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

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Inês Souto-Ribeiro, Senior Research Assistant
Lois Woods, Senior Research Assistant
Emma Maund, Research Fellow
David Alexander Scott, Principal Research Fellow
Joanne Lord, Professor, Health Economics
Joanna Picot, Senior Research Fellow
Jonathan Shepherd Principal Research Fellow

Correspondence to Dr Jonathan Shepherd
Principal Research Fellow
Southampton Health Technology Assessments Centre (SHTAC)
University of Southampton
[redacted]
Email: [redacted]

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Contributions of authors

Inês Souto-Ribeiro carried out the review of economic evaluations, developed the independent economic model, and drafted the report; Lois Woods conducted literature searches, carried out the systematic review of diagnostic test evaluation and clinical effectiveness, and drafted the report; Emma Maund carried out the systematic review of diagnostic test evaluation and clinical effectiveness, and drafted the report; David Alexander Scott conducted the network meta-analysis and drafted the report; Joanne Lord carried out the review of economic evaluations, developed the independent economic model, and drafted the report; Joanna Picot 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 carried out the systematic review of diagnostic test evaluation and clinical effectiveness, drafted the report, managed the project, and is the project guarantor.

ABSTRACT

Background

People with suspected prostate cancer are usually offered either a local anaesthetic transrectal ultrasound-guided prostate (LATRUS) biopsy or a general anaesthetic transperineal prostate (GATP) 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 (LATP) 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 LATP may also help practitioners performing prostate biopsies.

Objectives

To evaluate the clinical effectiveness and cost-effectiveness of LATP compared to LATRUS and GATP prostate biopsy for people with suspected prostate cancer, and LATP with specific freehand devices in comparison with LATRUS 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 that compared the diagnostic performance 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 studies) as well as 4 single-arm studies for freehand devices for which there was no comparative evidence. Based on the randomised studies, there were no statistically significant differences in cancer detection rates. LATP with a freehand device showed a non-significant improvement compared with LATRUS (1.40 95%CI 0.69 to 2.04), which was supported by the observational evidence. The economic analysis indicated that LATP with a freehand device is the most cost-effective strategy, with an ICER of £8,447 per QALY for people with MRI Likert score of 3 or more at first biopsy, and £18,196 per QALY for people with an MRI Likert score 1 or 2 at first biopsy.

Limitations

There is limited evidence for efficacy in detecting clinically significant cancer detection rates. There is comparative evidence for the PrecisionPoint™ Transperineal Access System but limited or no evidence for the other freehand devices. Evidence for other outcomes is sparse.

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. LATP is associated with urinary retention type complications whereas LATRUS has a higher infection rate. For people at high risk of prostate cancer, LATP biopsy with a freehand device appears to meet conventional levels of cost effectiveness.

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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.

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 (DRE) 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 5-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 an 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 whilst 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; PrecisionPoint™ Transperineal Access System (BXTAccelyon Ltd, Burnham,

UK); SureFire Guide (LeapMed, Jiangsu, China); Trinity® Perine Grid (KOELIS®, New Jersey, USA); UA1232 puncture attachment (BK Medical, Massachusetts, USA).

Objectives

The aim of this review is to evaluate the diagnostic efficacy, 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 local anaesthetic transperineal (LATP) prostate biopsies in patients with suspected prostate cancer represent a clinically and cost-effective use of 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 efficacy 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 efficacy, e.g., 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 was 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 strategy was the same as for the clinical effectiveness review, but the outcomes and study design differed. 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 our economic model.

External Assessment Group (EAG) 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 MRI results (Likert 1 or 2; or Liker 3 or more) and history of prostate biopsy (none; previous negative biopsy).

The decision tree used published results from the economic evaluation of the PROMIS study to estimate baseline prevalence in the subgroups of interest, and diagnostic performance of LATRUS biopsy. Cancer detection rates were adjusted for the other biopsy methods using relative risks 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 micro-costing analysis, as well as from submitted evidence and published sources. The Markov model was based on 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 published sources.

Results

Systematic review of diagnostic efficacy and clinical effectiveness

The literature searches identified a total of 2008 references of which 119 references were subjected to full text screening. Twenty-seven publications reported twenty-three studies meeting the inclusion criteria for this review: nineteen comparative studies of which six were randomised controlled trials and thirteen were observational studies (one of which is unpublished); and four single-arm studies for LATP-freehand devices where no comparative evidence was identified.

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 (risk ratio 1.40, 95%CI 0.96 to 2.04). This finding was supported by analysis of observational evidence, which indicated a significant advantage for LATP using a freehand device compared to LATRUS (1.21, 95%CI 1.08 to 1.34). Otherwise, there was no statistically significant differences in cancer detection rates between the biopsy methods. Evidence from the systematic review for other outcomes of interest 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 suggests that LATP using the CamPROBE freehand device is more cost-effective than LATRUS, assuming a zero rate of infection for LATP and equal diagnostic accuracy for LATP using CamPROBE and LATRUS. There is, however, a high degree of uncertainty in the study. Thirteen excluded studies were used separately to inform model structure and inputs, in particular the cost-effectiveness analysis for the PROMIS study and the analysis by the NICE Guideline Updates Team for the update of the NICE guideline on prostate cancer published in May 2019 (NG131).

Evidence from the BXTAccelyon company submission includes a cost minimisation study developed in 2020 by the York Health Consortium (YHEC) that compares the costs of LATP (with the PrecisionPoint™ freehand device) against 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 performance of the different biopsy methods.

Independent economic assessment

The base case economic analysis comparing LATP (all methods) with LATRUS and GATP indicates that LATRUS is likely to be the most cost-effective option in all four subgroups: with high ICER estimates for LATP compared with LATRUS (over £70,000 per QALY gained) and GATP being more expensive and less effective (yielding fewer QALYs) than LATP. This conclusion was supported by probabilistic sensitivity analysis, although scenario analysis based on different assumptions and sources of evidence indicated that results are sensitive to uncertainties over the relative costs and rate of hospital admissions associated with LATP and LA-TRUS.

However, results were different for the economic analysis including LATP freehand compared with other LATP methods, as well as LATRUS and GATP. This indicated that LATP with a freehand device was the most cost-effective strategy, with an ICER of £8,447 per QALY for the highest risk subgroup with MRI Likert score of 3 or more at first biopsy, and £18,196 per QALY for the subgroup with an MRI Likert score 1 or 2 at first biopsy. For the subgroups with a previous negative biopsy, the ICER is higher than £30,000 per QALY. Again, probabilistic sensitivity analysis supported this conclusion, but scenario analysis

highlighted uncertainty related to the cost of the devices and use of other sources of evidence for cancer detection rates and biopsy complication rates.

The more favourable ICER estimates for LATP with a freehand device are mostly driven by the cancer detection rates, which rests on a single randomised controlled trial 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 below £20,000 per QALY for the highest-risk subgroup. Similarly, increasing the cost of LATP with a freehand device by assuming the cost of the most expensive device (£584), the ICER remained below £20,000 per QALY for the highest-risk subgroup but not for the other subgroups (with ICERs above £30,000 per QALY).

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 randomised controlled trial, supported by observational studies suggest 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 indicted by previous MRI results. This result is sensitive to the estimated cost of the freehand device and the sources for cancer detection rates and 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 to 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 randomised controlled trial 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 multi-centre randomised study across 9 NHS Trusts in England.

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PLAIN ENGLISH 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 or through the skin of the perineum. 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 similar rates of detecting prostate cancer as the other biopsy methods. But if the clinician also used a freehand device to help 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 biopsy may be a cost-effective use of NHS resources for patients who have not had a previous prostate biopsy and have had a suspicious MRI scan.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary and list of abbreviations is provided for the non-specialist reader.

GLOSSARY

Term	Description
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.
Fusion biopsy	A fusion biopsy combines the pre-biopsy MRI 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 mpMRI 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 mpMRI and the real-time ultrasound creating a detailed 3D image for the urologist to use.
GATP grid and stepping device	For the purpose of this assessment report, 'GATP- 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.
LATP-any	For the purpose of this assessment report, 'LATP-any' refers to local anaesthetic transperineal prostate biopsy done by any

	method with the NICE scope (i.e. prostate biopsy using a grid and stepping device, a coaxial needle (‘double freehand’), or a freehand device).
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 NICE scope. This is a sub-category of the LATP-any grouping of biopsy methods.
Likert score	A Likert score is reported using a 5-point Likert scale. The Likert scale, when used in the diagnosis of prostate cancer, takes into account clinical factors and lesion size on mpMRI. 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 PI-RADS score in that it takes into account clinical factors and does not require specific sequential review of MRI sequences.
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.
PI-RADS score	The Prostate Imaging Reporting and Data System (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.
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
AEs	Adverse events
AIC	Academic in confidence
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CIC	Commercial in confidence
CNS	Clinically non-significant
CRD	Centre for Reviews and Dissemination
CS	Clinically significant
CrI	Credible interval
CT	Computerized tomography
DRE	Digital rectal examination
EAG	Evidence Assessment Group
eMIT	Electronic market information tool
EPI	ExoDx™ Prostate [Intelli-Score]
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
GATP	General anaesthetic transperineal biopsy
GP	General practitioner
HES	Hospital Episode Statistics
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
HUI	Health Utilities Index
ICER	Incremental cost-effectiveness ratio
IMRT	Intensity modulated radiation therapy

Incr	Incremental
ISPOR	The Professional Society for Health Economics and Outcomes Research
ITT	Intent to treat
IV	Intravenous
KM	Kaplan Meier
LATP biopsy	Local anaesthetic transperineal biopsy
LATRUS biopsy	Local anaesthetic transrectal ultrasound biopsy
LHRH	Luteinizing hormone-releasing hormone
LY	Life-years
LYG	Life-years gain
MD	Metastatic disease
mpMRI	Multi parametric magnetic resonance imaging
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MRU	Medical resource use
NPCA	National Prostate Cancer Audit
NG131	NICE Guideline 131
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NPCA	National Prostate Cancer Audit
NR	Not reported
OS	Overall survival
PC	Prostate cancer
PCA3	Prostate cancer antigen 3
PHI	Prostate Health Index
PI-RADS	Prostate imaging - reporting and data system
PFS	Progression free survival
PSA	Prostate specific antigen
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QALYs	Quality-adjusted life years

QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SAE	Serious adverse event
SCM	Specialist Committee Member
SD	Standard deviation
SE	Standard error
SF-6D	Short Form questionnaire-6 items
SF-12	Short Form questionnaire-12 items
SF-36	Short Form questionnaire-36 items
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TP	Transperineal biopsy
TPM	Template prostate mapping
TRUS	Transrectal ultrasound
TSD	Technical Support Document
UK	United Kingdom
US	United States
UTI	Urinary tract infection
UTIs	Urinary tract infections
VAS	Visual analogue scale
YHEC	York Health Economics Consortium

1 BACKGROUND

1.1 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 five 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.

1.1.1 Epidemiology

In 2018, there were 49,810 new diagnoses of prostate cancer in England, an increase of 7,985 more registrations than the previous year.[5] The age-standardised incidence rate in England is 204.7 per 100,000 in 2018 which has increased 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 (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] (2013-2017).[1] Cancer Research UK states that “Prostate cancer is most common in Black males, then White males and least common in Asian males”.[1]

1.2 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), NICE's guideline on suspected cancer: recognition and referral (NG12[7]) advises the following:

- Consider a prostate-specific antigen (PSA) test and digital rectal examination 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 two weeks) for prostate cancer if their:
    - PSA levels are above the age-specific reference range or
    - prostate feels malignant on digital rectal examination.

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 5-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 cancer (where 1 is very low and 5 is very

high). The 2018 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 less than 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 an 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.

1.2.1 Transrectal ultrasound (TRUS) prostate biopsy

During a TRUS prostate biopsy a transrectal ultrasound 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, and this has been accelerated over the last year due to the COVID-19 pandemic. A strategy document issued by the British Association of Urological Surgeons section of oncology for the interim management of

prostate cancer during the pandemic[15] recommended that TRUS biopsies should be avoided if possible.

1.2.2 Transperineal prostate biopsy

In common with TRUS, a transperineal prostate biopsy also uses a transrectal ultrasound 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 stepper 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 stabilizer that is either mounted onto a table or supported by a floor stand.

Transperineal prostate biopsy using a coaxial needle (double freehand)

More recent transperineal biopsy 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 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 transperineal biopsy 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 distributer 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, Massachusetts, 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 either by autoclave or immersion in a suitable disinfectant solution.

Cambridge Prostate Biopsy Device (CamPROBE) (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 is currently for research use only whilst an application for CE marking is under consideration. Full availability is anticipated in early 2022.

Trinity® Perine (KOELIS®, New Jersey, USA)
The Trinity® Perine system, manufactured by KOELIS and distributed in the UK by Kebomed UK, includes reusable guides Perine grids. The reusable guides 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 side 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 bi-plane 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 cm to 5 cm. The puncture guide fixture is compatible with 14-gauge and 18-gauge needles.

1.3 Care pathway

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

- 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 clinically significant/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.

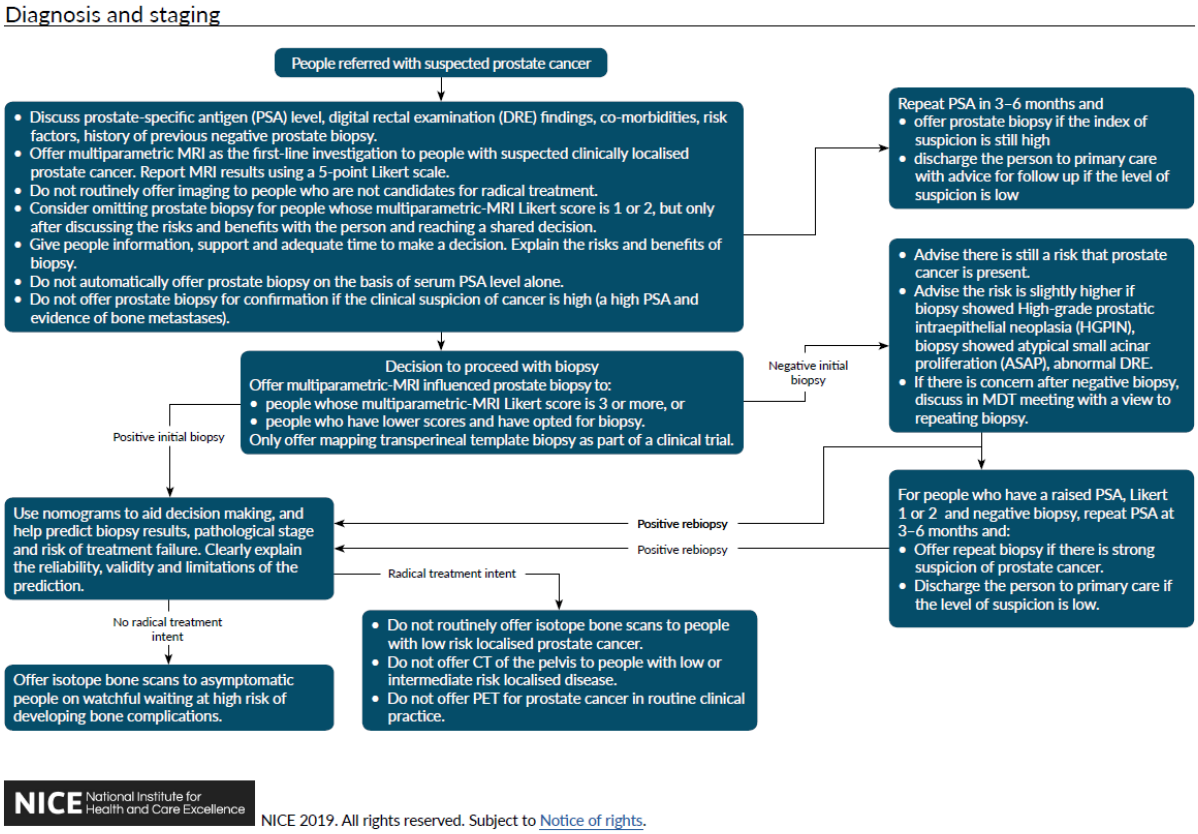


Figure 1 NICE pathway for diagnosing and staging prostate cancer

1.3.1 Clinically significant prostate cancer

When prostate cancer is diagnosed it is often distinguished in terms of whether the cancer is clinically significant or insignificant. The purpose is to assess how rapid 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 clinically significant prostate cancer. There are varying definitions available in the literature. For example, clinicians at University College London (UCL) devised criteria for defining clinically significant 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 clinically significant 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 multi-parametric MRI and TRUS biopsy in prostate cancer. [16]

The NICE clinical guideline prostate cancer diagnosis and management (NG131) defines clinically significant prostate cancer as any prostate cancer of Gleason score 7 and above. [17]

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 transperineal biopsy approach conducted under general anaesthetic (GATP) 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 local anaesthetic transperineal (LATP) prostate biopsies in patients with suspected prostate cancer represent a clinically and cost-effective use of 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?

