT: 32.0%	Expert opinion that use of enzalutamide is growing and ADT alone is reducing	£4658	Dominant	Dominant	Dominant	Dominant
16	Exclusion of APA + ADT and ENZA + ADT for mHSPC	Included	Excluded	The model is not coded to account for the long-term benefits of these treatments	£6514	Dominant	£1540	Dominant	Dominant
17	Duration of ADT alone APA + ADT and ENZA + ADT for mHSPC	2 years	3 years	According to a SCM	£5754	Dominant	£615	Dominant	Dominant
18	Disutility for mild biopsy-related AE	−0.289 for 3 days	−0.289 for 30 days	To test sensitivity to QALY loss for less serious complications	£6642	Dominant	£729	Dominant	Dominant
19	Disutility for biopsy-related admission	−0.490 for 30 days	−0.490 for 10 days	To test sensitivity to QALY loss for serious complications	£5904	Dominant	£746	Dominant	Dominant
20			−0.490 for 90 days		£5729	Dominant	£735	Dominant	Dominant

TABLE 88 Other scenario analyses: subgroup A (first biopsy with MRI Likert score 3+) (*continued*)

					ICER (£ per QALY gained)				
					Decision question 1		Decision question 2		
	Element	Base case	Scenario analysis	Justification	LATP vs. LATRUS	LATP vs. GATP	LATP-fh vs. LATRUS	LATP-fh vs. LATP-other	LATP-fh vs. GATP
21	Disutility for patients with FN result and true MD	−0.019	−0.137	Apply the same disutility as for patients diagnosed with MD	£5884	Dominant	£747	Dominant	Dominant

AE, adverse event; APA, apalutamide; AS, active surveillance; CS, clinically significant prostate cancer; ENZA, enzalutamide; FP, false positive; HR, high-risk localised prostate cancer; LATP-fh, local anaesthetic transperineal biopsy conducted with freehand device; LR, low-risk localised prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; WW, watchful waiting.

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