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

2.1 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.

2.2 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 section 1.2. To recap, the six freehand devices within the NICE scope of this assessment are: PrecisionPoint™ ; EZU-PA3U; CamPROBE; Trinity® Perine; SureFire Guide and UA1232.

2.3 The comparator

There are three comparators relevant to this assessment:

- Local anaesthetic transrectal ultrasound biopsy (LATRUS)
- Local anaesthetic transperineal (LATP) biopsy using a grid or template and stepping device
- General anaesthetic transperineal biopsy (GATP) using a grid or template and stepping device

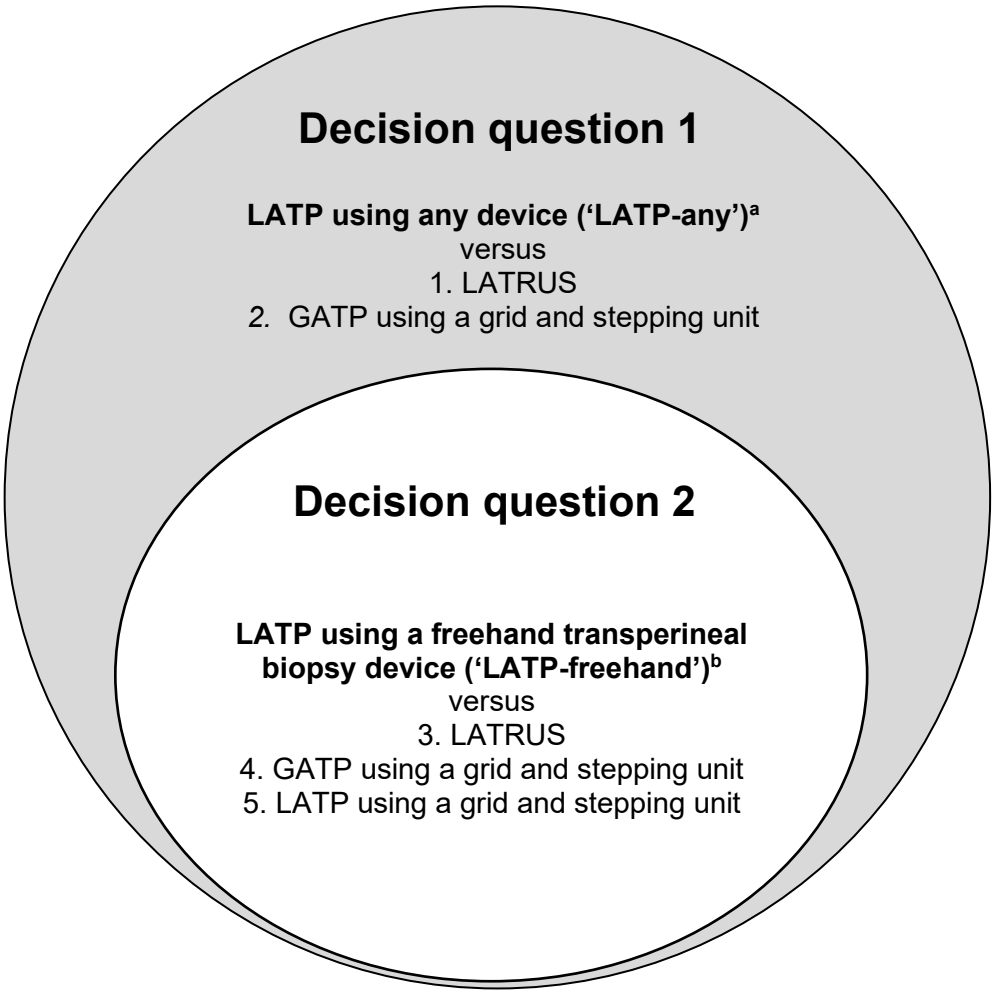
Details of these three types of biopsy are given above in section 1.2.
For each of these three comparators the biopsy could be 'targeted' (i.e. mpMRI is used to identify lesions from which a small number of tissue samples or cores are taken) or 'systematic' (multiple samples are taken from different 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.

Table 1 Interventions and comparators for each decision question

Decision question	**Decision question**
1. Do local anaesthetic transperineal prostate LATP biopsies in people with suspected prostate cancer represent a clinically and cost-effective use of NHS resources?	2. Do freehand transperineal biopsy 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	**Intervention** LATP biopsy using a freehand transperineal biopsy device within the NICE scope

freehand') or a freehand device within the NICE scope	
Comparator Local anaesthetic transrectal ultrasound prostate biopsy (LATRUS)	**Comparator** Local anaesthetic transrectal ultrasound prostate biopsy (LATRUS)
Comparator General anaesthetic transperineal prostate (GATP) biopsy using a grid and stepping device	**Comparator** General anaesthetic transperineal prostate (GATP) biopsy using a grid and stepping device
	Comparator Local anaesthetic transperineal prostate (LATP) biopsy using a grid and stepping device
NB. The shaded cell indicates that the comparator does not apply to this decision question	



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))

Figure 2 Visual summary of the decision problem for this assessment

2.4 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 health care decisions.

Intermediate outcomes evaluate the measures of the diagnostic performance of the biopsy, including measures of diagnostic accuracy (e.g. sensitivity and specificity), cancer detection rates (clinically significant/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 six months.

Clinical outcomes evaluate measures the performance of the biopsy in minimising unintended adverse effects. This is assessed in terms of 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 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.

2.5 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:

1. To conduct a systematic review of diagnostic test performance 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 reviews of cost-effectiveness studies of LATP prostate biopsies in people with suspected prostate cancer; and of health-related quality of life (utility) studies. We will take a systematic approach to identifying relevant resource use and cost data relating 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.

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 sub-sections report further detail on the methods used, noting instances where changes to the protocol were necessary, with a suitable justification.

3.1 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 9th 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 HTA 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 10th June 2021: ClinicalTrials.gov; NIHR Be Part of Research, and the NIHR Clinical Research Network Portfolio. We re-ran all of the above database searches on 19th October 2021 to identify relevant references added in the three 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; British Association of Urological Surgeons (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 companies associated with manufacture and/or distribution of the freehand transperineal biopsy 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*

3.2 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 tabulation of these criteria is included in *Appendix 2* . This table is the basis of the worksheet we used to systematically apply the criteria to each study screened.

3.2.1 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 (for example, 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.

3.2.2 Interventions and comparators

LATP 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 transperineal biopsy 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 assess differences or similarity 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 stepper 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, includes LATP using a grid and stepper unit. (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 multiparametric MRI imaging 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.

3.2.3 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 sections 4.8 to 4.10).

Intermediate and diagnostic outcomes of relevance were: measures of diagnostic accuracy (e.g. sensitivity/specificity); cancer detection rates; clinically significant 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 six 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 chapter 5).

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 outcomes of relevance were health-related quality of life; patient reported tolerability. We added biopsy procedure time to the inclusion criteria for outcomes because it impacts on the cost of the procedure.

3.2.4 Study design

Any primary comparative research study evaluating the biopsy methods outlined in the 'Interventions and comparators' subheading above are 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.

3.3 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 *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 tile 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 ERG 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 received the anaesthesia relevant to the comparison of relevance to this review was at least 70%.
- **Definitions of local anaesthesia:** local anaesthetic is 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 our inclusion criterion regarding relevant type of anaesthetic. We did not include studies describing use of sedation rather than local anaesthesia.
- **Intra-participant 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.

3.4 Data extraction strategy

Relevant data was 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 4* for the data extraction template). The extracted data was 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 multiple publications describing that study, as applicable.

3.5 Assessment of study validity

As stated in the research protocol, we planned to use the QUADAS 2 tool [18] to appraise the risk of bias of diagnostic test evaluation studies. 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 section 4), studies meeting our inclusion criteria did not evaluate the diagnostic performance of 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. [19] 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).[20] 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 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 section 4.7 and reported in full in Appendix 9.

3.6 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. This outcome was selected because it directly informs estimates of biopsy clinical effectiveness in our economic model (see section 5). 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) software to conduct pairwise meta-analysis of cancer detection rates, expressing effects as relative risks with 95% confidence intervals. We conducted pairwise meta-analyses for each biopsy comparison relevant to the decision problem (e.g. LATP versus LATRUS), where data were available. We analysed randomised and non-randomised studies separately, as recommended by methodological guidance[21], 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 (section 5.7). The NMA was restricted to RCTs and was conducted using MetaInsight software using the frequentist *netmeta*

package.[22] Effect estimates were presented as relative risks (RRs), with LATRUS as the reference treatment. We used random effects in preference to fixed-effect models due to apparent clinical heterogeneity between studies.

4 RESULTS OF CLINICAL AND DIAGNOSTIC ASSESSMENTS

4.1 Quantity and validity of research available

After removing duplicate references, a total of 1969 potentially relevant references were identified from our literature searches (run in July 2021) and other sources e.g. information submitted to NICE by stakeholder companies. Independent screening of titles and (where provided) abstracts by two reviewers determined that 1858 of these references did not meet the inclusion criteria, whilst the full text of the remaining 111 references were obtained for further screening. Of the 111 full texts, 36 were unclear whether they met our inclusion criteria. Of the 36 unclear full texts, we were able to contact 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 committee's consideration when the only alternative would be no evidence at all for these devices.

We re-ran the database search in October 2021 to identify any relevant literature published since the July 2021 search. A further 37 unique references were identified and 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 PRISMA 2020 flowchart in Figure 3 illustrates the flow of studies during the stages of screening.

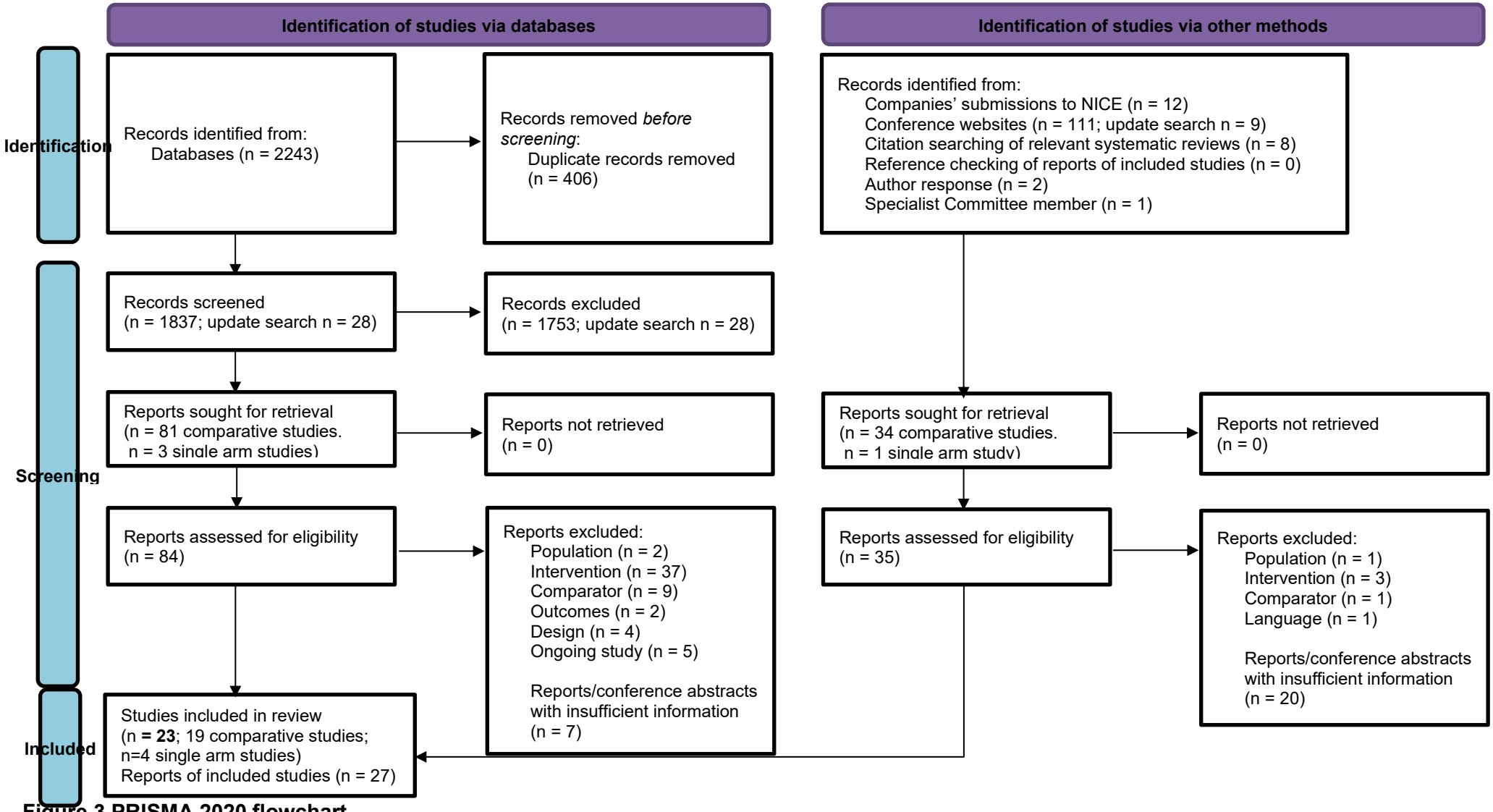


Figure 3 PRISMA 2020 flowchart

Table 2 provides an overview of the number of included studies according to their relevant decision question and comparison, and *Table 3* reports the number of included studies for each comparison grouped by study evaluation design.

Table 2 Number of included studies by comparison and decision question

Comparison (Intervention vs comparator)	Number of studies	DQ1	DQ2
1. LATP-any vs LATRUS	15	✓	
2. LATP-any vs GATP grid and stepping device	4	✓	
3. LATP-freehand vs LATRUS	7		✓
4. LATP-freehand vs GATP grid and stepping device	1		✓
5. LATP-freehand vs LATP grid and stepping device	0		✓
DQ Decision question; ✓ the comparison is primarily relevant to this decision question			

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 sub-set 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 the Table 3 (bold type is used to highlight this). Of the six freehand transperineal biopsy devices in the NICE scope, relevant comparative evidence was identified for just one device, PrecisionPoint™ (BXTAccelyon). Single arm non-comparative studies were included for the remaining devices where available.

Table 3 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 transperineal biopsy device within the NICE scope. **('LATP-freehand')**

Comparator: LATRUS (n=15 studies)
• 5 RCTs
  ○ Cerruto 2014 [23]
  ○ Guo 2015 [24]
  ○ Hara 2008 [25]
  ○ **Lam 2021 (AB)** [26]
  ○ Takenaka 2008 [27]
• 7 non-randomised prospective studies
  ○ **Bojin 2019 (unpublished slide set)** [28]
  ○ **Chen 2021** [29]
  ○ Emiliozzi 2003 [30]
  ○ **Hung 2020 (AB)** [31]
  ○ **Kum 2018 (AB)** [32]
  ○ **Starmer 2021** [33]
  ○ Watanabe 2005 [34]
• 3 retrospective studies
  ○ Abdollah 2011 [35]
  ○ Jiang 2019 [36]
  ○ **Szabo 2021**[a] [37]
	Comparator: LATRUS (n=7 studies)
	• 1 RCT
	  ○ **Lam 2021 (AB)** [26] (PrecisionPoint™)
	• 5 non-randomised prospective studies
	  ○ **Bojin 2019 (unpublished slide set** [28] (PrecisionPoint™)
	  ○ **Chen 2021** [29] (PrecisionPoint™)
	  ○ **Hung 2020 (AB)** [31] (PrecisionPoint™)
	  ○ **Kum 2018 (AB)** [32] (PrecisionPoint™)
	  ○ **Starmer 2021** [33] (PrecisionPoint™)
	• 1 retrospective study
	  ○ **Szabo 2021** [37] (PrecisionPoint™)

Comparator: GATP using a grid and stepping device (n=4 studies)
• 1 RCT
  ○ Lv 2020 [38]
• 2 Non-randomised prospective studies
  ○ Takuma 2012 (AB) [39]
  ○ Walters 2021 (AB) [40]
• 1 retrospective study
  ○ **Rij 2020 (AB)** [41]
	Comparator: GATP using a grid and stepping device (n=1 study)
	• 1 retrospective study
	  ○ **Rij 2020 (AB)** [41] (PrecisionPoint™)

	Comparator: LATP using a grid and stepping device No studies met inclusion criteria

	Comparator: None[b]
	• 4 prospective single-arm studies:
	  ○ Gnanapragasam 2020 [42] (CamPROBE)
	  ○ Lau 2020 (AB) [43] (UA1232)
	  ○ Yamamoto 2019 (AB) [44] (UA1232)
	  ○ Yamamoto 2020 (AB) [45] (UA1232)

AB means publication by conference abstract
[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.

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; AB: conference abstract.

4.2 Characteristics of studies comparing LATP prostate biopsy by any method versus LATRUS prostate biopsy (decision question 1)

4.2.1 Overview of general study characteristics

Table 4 gives an overview of the LATP prostate biopsy versus LATRUS biopsy studies included in the review.

Table 4 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 [23]	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 [24]	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 [25]	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 [26]	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 [27]	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 [28]	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 [29]	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 [30]	Italy. Single centre	Prospective single cohort study; transperineal and transrectal biopsies obtained in all	TRUS guided LATP biopsy (device not reported); n=107	LATRUS biopsy; n=107	Prostate biopsy naïve participants with suspected prostate cancer

		patients in the same session; n=107			
Hung et al 2020 [31]	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
Kum et al 2018 [32]	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 [33]	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 [34]	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 [35]	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 [36]	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 [37]	USA. Single centre	Retrospective case series; n=375	(i) Ultrasound guided LATP biopsy using the PrecisionPoint™ freehand device n=242; (ii) 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
LATP Local anaesthetic transperineal biopsy; LATRUS Local anaesthetic transrectal ultrasound biopsy; RCT Randomised controlled trial.					

Of the fifteen included studies comparing LATP-any versus LATRUS biopsies, five are RCTs, seven prospective cohort studies, and three retrospective cohort studies.

The RCTs were conducted in Japan (Hara et al 2008 [25], Takenaka et al 2008 [27]), China (Guo et al 2015 [24]), Hong Kong (Lam et al 2021 [26])) and Italy (Cerruto et al 2014 [23]), 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 (Cerruto et al 2014 [23]), another used an unnamed attachment for needle guidance (Takenaka et al 2008 [27]), another used PrecisionPoint™ (Lam et al 2021 [26]), and two studies did not specify a device (Guo et al 2015 [24], Hara et al 2008 [25]).

The seven prospective cohort studies are all single centre studies, set in England (Bojin 2019 [28], Kum et al 2018 [32], Starmer et al 2021 [33]), Hong Kong (Hung et al 2020 [31]), Japan (Watanabe et al 2005 [34]) and Italy (Emiliozzi et al 2003 [30]). They comprise two studies which carried out both transperineal and transrectal biopsies in the same participants in the same session (Emiliozzi et al 2003 [30], Watanabe et al 2005 [34]), three studies where the LATRUS arm is a historical comparison group [28] Chen et al 2021 [29], Kum et al 2018 [32]), one study that assigned participants to study arms according to pre-biopsy MRI findings and other criteria (Starmer et al 2021 [33]), and one study that does not report how it assigned participants to study arms (Hung et al 2020 [31]).

The participants in the two 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 (Bojin 2019 [28], Kum et al 2018 [32], Starmer et al 2021 [33]), as did the Hong Kong study (Hung et al 2020 [31]), and the earlier studies do not report any device (Emiliozzi et al 2003 [30], Watanabe et al 2005 [34]).

One of the studies (Hung et al 2020 [31]) is reported only in a conference abstract and another is an unpublished slide set presentation (Bojin 2019) [28] and so they have limited information. The other studies are reported in full publications.

The retrospective studies were set in Italy (Abdollah et al 2019 [35]), China (Jiang et al 2019 [36]) and the USA (Szabo et al 2021 [37]). The Italian and Chinese studies were multi-centre (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 (Abdollah et al 2019 [35]), one study consists entirely of biopsy naïve participants (Jiang et al 2019 [36]), and one study included a mixed population of biopsy naïve, repeat biopsy and active surveillance participants (Szabo et al 2021 [37]). Two studies performed propensity score matching of the participants: one study reports propensity score matched results only (Abdollah et al 2011 [35]) and the other reports both the unmatched and propensity score matched results (Jiang et al 2019 [36]). The LATP techniques varied according to device used: one study used a coaxial needle (Abdollah et al 2011 [35]), one study used the PrecisionPoint™ freehand device (Szabo et al 2021 [37]), and one study did not report using a device (Jiang et al 2019 [36]).

4.2.2 Details of LATP-any biopsy procedures

Table 5 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 50ml (Guo et al 2015 [24]), and another study reports that the samples were spaced 1 cm apart (Szabo et al 2021 [37]).

Where targeted biopsy sampling was performed this could be in addition to systematic sampling biopsies, or targeted sampling alone (Kum et al 2018 [32]). Reasons to prompt additional targeted sampling were: suspicious areas detected by TRUS or DRE (Guo et al 2015 [24]), any hypoechoic areas noted (Emiliozzi et al 2003 [30]), PI-RADS score >2 on pre-biopsy mpMRI (Starmer et al 2021 [33]), hypoechoic lesions or palpable nodules on DRE (Watanabe et al 2005 [34]), or participants with pre-biopsy mpMRI PI-RADS score of 4 or 5 (Szabo et al 2021 [33]).

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.

Table **5 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 [23]	Coaxial needle	Systematic	14	Not reported	TRUS	Mepivacaine (1%) 2 ml at the level of the prostate apex.
Guo et al 2015 [24]	Not reported[a]	Systematic	12 cores if PV >50ml; 8 cores if PV <50ml; 2 cores per suspicious area detected by TRUS/DRE	Not reported	TRUS	Periprostatic nerve block: lidocaine (2%) 2ml; additional lidocaine (2%) 2ml administered where participant could not tolerate pain.
Hara et al 2008 [25]	Not reported[a]	Systematic	12	Not reported	TRUS	Spinal anaesthesia: bupivacaine (0.5%)
Lam et al 2021 [26]	Freehand PrecisionPoint™	Systematic	Not reported (modified Ginsburg protocol)	Not reported	Not reported	Local anaesthetic (details not reported)
Takenaka et al 2008 [27]	Attachment for needle guidance	Systematic	12	Not reported	TRUS	"Saddle blockade": bupivacaine (0.5%)
Other prospective studies						
Bojin [2019][28]	Freehand PrecisionPoint™	Systematic and targeted	Not reported (up to 24 for participants needing the full template)	Unclear	TRUS	Peri-prostatic block: lignocaine (1%) 13-20mls
Chen et al 2021 [29]	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%) 10ml given on each side.
Emiliozzi et al 2003 [30]	Not reported[a]	Targeted and systematic (Fan technique but any hypoechoic	6	Not reported	TRUS	Mepivacaine (2%) two 10ml transperineal injections, one in each lobe.

Study	LATP device/ approach	Sampling	Number of cores taken	Pre-biopsy imaging (MRI)	Prostate biopsy image guidance	Anaesthesia
		area was also included)				
Hung et al 2020 [31]	Freehand PrecisionPoint™	Not reported	Not reported	Not reported	Not reported	Local anaesthetic (details not reported).
Kum 2018 [32]	Freehand PrecisionPoint™	Systematic (52%), targeted (25%), and systematic and targeted (23%).	Not reported	Not reported	TRUS	Lidocaine (1%) approximately 10-12mls (up to 30mls 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 [33]	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%) 10ml[a] and chirocaine[b] (0.5%) 10ml.
Watanabe et al 2005 [34]	Not reported[a]	Systematic with additional targeted biopsies for any hypoechoiec lesions or palpable nodules on DRE	6	Not reported	Ultrasound	Spinal anaesthesia (details not reported).
Retrospective studies						
Abdollah et al 2011 [35]	Coaxial needle	Saturation	24	Not reported	TRUS	Anaesthetic block of the periprostatic plexus: mepivacaine (1%) 2ml at prostate apex.
Jiang et al 2019 [36]	Not reported[a]	Systematic	12	Pre-biopsy MRI	TRUS	Subcutaneous infiltration plus periprostatic nerve block: lidocaine (1%)

Study	LATP device/ approach	Sampling	Number of cores taken	Pre-biopsy imaging (MRI)	Prostate biopsy image guidance	Anaesthesia
				performed in some participants (proportion not reported).		
Szabo et al 2021 [37]	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 1cm apart).	31% had pre-biopsy MRI	Ultrasound	Lidocaine gel (2%) 10ml into the rectum and lidocaine (0.5%) 5ml mixed with 8.4% sodium bicarbonate injected into the perineal skin; additional 10ml anaesthetic solution infiltrated into the ischiorectal fat, pelvic diaphragm, and periapical triangle. Maximum dose: 4.5mg/kg.
Szabo et al 2021 [37]	Freehand co-axial needle (without PrecisionPoint™)	Not reported	Not reported	Not reported	Not reported	Not reported

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

4.2.3 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 (*Table 6*).

Table 6 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 [23] *LATP* *LATRUS*	66.50 (8.87) 67.30 (8.05)	15.95 (41.04) 12.36 (36.95)	56.29 (31.33) 61.49 (33.39)	11/54 (20.37) 10/54 (18.2)	Not reported Not reported
Guo et al 2015 [24] *LATP* *LATRUS*	67.18 (6.76) 67.35 (7.28)	8.81 (3.6–56.0)[a] 10.48 (6.2–69.0)[a]	47.2 (12.9–97.7) 45.9 (20.0–98.0)	20/173 (11.6) 19/166 (11.5)	40/173 (23.1)[b] 30/166 (20.1)[b]
Hara et al 2008 [25] *LATP* *LATRUS*	71.0 (7.29) 71.7 (7.55)	8.34 (3.44) 8.48 (3.90)	33.2 (15.2) 36.0 (17.1)	14/126 (11) 22/120 (18)	23/126 (18)[b] 12/120 (10)[b]
Lam et al 2021 [26] *LATP* *LATRUS*	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported	Not reported Not reported
Takenaka et al 2008 [27] *LATP* *LATRUS*	71.1 (7.53) 72.1 (7.42)	17.1 (30.1) 19.6 (43.2)	34.5 (18.9)[c] 37.2 (19.7)[c]	16/100 (16) 28/100 (28)	28/100 (28)[b] 22/100 (22)[b]
Other prospective studies					
Bojin 2019 *LATP* *LATRUS*	65 (45-82)[e] 69 (43-88)[e]	10.5 (3.6-89)[i] 32.44 (1-1581)[i]	57 (15-210)[e] 51.6 (16-175)[e]	Not reported Not reported	Unclear Unclear
Chen et al 2021 [29] *LATP* *LATRUS*	69.40 (7.75) 68.24 (7.98)	13.17 (6.82–47.13)[a] 10.76 (6.45–50.97)[a]	45.08 (26.78)[c] 49.62 (27.76)[c]	102/205 77/177	Unclear Not reported
Emiliozzi et al 2003 [30] *LATP & LATRUS*[d]	68 (52-88)[e]	8.2 (4.1 to 240)[e]	Not reported	26/107 (24)	29/107 (27)[b]
Hung et al 2020 [31] *LATP & LATRUS*[f]	Median 68	7.66 (3.23)	Not reported	Not reported	Not reported
Kum et al 2018 [32] *LATP* *LATRUS*	65 (36-83)[e] Not reported	7.9 (0.7-1374)[e] Not reported	45 (15-157)[e] Not reported	Not reported Not reported	Not reported Not reported

Starmer et al 2021 [33] *LATP* *LATRUS*	66.8 (53-80)[g] 66.5 (52-78)[g]	10.7 (2.2–55.6)[g] 18.15 (1.2–160)[g]	47.8 (20–100)[gh] 48.0 (14–147)[gh]	Not reported Not reported	Not reported Not reported
Watanabe et al 2005 [34] *LATP & LATRUS*[d]	72.5 (41 to 98)[e]	Median 10.3	Not reported	130 (32.3)	Not reported
Retrospective studies					
Abdollah et al 2011 [35] *LATP* *LATRUS*	66.4 (52.0-79.0)[e] 66.2 (47.6-82.1)[e]	10 (0.9 to 31.5)[e] 9.7 (2.1 to 26.2)[e]	62.3 (17.0-98.0)[c] 65.4 (15.0-93.0)[c]	15/140 (10.7) 16/140 (11.4)	Not reported Not reported
Jiang et al 2019 [36] *LATP* *LATRUS*	69.72 (8.93) 69.20 (8.03)	38.02 (91.11) 40.31 (130.08)	51.75 (23.94)[c] 59.64 (33.44)[c]	Not reported Not reported	Not reported Not reported
Szabo et al 2021 [37] *LATP using PrecisonPoint* *LATP coaxial needle* *LATRUS*	63 (9) Not reported Not reported	7.2 (7.7) Not reported Not reported	50 (35.7)[c] Not reported Not reported	Not reported Not reported Not reported	Not reported Not reported Not reported

SD: standard deviation; [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)

Age is reported in various combinations of mean or median with IQR, range or SD, however, the average age of participants would appear to be between 63 and 72 years across all studies. PSA level is also reported in various combinations of mean or median with IQR, range or SD, however, it can be seen that studies average levels either around 7-8ml or around 12-19ml, with one of the retrospective studies having participants with PSA levels 38-40 (Jiang 2019). Prostate volume is measured variously in different units (mL, cc or cm^3) making it difficult to compare. Only five studies reported PSA density (Takenaka et al 2008 [27], Bojin 2019,[28] Chen et al 2021 [29], Kum et al 2018 [32], Szabo et al 2021 [37]) with the RCT's participant's PSA density being slightly higher than the others (Takenaka et al 2008 [27]).

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 (Kum et al 2018 [32]). The other reports the proportion of participants with PI-RADS 4 or 5 (Szabo et al 2021 [37]). None reported the location of lesions identified in pre-biopsy imaging.

Two studies reported BMI (Cerruto et al 2014 [23], Guo et al 2015 [24]), one study reported ethnicity (Szabo et al 2021 [37]). 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).

4.2.4 Summary

The comparison of LATP-any vs 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 transperineal 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 whole evidence base as a whole.

4.3 Characteristics of studies comparing LATP prostate biopsy by any method versus GATP prostate biopsy using a grid and stepping device (decision question 1)

4.3.1 Overview of general study characteristics

Table 7 gives an overview of the four studies comparing LATP-any biopsy versus GATP biopsy with grid and stepping device. Three of the studies [39])[40 41] are available only as conference abstracts currently, thus some of the necessary detail in the following sub-sections are limited.

Table **7 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 [38]	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)[39]	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 1 or more previous negative biopsies.
Walters et al 2021 (AB)[40]	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 transperineal biopsy identified from a prospective prostate cancer diagnostic registry.
Retrospective studies					
Rij et al 2020 (AB) [41]	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 transperineal biopsy. Prior biopsy experience and reasons for suspected prostate cancer are not reported.
AB refers to conference abstract					

Of the four studies, one was an RCT set in China (Lv et al 2020 [38]), two were prospective non-randomised studies set in England (Walters et al 2021 [40]) and Japan (Takuma et al 2012 [39]) respectively, whilst the fourth was a retrospective study set in New Zealand. (Rij et al 2020 [41])

One study (Lv et al 2020[38] used a grid and stepping device to perform LATP biopsy; another performed LATP using the PrecisionPoint™ freehand device (Rij et al 2020)[41] and two studies did not specify use of a device (Walters et al 2021 [40], Takuma et al 2012[39]).

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.[39]

4.3.2 Details of LATP-any biopsy procedures

Table 8 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.

Table 8 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 [38]	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%) 5ml and 1:200,000 adrenaline. Followed by deep periprostatic anaesthesia on right then left side of prostate.
Other prospective studies						
Takuma et al 2012 [39]	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 [40]	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Retrospective studies						
Rij et al 2020 [41]	Freehand Precision Point™	Systematic (Ginsburg consensus method); plus targeted for 88% participants with an 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).

4.3.3 Participant characteristics

Available information on the characteristics of study participants (e.g. age, PSA level, prostate volume) is extremely limited, and only one study[38]) adequate detail (*Table 9).*

Table 9 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 [38] *LATP* *GATP*	66.50 (9.48) 67.06 (7.55)	22.00 (22.59) 22.97 (24.78)	53.05 (15.43) 54.00 (19.04)	90/108 (83.33) 81/108 (75.00)	105/108 (97.22) 102/108 (94.44)
Other studies (observational)					
No information reported by: Takuma et al 2012 [39] Walters et al 2021 [40] Rij et al 2020 [41]					

The RCT (Lv et al 2020 [38]) also reports weight and height, but not BMI. Likert or PI-RADS scores are not reported. The paper describes the ethnicity of the participants as Asian.

4.3.4 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 and limited information is available.

4.4 Characteristics of studies comparing LATP prostate biopsy using a freehand device versus LATRUS prostate biopsy (decision question 2)

4.4.1 Overview of general study characteristics

Seven studies were identified that compare LATP biopsy using a freehand device compared with LATRUS biopsy. All freehand devices are the PrecisionPoint™ device. See Table 9

below. In contrast, only one study compares LATP biopsy using a specific freehand device with GATP (n=1, PrecisionPoint™ device), see Table 10 below. 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 [42]. Three conference abstracts report three separate single cohort studies that used the UA1232 device [43] [44] [45]. See Table 11 below.

Table 10 gives an overview of the LATP-PrecisionPoint™ vs LATRUS biopsy studies.

Table 10 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 [26]	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 [28]	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 [29]	Singapore . Single centre	Prospective cohort with historical comparison group; n=390	TRUS guided LATP biopsy using the PrecisionPoint™ device; n=212	LATRUS biopsy; n=178	Prostate biopsy naïve participants (>90%)
Hung et al 2020 [31]	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 [32]	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 [33]	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 [37]	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
LATP Local anaesthetic transperineal biopsy; LATRUS Local anaesthetic transrectal ultrasound biopsy; RCT Randomised controlled trial					

Of the seven studies comparing LATP-PrecisionPoint™ to LATRUS, one is an RCT (Lam et al 2021 [26]), five were prospective cohorts (Bojin 2019) [28] Chen et al 2021 [29], Hung et al 2020 [31], Kum et al 2018 [32], Starmer et al 2021 [33]), and one was a retrospective case series (Szabo et al 2021 [37]). 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 (Chen et al 2021 [29],) and 24 cores (Bojin 2019) [28]

4.4.2 Participant characteristics

Participant characteristics are reported for the LATP freehand device PrecisionPoint™ versus LATRUS studies and are summarised in *Table 11* below.

Table 11 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[26] LATP LATRUS	 Not reported Not reported	 Not reported Not reported	 Not reported Not reported	 Not reported Not reported	 Not reported Not reported
Other prospective studies					
Bojin 2019 [28] LATP LATRUS	 65 (45-82)[e] 69 (43-88)[e]	 10.5 (3.6-89)[i] 32.44 (1-1581)[i]	 57 (15-210)[e] 51.6 (16-175)[e]	 Not reported Not reported	 Unclear Unclear
Chen et al 2021 [29] LATP LATRUS	 69.40 (7.75) 68.24 (7.98)	 13.17 (6.82–47.13)[a] 10.76 (6.45–50.97)[a]	 45.08 (26.78)[c] 49.62 (27.76)[c]	 102/205 77/177	 Unclear Not reported
Hung et al 2020 [31] LATP & LATRUS[f]	 Median 68	 7.66 (3.23)	 Not reported	 Not reported	 Not reported
Kum et al 2018 [32] LATP using PrecisionPoint™ LATRUS	 65 (36-83)[a] Not reported	 7.9 (0.7-1374)[a] Not reported	 45 (15-157)[a] Not reported	 Not reported Not reported	 Not reported Not reported
Starmer et al 2021 [33] LATP using PrecisionPoint™ LATRUS	 66.8 (53-80)[b] 66.5 (52-78)[b]	 10.7 (2.2–55.6)[b] 18.15 (1.2–160)[b]	 47.8 (20–100)[bc] 48.0 (14–147)[bc]	 Not reported Not reported	 Not reported Not reported
Retrospective studies					
Szabo et al 2021 [37] LATP using PrecisonPoint LATRUS	 63 (9) Not reported	 7.2 (7.7) Not reported	 50 (35.7)[d] 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

4.4.3 Summary

The evidence for this comparison (LATP-freehand vs LATRUS, decision question 2) is a subset of the evidence for the LATP-any vs 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.

4.5 Characteristics of studies comparing LATP prostate biopsy using a freehand device versus GATP prostate biopsy by grid and stepping device (decision question 2)

4.5.1 Overview of general study characteristics

Table 12 gives an overview of the single study comparing LATP-PrecisionPoint™ versus GATP biopsy (Rij et al 2020).[41]).

Table 12 Overview of included studies for decision question 2 (LATP using a freehand device versus GATP)

Study	Country. No. centres	Design	Intervention	Comparator	Study population
Retrospective					
Rij et al 2020 [41]	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 transperineal biopsy. Prior biopsy experience and reasons for suspected prostate cancer are not reported.

Rij et al 2020 report a retrospective cohort study conducted in a single centre in New Zealand. [41] 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

4.6 Characteristics of single arm studies evaluating LATP biopsy using a freehand device where no comparative evidence was identified

4.6.1 Overview of general study characteristics

No comparative evidence was identified for the LATP freehand devices CamPROBE, UA1232, SureFire, EZU-PA3U and Trinity® Perine Grid. Therefore, we included any single-arm studies that were identified. Even so, we did not identify any evidence for 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 13* gives an overview of the CamPROBE and UA1232 studies.

Table 13 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 [42]	England. Multicentre (a lead centre provided training to the 5 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 [43]	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 [44]	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 [45]	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

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

population. The indications for prostate biopsy were not reported and two devices were used per patient per biopsy; one 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. 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.

4.6.2 Participant characteristics

The reporting of participant characteristics for the single arm studies for CamPROBE and UA1232 is minimal: the CamPROBE study (Gnanapragasam et al 2020 [42]) reports participants' median and range for age; and one of the UA1232 studies (Lau et al 2020 [43]) reports median age and median PSA level.

4.6.3 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[42] with a small population; and UA1232 with limited information from three conference abstracts.[43-45] There is no evidence for the other devices in the NICE scope. Details of study characteristics and participant characteristics are limited.

4.7 Critical appraisal of study validity

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.

4.7.1 Critical appraisal of RCTs

We used the Cochrane risk of bias tool (version 1) [19] to critically appraise the six RCTs in our review.[23] [24] [25] [26] [38] [27] The tool covers five domains, each representing one or more types of bias related to study conduct. Judgements are expressed in terms of high, low or unclear risk of bias for each domain.

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, including a tabulation (Table 14), of our findings; full details are reported in Appendix 5

Table 14 Summary risk of bias assessments of RCTs

	Random sequence generation	Allocation concealment	Blinding (participants; personnel)	Blinding (outcome assessors)	Incomplete outcome data	Selective reporting
Study						
Cerruto et al 2014 [23]	Unclear	Unclear	High	Unclear	Low	Unclear
Guo et al 2015 [24]	Low	Unclear	High	Low	Low	Low
Hara et al 2008 [25]	Unclear	Unclear	High	Unclear	Low	Unclear
Lam et al 2021 [26]	Unclear	Unclear	High	Unclear	Low	Unclear
Lv et al 2020 [38]	Low	Unclear	High	Unclear	Low	Unclear
Takenaka et al 2008 [27]	Unclear	Unclear	High	Unclear	Low	Unclear

There was a lack of detail given on the methods used for random sequence generation in four of the trials, [23 25 26 27] 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.[23 25 26 27] The trial by Guo et al (2015)[24] was at low risk of bias for the greatest number of domains. Specifically, low risk of detection bias due to blinding of the outcome assessor (pathologist), low risk 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.

4.7.2 Critical appraisal of observational studies

We used the checklists from the Joanna Briggs Institute (JBI) suite of critical appraisal tools to critically appraise observational studies.[20] The checklists address factors such confounding, validity and reliability of data collection and analysis, bias from loss to follow up and statistical analysis. We edited questions two and three in the checklist for cohort studies to replace ‘exposures’ with relevant biopsy details. Responses are expressed as yes, no, unclear or not applicable, and we have commented below in terms of low, unclear, or high risk of bias according to the relevant domains of bias. Eleven of the 13 observational studies were assessed using the JBI checklist for cohort studies[46] and the remaining two studies were assessed using the JBI checklist for case series.[47]

Most of the cohort studies recruited biopsy comparison groups from the same or 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, e.g., 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 to 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.

Table 15 and *Table 16* below summarise our critical appraisal judgements for the cohort studies and the case series respectively. Further details of our assessments are in *Appendix 5.*

Table 15 Summary of Risk of Bias assessments of cohort studies (n=11)

JBI Checklist for cohort studies [46]	Number of cohort studies to which the EAG judgment applies (n=11)			
	Yes	**No**	**Unclear**	**Not applicable**
1. Were the two groups similar and recruited from the same population?	7[b]	1[b]	4	0
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]	9	1	1	0
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]	6	0	5	0
4. Were confounding factors identified?	4	4	1	2
5. Were strategies to deal with confounding factors stated?	4	5	0	2
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	5	0	6	0
7. Were the outcomes measured in a valid and reliable way?				
Outcome: cancer detection rates	8	0	3	0
Outcome: complications	1	0	5	5
Outcome: pain/tolerability	1	0	2	8
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	2[c]	0	7[c]	3
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	2[d]	0	8[d]	2
10. Were strategies to address incomplete follow up utilized?	0	0	9	2
11. Was appropriate statistical analysis used?	10	0	1	0

[a] Questions edited by EAG to accommodate biopsy methods as an 'exposure'; [b] one study both 'Yes' and 'No' – clear inclusion criteria, clear reporting, participants allocated to groups for different reasons; [c] one study both 'Unclear' and 'Not applicable' for different outcomes; [d] one study both 'Yes' and 'Unclear' for different outcomes;

Table 16 Summary of Risk of Bias assessments of case series studies (n=2)

JBI Checklist for case series[47]	Number of case series to which the EAG judgment applies (n=2)			
	Yes	**No**	**Unclear**	**Not applicable**
1. Were there clear criteria for inclusion in the case series?	0	2	0	0
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	1	0	1	0

3. Were valid methods used for identification of the condition for all participants included in the case series?	0	0	2	0
4. Did the case series have consecutive inclusion of participants?	2	0	0	0
5. Did the case series have complete inclusion of participants?	2	0	0	0
6. Was there clear reporting of the demographics of the participants in the study?	0	1	1	0
7. Was there clear reporting of clinical information of the participants?	0	1	1	0
8. Were the outcomes or follow-up results of cases clearly reported?	1	0	1	0
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	0	0	2	0
10. Was statistical analysis appropriate?	1	0	1	0

4.8 Intermediate outcomes

Below we present a synthesis of outcomes measuring the diagnostic performance of LATP prostate biopsy in suspected prostate cancer. We take each relevant outcome measure in turn and present study results according to the biopsy comparisons relevant to this assessment (see Table 2).

4.8.1 Prostate cancer detection (LATP-any biopsy versus LATRUS, 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 2021 did not report this outcome. [33] In marked contrast, clinically significant prostate cancer detection, informative for assessing the risk of rapid cancer progression, was reported in just five studies (Bojin (2019) [28], Hung et al 2020 [31], Kum et al 2018 [32], Lam et al 2021 [26], Szabo et al 2021 [37]). Table 17 reports study cancer detection rates, including clinically significant cancer rates, where available.

Table 17 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 [23]	Cancer detection rate, n/N (%)	24/54 (44.4)	25/54 (46.29)	0.846
Guo et al 2015 [24]	Cancer detection rate: positive rate, n/N (%)	61/173 (35.3)	53/166 (31.9)	0.566
Hara et al 2008 [25]	Cancer detection rate, n/N (%)	53/126 (42.1)	58/120 (48.3)	0.323
	Cancer detection rate, n/N (%)	47/134 (35.1)	33/132 (25.0)	<0.05

Study	Outcome measure	Intervention LATP-any	Comparator LATRUS	Statistical significance (p-value)
Lam et al 2021 [26]	Clinically significant cancer detection rate[a]	22/134 (16.4)	19/132(14.4)	p=0.74
Takenaka et al 2008 [27]	Cancer detection rates overall, n/N (%)	47/100 (47)	53/100 (53)	0.333
Other prospective studies				
Bojin (2019) [28]	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
	Clinically significant cancer pick up, n/N (%)[b]	51/76 (67.1)	48/117 (41.2)	Not reported
Chen et al 2021 [29]	Cancer detection rate in biopsy naïve patients, n/N (%)	127/200 (63.5)	86/172 (50)	0.0115
Emiliozzi et al 2003 [30]	Cancer detection rate, n/N (%)[c]	43/107 (40)	34/107 (32)	0.012
Hung et al 2020 [31]	Cancer detection rate (%)	20/63 (31.7)	14/57 (24.6)	0.851
	Clinically significant prostate cancer, (%)	57.1	45.0	0.501
Kum et al 2018 [32]	Cancer detection rate, overall n/N (%)	139/176 (79)	Not reported	Not reported
	Clinically significant cancer detection [d e] n/N (%) Systematic	28/46 (60.9)	25/43 (58.1)	P=0.80
	Targeted & systematic	29/35 (82.9)	Not reported	Not reported
	Targeted	33/38 (86.8)	Not reported	Not reported
Takuma et al 2012 [39]	Cancer detection rate, overall n/N (%)	9/37 (24)	15/29 (51)	0.041
Walters et al 2021 [40]	Histology outcomes	"No significant differences in histology outcome" between the different anaesthetic methods		Not reported
Watanabe et al 2005 [34]	Positive biopsy, n/N (%)	166/402 (41.3)	161/402 (40.0)	Not reported
Retrospective studies				
Abdollah et al 2011 [35]	Prostate cancer diagnosis rate, n/N (%)	36/140 (25.7)	44/140 (31.4)	0.3
Jiang et al 2019 [36]	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 I [37]	Overall cancer detection rate, n/N (%)	105/242 (43.4)	52/133 (39)	0.4451
Szabo et al II [37]	Overall cancer detection rate, n/N (%)	20/62 (32)	52/133 (39)	Not reported
Szabo et al I & II [37]	Clinically significant cancer detection rate, n/N (%)[f]	35/242 (14)	Not reported	Not reported

LATP Local anaesthetic transperineal biopsy; LATRUS Local anaesthetic transrectal ultrasound biopsy; RCT Randomised controlled trial.

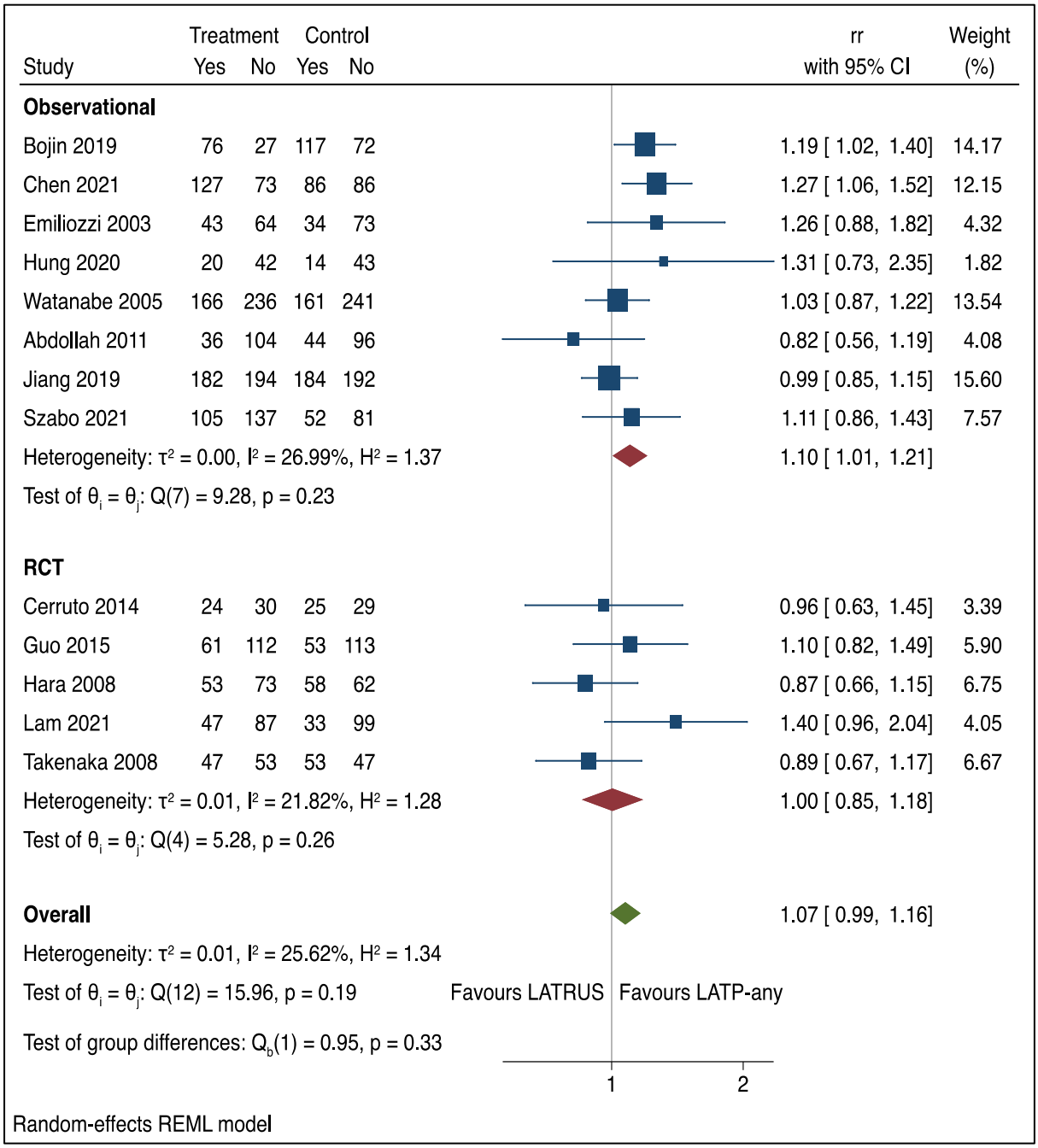
Szabo I refers to the comparison of LATP using PrecisionPoint™ Transperineal Access System vs LATRUS from this study; Szabo II refers to the comparison of LATP using a coaxial needle sheath vs LATRUS from this study.

[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

There was variation between the studies in overall cancer detection rates, which highlights the heterogeneous evidence base. In terms of differences in detection rates between LATP and LATRUS, the results are mixed. Some studies reported similar detection rates between, whilst others reported differences. There isn't 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 prevalent use 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 study participant random allocation to LATP biopsy or LATRUS biopsy.

We conducted a pairwise meta-analysis of LATP versus LATRUS on cancer detection rates and clinically significant cancer detection rates, based on the data in Table 17. Given the apparent clinical heterogeneity between studies we considered it appropriate to use random effects rather than a fixed-effect model. RCT and observational evidence were pooled separately in the meta-analysis.

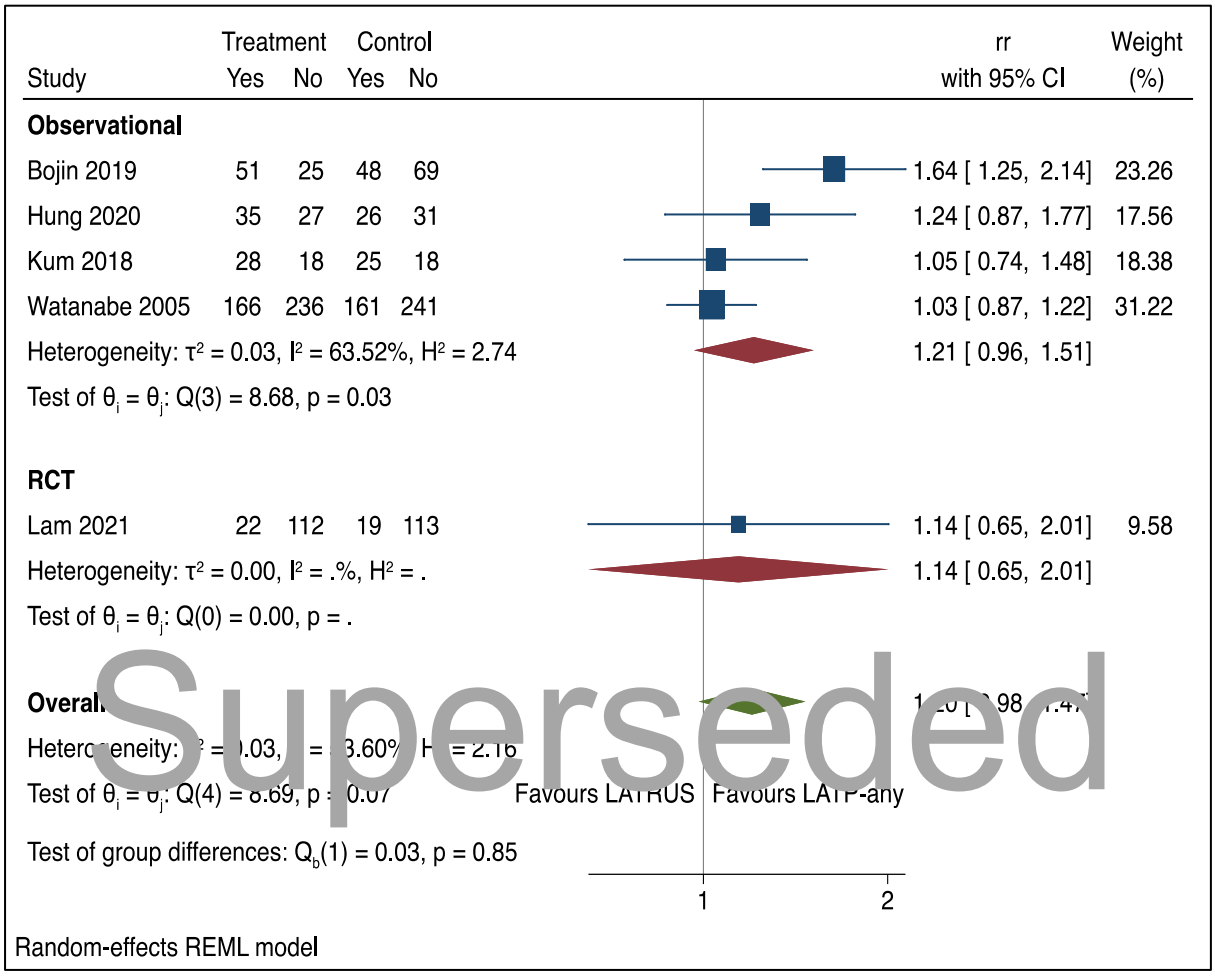
Figure 4 shows the distribution of individual study effect estimates and the pooled effect estimate, expressed as relative risks (RR) for detection of prostate cancer. The overall finding is that there is no statistically significant difference between LATP-any biopsy and LATRUS biopsy in detection of prostate cancer. Heterogeneity was not statistically significant as reflected by relatively narrow confidence intervals for the pooled effect estimates. There is little difference in pooled effect estimates between the RCT evidence and the observational evidence, indicating good consistency. These factors increase the certainty of the meta-analysis results, however, caution is advised given that the overall risk of bias in the RCTs is unclear due to limited available study details (see section 4.7). Furthermore, although there was no apparent statistical heterogeneity we do note the presence of clinical heterogeneity across the studies.



REML = Random effects maximum likelihood

Figure 4 Meta-analysis forest plot of cancer detection rates for LATP-any versus LATRUS (decision question 1)

Similarly, there is no statistically significant difference between LATP-any biopsy and LATRUS biopsy in detection of clinically significant prostate cancer (Figure 5).



REML = Random effects maximum likelihood

Figure 5 Meta-analysis forest plot of clinically significant cancer detection rates for LATP-any versus LATRUS

4.8.2 Prostate cancer detection (LATP-any vs GATP grid and stepping device, decision question 1)

Table 18 reports study cancer detection rates from the four studies which compared LATP-any biopsy versus GATP biopsy using grid and stepping device, and Figure 6 shows a meta-analysis forest plot containing three of the four studies (NB. The study publication by Walters et al 2021 did not provide numerical cancer detection rates and was therefore not included in the meta-analysis [40]). There was some inconsistency between the studies in the direction of effects, with two studies marginally favouring GATP (Lv et al 2020 [38]; Rij et al 2020 [41]) and another (smaller) study showing a large effect in favour of LATP-any (Takuma et al 2012 [39]). Overall, there is no statistically significant difference between the two biopsy modalities in detection of prostate cancer.

Table 18 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 [38]	Cancer positive detectable rate, n (%)	45 (41.67)	43 (39.81)	0.782
Other prospective studies				
Takuma et al 2012 [39]	Cancer detection rate, n/N (%)	9/37 (24)	15/29 (51)	0.041
Walters et al 2021	Histology outcomes	"No significant differences in histology outcome" between the different anaesthetic methods (LATP vs LATRUS)		Not reported
Retrospective studies				
Rij et al 2020 [41]	Cancers detected, n/N (%)	65/72 (90%)	59/71 (83%)	Not reported

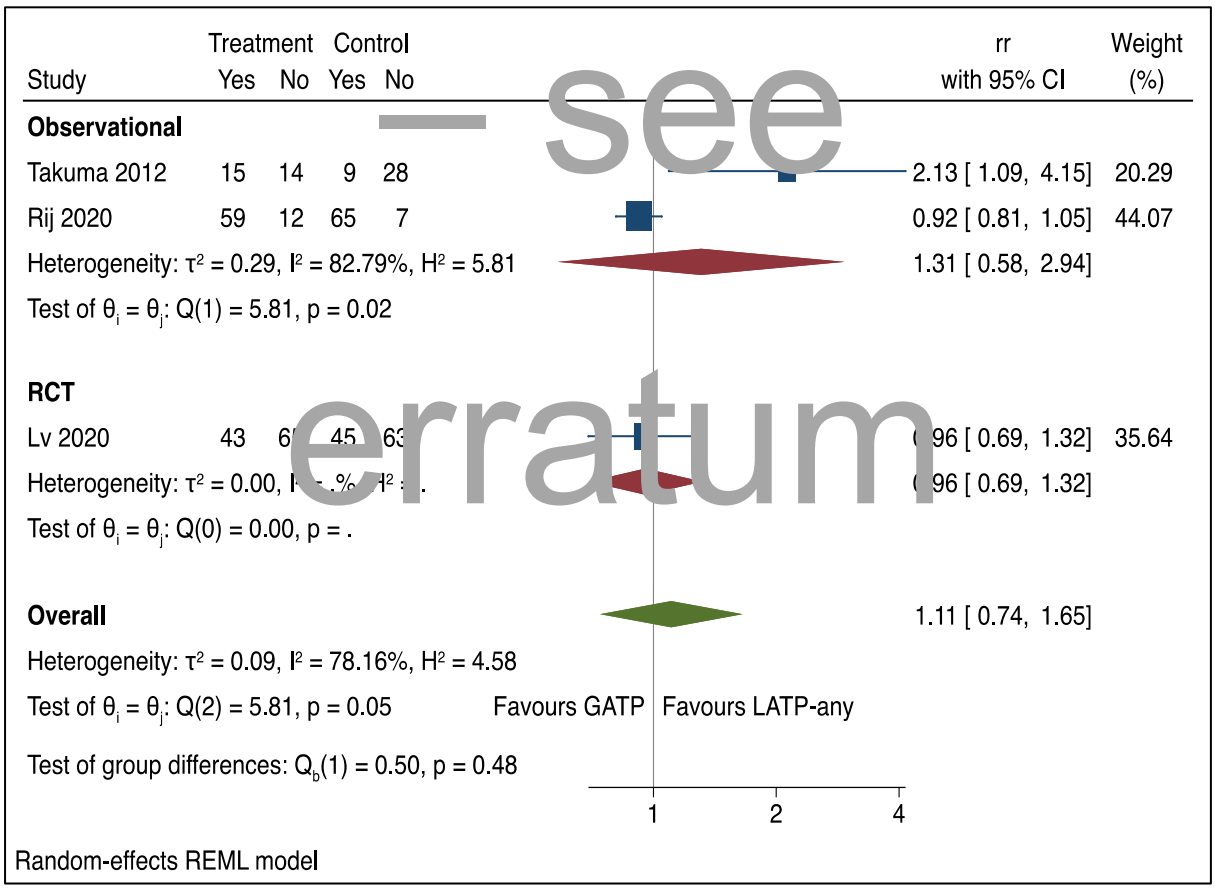


Figure 6 Meta-analysis forest plot of cancer detection rates for LATP-any vs GATP grid and stepping device (decision question 1)

4.8.3 Prostate cancer detection (Network meta-analysis of LATP-any vs LATRUS vs GATP grid and stepping device, decision question 1)

We used MetaInsight software (Owen et al 2019 [22]) to conduct a frequentist random effects network meta-analysis (NMA) of cancer detection rates for the biopsy modalities relevant to decision question 1 (Figure 7

Figure 7). The NMA provides an indirect comparison between LATP-any, LATRUS, and GATP grid and stepping device to inform clinical effect estimates in our economic analysis (see section 5.7). We restricted this analysis to the six available RCTs because, in principle, randomised study designs have greater internal validity than observational studies (notwithstanding the uncertain risk of bias we discussed earlier– see section 4.7).

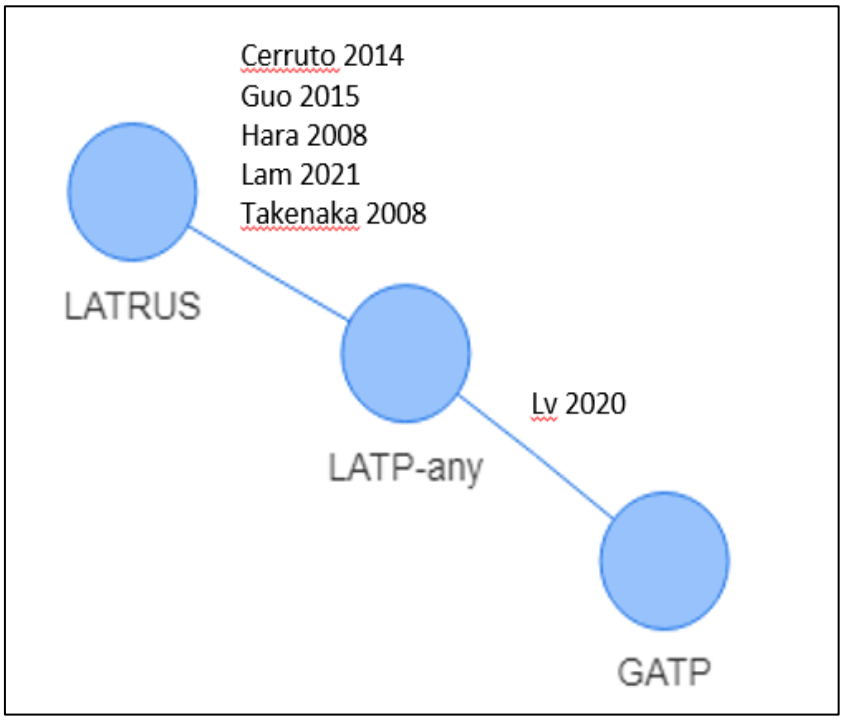
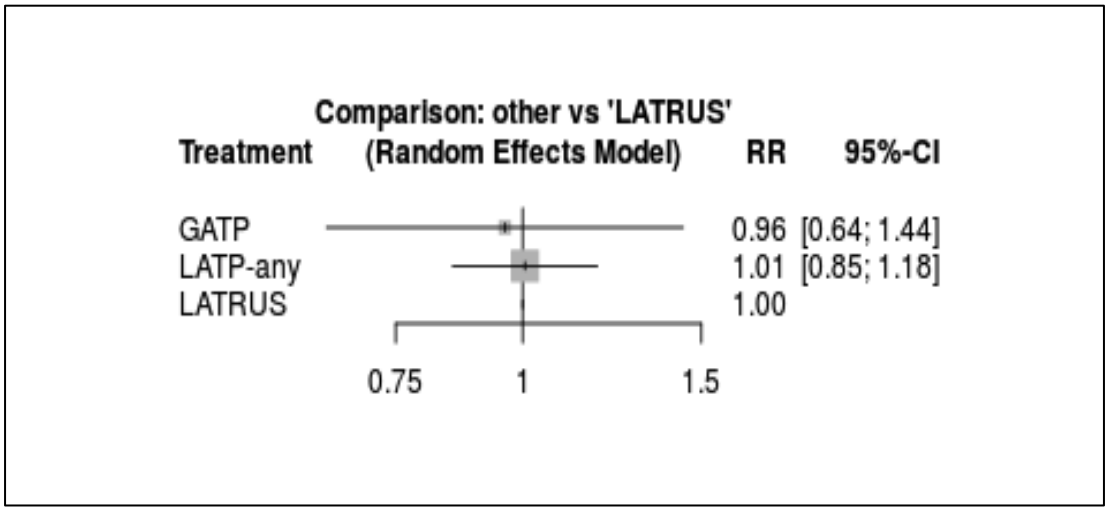


Figure 7 Evidence network for indirect comparison of LATP-any, LATRUS, and GATP grid and stepping device (decision question 1)

Consistent with the pairwise meta-analyses above, there were no statistically significant differences in cancer detection rates between the three biopsy modalities (Figure 8).



NB. LATRUS is the reference treatment to which all other treatments are compared against

Figure 8 Network meta-analysis forest plot of cancer detection rates for LATP-any vs LATRUS vs GATP grid and stepping device (decision question 1)

4.8.4 Prostate cancer detection (LATP-freehand vs LATRUS, decision question 2)

Cancer detection rates, including clinically significant cancer rates (where available), for six of the seven studies comparing LATP-freehand versus LATRUS are reported Table 19 (NB. The remaining studyehand device was evaluated in all six studies, and collectively the studies comprise , Starmer et al, did not report cancer detection as an outcome). The PrecisionPoint™ fre a sub-set of the LATP-any studies for decision question 1 presented earlier.

Table 19 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 [26]	Cancer detection rate, n/N (%)	47/134 (35.1)	33/132 (25.0)	<0.05
	Clinically significant cancer detection rate[a]	22/134 (16.4)	19/132(14.4)	p=0.74
Prospective studies				
Bojin 2019 [28]	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
	Clinically significant cancer pick up, n/N (%)[b]	51/76 (67.1)	48/117 (41.2)	Not reported
Chen et al 2021 [29]	Cancer detection rate in biopsy naïve patients, n/N (%)	127/200 (63.5)	86/172 (50)	0.0115
	Cancer detection rate (%)	20/63 (31.7)	14/57 (24.6)	0.851

Hung et al 2020 [31]	Clinically significant prostate cancer, (%)	57.1	45.0	0.501
Kum et al 2018 [32]	Cancer detection rate, overall, n/N (%)	139/176 (79)	Not reported	Not reported
	Malignant primary biopsy, n/N (%)[c] Systematic	46/75 (61.3)	43/77[d] (55.8)	P=0.50
	Targeted & systematic	35/40 (88.6)	Not reported	Not reported
	Targeted	38/41 (92.7)	Not reported	Not reported
	Clinically significant cancer detection[e f] n/N (%) Systematic	28/46 (60.9)	25/43 (58.1)	P=0.80
	Targeted & systematic	29/35 (82.9)	Not reported	Not reported
	Targeted	33/38 (86.8)	Not reported	Not reported
Retrospective studies				
Szabo et al I [37]	Overall cancer detection rate, n/N (%)	105/242 (43.4)[g]	52/133 (39)	0.4451
	Clinically significant cancer detection rate, n/N (%)[h]	35/242 (14)	Not reported	Not reported

Szabo I refers to the comparison of LATP using PrecisionPoint™ Transperineal Access System vs LATRUS from this study

[a] definition of clinical significance not reported in study publication; [b] clinical significance defined as Gleason >3+4;
[c] 156/176 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

We conducted pairwise meta-analyses of cancer detection rates for LATP-freehand versus LATRUS (*Figure 9*). N.B It was not possible to include the study by Kum et al in the meta-analysis as it did not report cancer detection rates for the LATRUS group). As decision question 2 focuses on LATP-freehand device biopsy, to permit incremental assessment of biosy effects in our economic model we split the 'LAPT-any' study category into respective biopsy subtypes, i.e. LATP-freehand, LATP grid and stepping device and LATP coaxial However, it was unclear from some of the LATP-any studies whether they could reliably be classified as LATP grid and stepping device or LATP coaxial needle (double freehand), hence we combined these into a category we refer to as 'LATP-other'. This assumes LATP using a grid and stepping device and LATP with a coaxial needle are necessarily equivalent in effects, which is a potential limitation of the analysis.

Whilst there is no statistically significant difference between LATP-freehand and LATRUS in either the observational or RCT data, when these study types are pooled in our exploratory analysis there is a statistically significant benefit (RR 1.22, 95% CI 1.10, 1.35) in favour of LATP-freehand (*Figure 9)*. *T*here is no statistically significant difference between LATP-other and LATRUS (*Figure 10*).

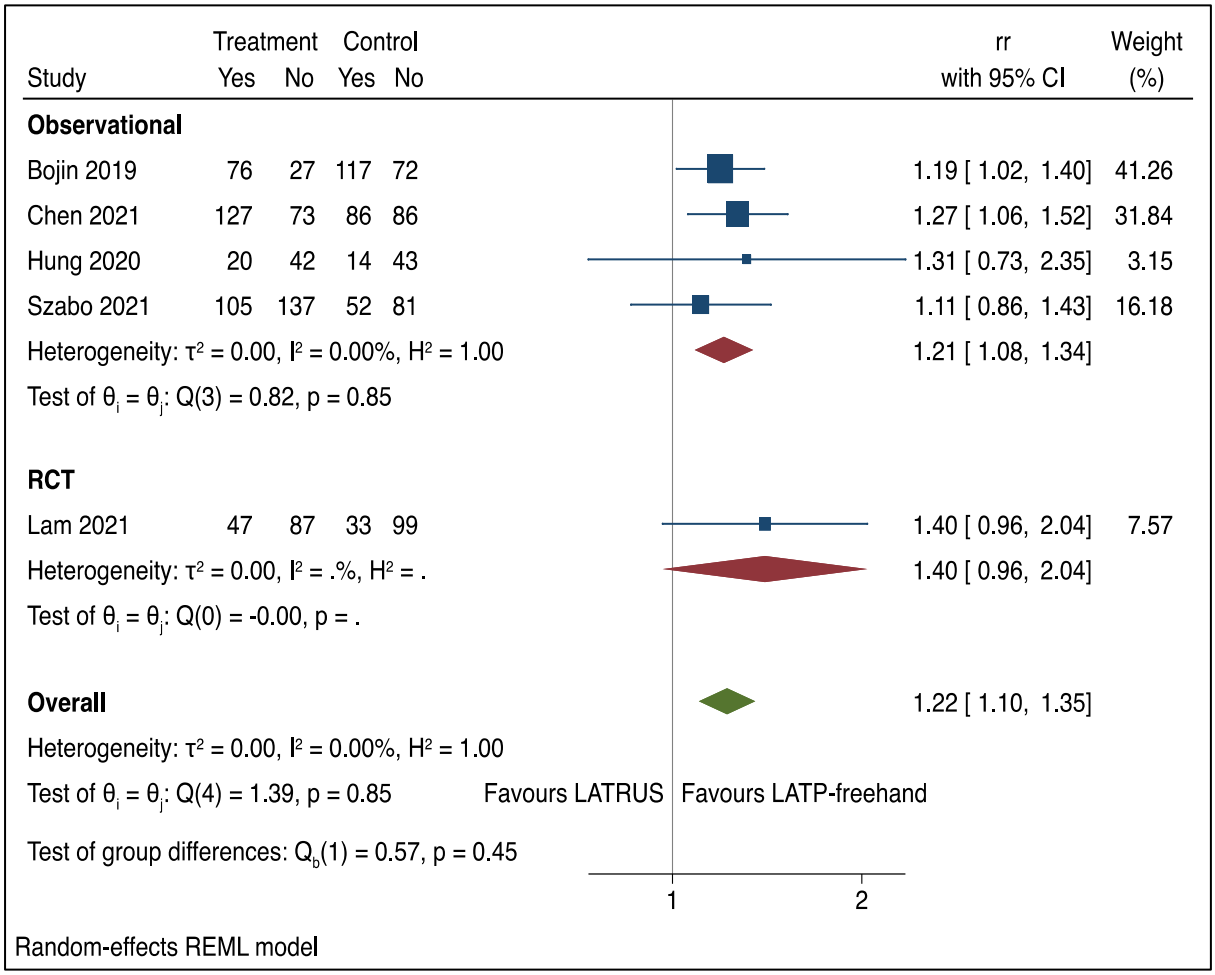


Figure 9 Meta-analysis forest plot of cancer detection rates for LATP-freehand vs LATRUS (decision question 2)

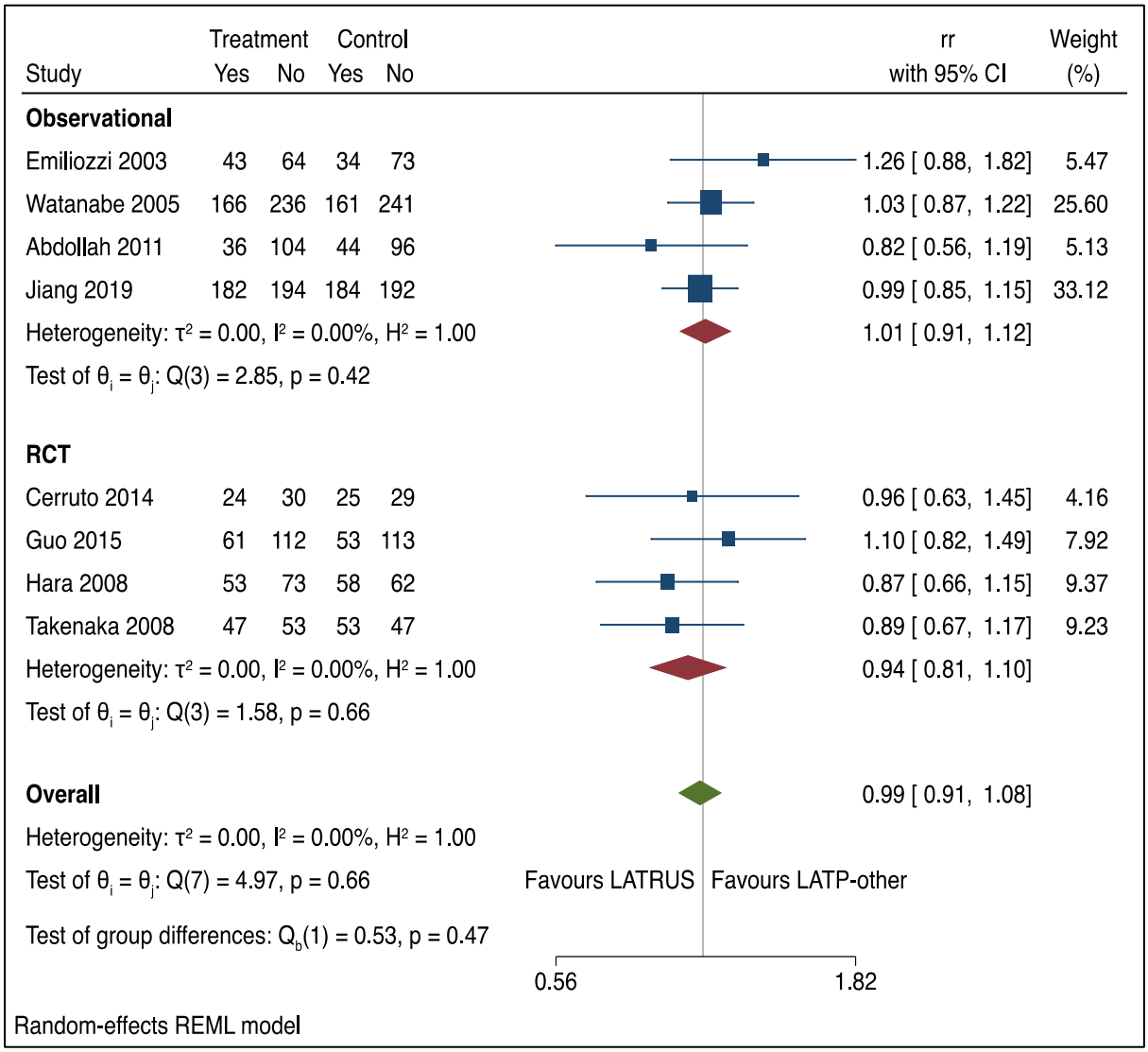


Figure 10 Meta-analysis forest plot of cancer detection rates for LATP-other versus LATRUS (decision question 2)

In terms of clinically significant prostate cancer detection, there is a statistically significant difference in favour of LATP-freehand in the observational evidence but not in the RCT evidence. When all the studies are pooled in our exploratory analysis, statistical significance is retained (*Figure 11*).

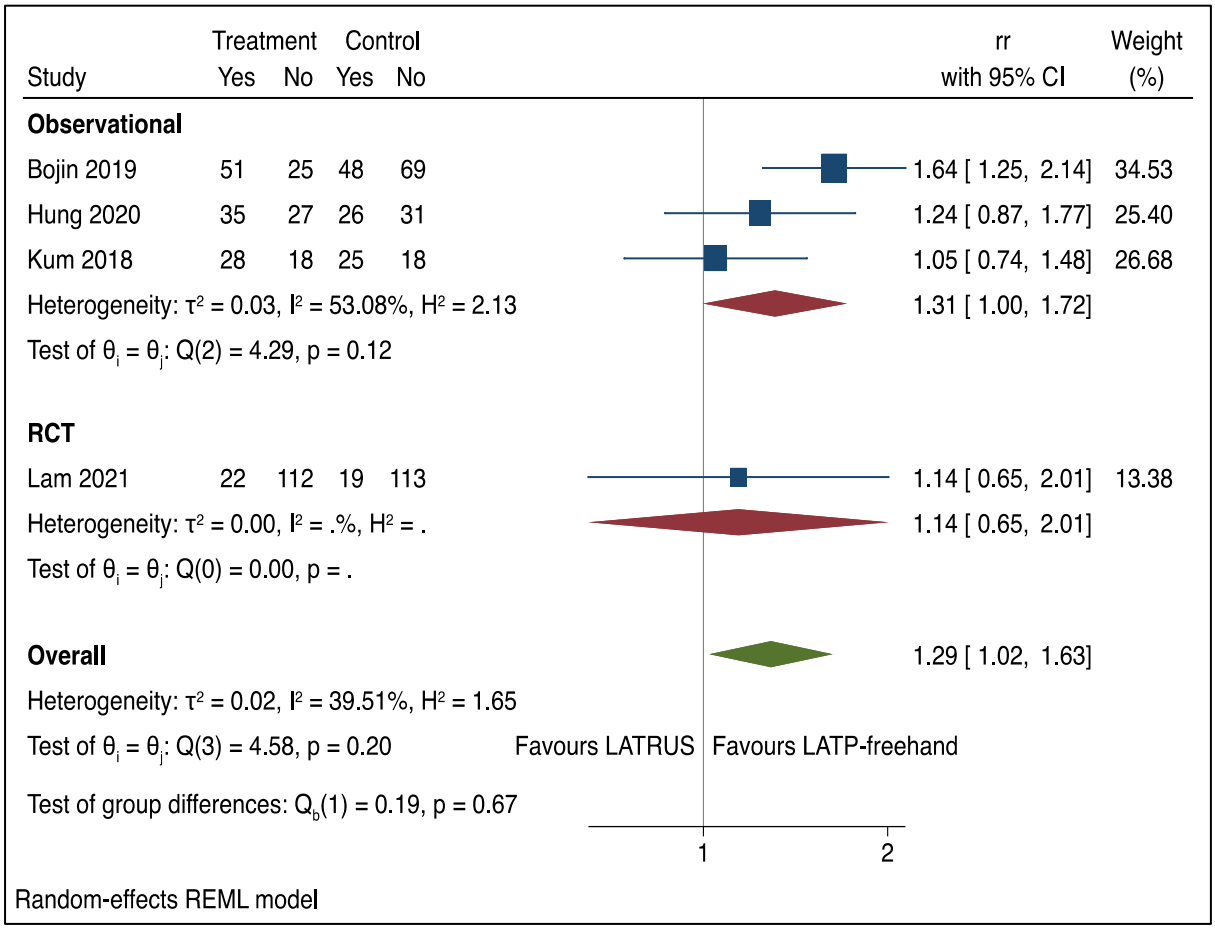


Figure 11 Meta-analysis forest plot of clinically significant cancer detection rates for LATP-freehand versus LATRUS (decision question 2)

4.8.5 Prostate cancer detection (LATP-freehand vs GATP grid and stepping device decision question 2)

Table 20 reports cancer detection rates for the single study comparing LATP-freehand (PrecisionPoint™) versus GATP grid and stepping device.[41] This is one of the studies included in the comparison of LATP-any versus GATP grid and stepping device presented earlier (section 4.8.2). 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™. Caution is advised in the interpretation of the results due to the retrospective study design.

Table 20 Prostate cancer detection rates (LATP-freehand vs GATP grid and stepping device)

Study	Outcome measure	Intervention LATP-freehand	Comparator GATP	Statistical significance (p-value)
Retrospective studies				
Rij et al 2020 [41]	Cancers detected, n/N (%)	65/72 (90%)	59/71 (83%)	Not reported

4.8.6 Prostate cancer detection (NMA of LATP-freehand versus LATP-other versus LATRUS versus GATP grid and stepping device, decision question 2)

We used MetaInsight software (Owen, 2019) [22] to conduct a frequentist random effects NMA of cancer detection rates for decision question 2 (*Figure 12*). This provided an indirect comparison between LATP-freehand versus LATP-other versus LATRUS versus GATP grid and stepping device, to inform our economic analysis (see section 5.7).

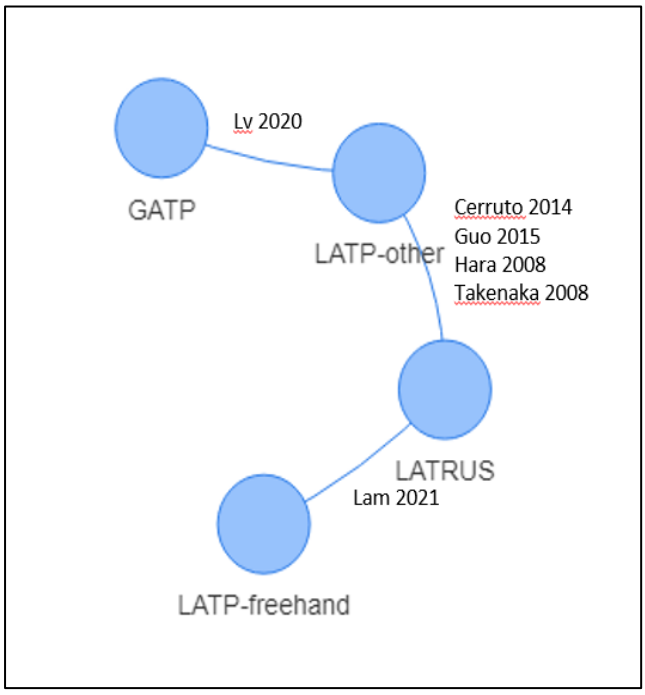


Figure 12 Evidence network for indirect comparison of LATP-freehand, LATP-other, LATRUS, and GATP grid and stepping device (decision question 2)

Consistent with the pairwise meta-analyses, the NMA shows no statistically significant differences in cancer detection rates between biopsies (*Figure 13*). It is only when observational evidence for LATP-freehand versus LATRUS is combined with RCT evidence that a statistically significant results is observed (*Figure 8*, above).

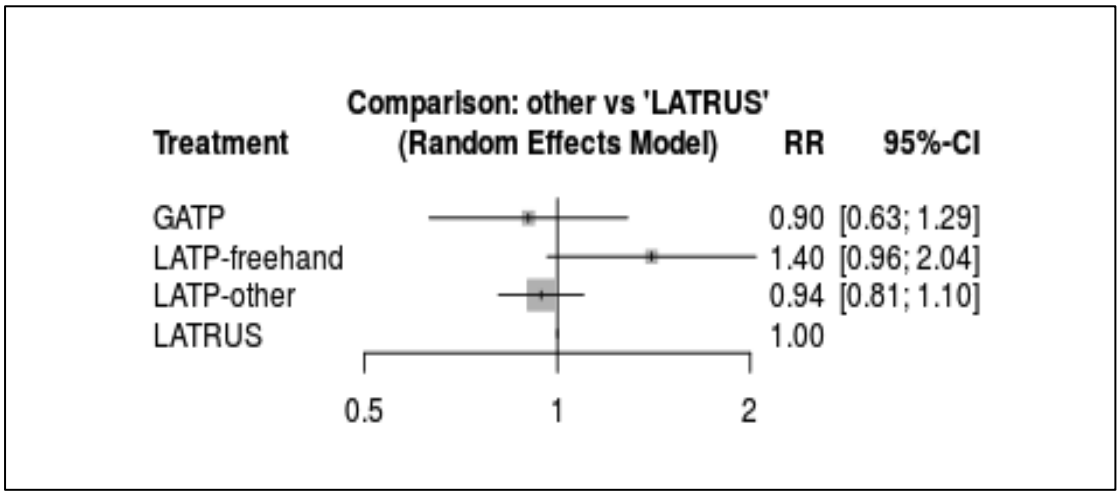


Figure 13 Forest plot of NMA results comparing cancer detection rates for LATP freehand, LATP other, GATP grid and stepping device and LATRUS

4.8.7 Prostate cancer detection risk classification

Table 21 compares risk classification scores for people with detected prostate cancers 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.[32] 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[32 37] are also relevant to the comparison of LATP-freehand versus LATRUS (decision question 2)

Table 21 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 2015 [24]	Gleason score, n/N (%) ≤6 =7 ≥8	 18/173 (10.4) 18/173 (10.4) 25/173 (14.5)	 18/166 (10.8) 15/166 (9.0) 18/166 (10.8)	 0.547 1.000 0.564
	Very-low-risk prostate cancer, n/N (%)	6/173 (3.5)	5/166 (3.0)	1.000
Other prospective studies				
Emiliozzi 2003 [30]	Gleason score, n/N (%) Gleason 5 Gleason 6 Gleason 7 Gleason 8-9	 2/41 (5) 20/41 (49) 17/41 (41) 2/41 (5)	 0 (0) 19/34 (56) 14/34 (41) 1/34 (3)	Not reported

Study	Risk classification of prostate cancer detected	Intervention LATP-any	Comparator LATRUS	Statistical significance (p-value)
Kum 2018 (AB) [32]	Low risk[a], n/N (%) Systematic Targeted and systematic Targeted	 36/91d 39 7/40d 17 6/45d 13	Not reported	Not reported
	Intermediate risk[b], n/N (%) Systematic Targeted and systematic Targeted	 52/91d 57 28/40d 69 26/45d 58	Not reported	Not reported
	High risk[a], n/N (%) Systematic Targeted and systematic Targeted	 4/91d 4 6/40d 14 13/45d 29	Not reported	Not reported
Watanabe 2005 [34]	Clinical stage[c], n/N (%) T1c T2 T3-T4	 29/39 (74.4) 71/86 (82.6) 66/70 (94.3)	 25/39 (64.1) 70/86 (81.4) 66/70 (94.3)	Not reported
	Gleason score, n/N (%) Gleason 2-4 Gleason 5-6 Gleason 7 Gleason 8-9	 25/37 (67.6) 59/70 (84.3) 47/52 (90.4) 35/36 (97.2)	 26/37 (70.3) 55/70 (78.6) 45/52 (86.5) 35/36 (97.2)	Not reported
Retrospective studies				
Jiang 2019 [36]	Gleason score, n/N (%)[d] ≤6 7 ≥8	 32/182 (17.6) 73/182 (40.1) 77/182 (42.3)	 58/184 (31.5) 90/184 (48.9) 36/184 (19.6)	Not reported <0.001 Not reported
Szabo et al I [37]	Gleason grade Grade group 1 Grade group 2 Grade group 3 Grade group 4 Grade group 5	 70/105 (66.7) 20/105 (19.0) 4/105 (3.8) 2/105 (1.9) 9/105 (8.6)	Not reported	Not reported

Szabo I refers to LATP using PrecisionPoint™ vs LATRUS; (AB) denotes conference abstract
[a] risk level not defined [b] Intermediate risk was defined as Gleason score 3+4 or >4mm cancer length
[c] According to the TNM 1997 classification. [d] Propensity score matched subgroup

A single (retrospective observational) study reported cancer risk classification for the comparison of LATP-any versus GATP grid and stepping device. [41]

Table 22 reports the proportion of participants in this study with detected prostate cancer classified by 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 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, but this was not statistically significant.

Table 22 LATP-any vs GATP grid and stepping device (decision question 1)

Study	Risk classification of prostate cancer detected	LATP-any biopsy	GATP biopsy grid & stepping device	Statistical significance
Retrospective studies				
Rij et al 2020 (AB) [41]	Detection rates for ISUP>2[a] cancers	35/65 (53.8%)	28/59 (47.5%)	0.48

(AB) denotes study only available as a conference abstract at the time of writing
[a] International Society of Urological Pathology (ISUP) grade group classification. A lower group number denotes less risk; group >2 equates to 'Low risk' to 'Intermediate Favourable risk'

4.8.8 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[41] 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). A reference standard was not reported either. This study is currently available only as a conference abstract, hence limited information.

Another study[39] reported the pathological accordance of Gleason scores based on biopsy with histological analysis of prostatectomy specimens (i.e. a reference standard). This resulted in a small proportion of participants having their Gleason scores upgraded and upstaged.

4.9 Clinical outcomes

4.9.1 Hospitalisation events after biopsy

Hospitalisation following prostate biopsy was reported by a total of ten studies, for four of the five biopsy comparisons relevant to the decision problem (Table 23; Table 24; Table 25, and Table 26 respectively). Studies tended to report the number of participants admitted to hospital at various timepoints after the biopsy (e.g. up to 30 days post biopsy), whilst 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 23 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 [27]	Major complications, [a] n/N (%) Total Macrohematuria Fever >38.5°C Urinary retention	 1/100 (1) 0/100 (0) 0/100 (0) 0/100 (0)	 4/100 (4) 1/100 (1) 2/100 (2) 1/100 (1)
Other prospective studies			
Chen et al 2021 [29]	Hospitalised for monitoring and discharged after 1 day, n/N (%)	1/212 (0.5)	0/178 (0)
Emiliozzi et al 2003 [30]	Post-biopsy hospitalisation, n/N (%)	0/107 (0)	0/107 (0)
Kum et al [32]	Hospitalisation overnight	1/176	Not reported
Starmer et al 2021[33]	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 [34]	Prolonged hospital stay, n/N (%)	0/402 (0)	
Retrospective studies			
Szabo et al I [37]	Hospital admission, n/N (%)	Not reported	1/133a (0.75)
Szabo et al II [37]	Hospital admission, n/N (%)	Not reported	1/133a (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

Table 24 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 & stepping device
RCTs			
Lv et al 2020 [38]	Duration of hospital stay, hours, mean (SD)	23.50 (±3.48)	23.12 (±2.85)
Retrospective studies			
Rij et al 2020 (AB) [41]	Readmission to hospital post biopsy, n/N (%)	0/72 (0)[a]	0/71 (0)[a]

Table 25 Hospitalisation events after biopsy (LATP-freehand biopsy vs LATRUS biopsy, decision question 2)

Study	Hospialisation outcome	LATP-freehand biopsy	LATRUS biopsy
Other prospective studies			
Chen et al 2021 [29]	Hospitalised for monitoring and discharged after 1 day, n/N (%)	1/212 (0.5)	0/178 (0)
Kum et al [32]	Hospitalisation overnight	1/176	Not reported

Starmer et al 2021[33]	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]
Retrospective studies			
Szabo et al I [37]	Hospital admission, n/N (%)	Not reported	1/133a (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;			

Table 26 Hospitalisation events after biopsy (LATP-freehand biopsy vs GATP biopsy using a grid and stepping device, decision question 2)

Study	Hospitalisation outcome	LATP-freehand biopsy	GATP biopsy grid & stepping device
Retrospective studies			
Rij et al 2020 (AB) [41]	Readmission to hospital post biopsy, n/N (%)	0/72 (0)[a]	0/71 (0)[a]

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 section 5.7.4.

4.9.2 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 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 27). Two of the six studies,[29 32] compared freehand transperineal devices versus LATRUS and therefore are also relevant to decision question 2.

Table 27 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 [23]	Overall complication rate[a,] n/N (%)	7/54 (12.96)	n = 7/54 (12.96)	Not significant
Guo et al 2015 [24]	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	1 (0.6%)	7 (4.3)	0.034

Takenaka et al 2008 [27]	Total complications (inclusive of major complications) n/N (%)	19/100 (19)	20/100 (20)	
Other prospective studies				
Chen et al 2021 [29b]	Overall complication rate, n/N (%)	13/212 (6.1)	20/178 (11.2)	0.0993
Kum et al [32b]	Complications (Clavien -Dindo I/II), n/N (%)	5/176 (2.8)	Not reported	Not reported
Watanabe et al 2005 [34]	Adverse event, n/N (%)	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

4.9.3 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), nine of the 15 included studies reported a relevant bleeding and/or haematuria outcome (Table 28). Generally, bleeding/haematuria rates were low (e.g. less than 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 2014 [23], but the sample size for this analysis was very small (<20 participants) and is unlikely to be sufficient to ensure a definitive effect.

Table 28 Bleeding and haematuria (LATP-any vs LATRUS, decision question 1)

Study	Outcome	LATP-any	LATRUS	Statistical significance
RCTs				
Cerruto et al 2014 [23]	Rectal bleeding, [a] n/N (%)	0/7 (0)	4/7 (57.16)	0.04
	Urethral bleeding,[a] n/N (%)	5/7 (71.43)	0/7 (0)	0.022
Guo et al 2015 [24]	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 [25]	Major rectal bleeding	0 (0)	0 (0)	N/A
	Haematuria >1 day	2 (1.6)	0 (0)	0.166
Takenaka et al 2008 [27]	Rectal bleeding	0/100 (0)	1/100 (1)	Not reported
	Macrohaematuria	11/100 (11)	12/100 (12)	Not reported
Other prospective studies				
Chen et al 2021 [29]	Haematuria, n/N (%)	2/212 (0.9)	3/178 (1.7)	0.6640
Emiliozzi et al 2003 [30]	Temporary haematuria, n/N (%)	33/107 (31)[b]		Not reported
Kum et al 2018 (AB) [32]	Clot retention (Clavien Dindo Grade II), n/N (%)	1/176 (0.6)	Not reported	Not reported
Watanabe et al 2005 [34]	Significant haematuria requiring transurethral coagulation of prostatic bleeding, n/N (%)	1/402 (0.2)		Not reported
Retrospective studies				
Szabo et al I [37]	Gross haematuria with clot retention, n/N (%)	3/242 (1.2)	Not reported	Not reported
Szabo et al II [37]	Gross haematuria with clot retention, n/N (%)	1/62 (1.6)	Not reported	Not reported

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.
[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

For the comparison between LATP-any biopsy and GATP biopsy with grid & stepping device, two of the four included studies reported bleeding-related outcomes (Table 29). Observation of the data gives a feint suggestion that bleeding is potentially worse for GATP biopsy grid & stepping device than LATP-any biopsy. However, this is based on a small number of events from a single RCT.[38] 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 2014.[23].

Table 29 Bleeding and haematuria (LATP-any vs GATP grid and stepping device, decision question 1)

Study	Outcome	LATP-any biopsy	GATP biopsy grid & stepping device	Statistical significance
RCTs				
Lv et al 2020 [38]	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 et al 2020 (AB) [41]	Prolonged haematuria, n/N (%)	2/72 (3)	Not reported	Not reported
	Perineal haematomas, n/N (%)	Not reported	3/71 (4)	Not reported

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

Moving on to decision question 2, three of the seven LATP freehand (PrecisionPoint™) device studies (all observational studies) assessed bleeding as a biopsy complication (Table **30).** 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 LATP-freehand biopsy versus GATP biopsy grid and stepping device, (Table 31) data are very sparse and, thus, inconclusive at present.

Table 30 Bleeding and haematuria (LATP-freehand vs LATRUS, decision question 2)

Study	Outcome	LATP-freehand	LATRUS	Statistical significance
Other prospective studies				
Chen et al 2021 [29]	Haematuria, n/N (%)	2/212 (0.9)	3/178 (1.7)	0.6640
Kum et al 2018 (AB) [32]	Clot retention (Clavien Dindo Grade II), n/N (%)	1/176 (0.6)	Not reported	Not reported
Retrospective studies				
Szabo et al I [37]	Gross haematuria with clot retention, n/N (%)	3/242 (1.2)	1/62 (1.6)	Not reported
Szabo I refers to the comparison of LATP using PrecisionPoint™ Transperineal Access System vs LATRUS from this study				

Table 31 Bleeding and haematuria (LATP-freehand biopsy vs GATP biopsy grid and stepping device, decision question 2)

Study	Outcome	LATP- freehand biopsy	GATP biopsy grid & stepping device	Statistical significance
Retrospective studies				
Rij et al 2020 (AB) [41]	Prolonged haematuria, n/N (%)	2/72 (3)	Not reported	Not reported
	Perineal haematomas, n/N (%)	Not reported	3/71 (4)	Not reported

Sepsis

Relatively few studies reported post-biopsy sepsis as an outcome measure. 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 (Table 32 and Table 33).

Table 32 Sepsis rates (LATP-any vs LATRUS, decision question 1)

Study	Outcome	LATP-any	LATRUS	Statistical significance
RCTs				
Guo et al 2015 [24]	Major complications: sepsis, n (%)	0 (0)	1 (0.6)	Not reported
Hara et al 2008 [25]	Major complications: Sepsis/mortality, n (%)	0 (0)	0 (0)	Not reported
Lam et al 2021 (AB) [26]	Post-biopsy sepsis	0/0 (0)	11/132 (8.3)	Not reported
Other prospective studies				
Chen et al 2021 [29]	Urosepsis,[a] n/N (%)	0/212 (0)	4/178 (2.2)	0.0431
Hung et al 2020 (AB) [31]	Sepsis, n/N (%)	0/63 (0)	3/57 (5.3)	0.045
Retrospective studies				
Szabo et al I [37]	Sepsis, n/N (%), Clavien grade	0/242 (0) Not applicable	1/133a (0.75) Clavien IVb	Not reported
Szabo et al II [37]	Sepsis, n/N (%), Clavien grade	0/62 (0) Not applicable	1/133a (0.75) Clavien IVb	Not reported

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
[a] defined as at least 2 out of 4 systemic inflammatory response syndrome (SIRS) criteria with a proven infection)

Table 33 Sepsis rates (LATP-freehand vs LATRUS, decision question 2)

Study	Outcome	LATP-any	LATRUS	Statistical significance
RCTs				
Lam et al 2021 (AB) [26]	Post-biopsy sepsis	0/0 (0)	11/132 (8.3)	Not reported
Other prospective studies				
Chen et al 2021 [29]	Urosepsis,[a] n/N (%)	0/212 (0)	4/178 (2.2)	0.0431
Hung et al 2020 (AB) [31]	Sepsis, n/N (%)	0/63 (0)	3/57 (5.3)	0.045
Retrospective studies				
Szabo et al I [37]	Sepsis, n/N (%), Clavien grade	0/242 (0) Not applicable	1/133a (0.75) Clavien IVb	Not reported
Szabo et al II [37]	Sepsis, n/N (%), Clavien grade	0/62 (0) Not applicable	1/133a (0.75) Clavien IVb	Not reported

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
[a] defined as at least 2 out of 4 systemic inflammatory response syndrome (SIRS) criteria with a proven infection),

None of the LATP-any vs GATP grid and stepping device studies (decision question 1) and none of the LATP-freehand biopsy vs 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 which compared LATP-any versus LATRUS (decision question 1). None of the LATP biopsy procedures involved use of a freehand device (Table 34**Error! Reference source not found.**). 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

Table 34 Fever rates (LATP-any vs LATRUS, decision question 1)

Study	Outcome	LATP-any	LATRUS	Statistical significance
RCTs				
Cerruto et al 2014 [23]	Fever >38.5°C[a], n/N (%)	0/7 (0)	1/7 (14.28)	0.315
Guo et al 2015 [24]	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 [25]	Fever >38.5°C , n (%)	0 (0)	2[a] (1.7)	0.136
Takenaka et al 2008 [27]	Fever >38.5°C , n/N (%)	1/100 (1)	2/100 (2)	Not reported

4.9.4 Rates of urinary retention

Post-biopsy urinary retention is reported by nine studies in total across three biopsy comparisons.(Table 35, Table 36, and Table 37) 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.

Table 35 Urinary retention rates (LATP-any vs LATRUS, decision question 1)

Study	Outcome	LATP-any	LATRUS	Statistical significance
RCTs				
Lam et al 2021 (AB) [26]	Post-biopsy urinary retention	"no statistically significant difference between both arms" p=0.107		p=0.107

Hara et al 2008 [25]	Urinary retention, n (%)	2 (1.6)	3 (2.5)	0.612
Takenaka et al 2008 [27]	Urinary retention, n (%)	2/100 (2)	3/100 (3)	Not reported
Other prospective studies				
Chen et al 2021 [29]	Acute urinary retention, n/N (%)	8/212 (3.8)	8/178 (4.5)	0.8008
Hung et al 2020 (AB) [31]	Urinary retention rate	"No statistical significant difference"		Not reported
Kum et al 2018 (AB) [32]	Urinary retention (Clavien Dindo Grade II), n/N (%)	1/176 (0.6)	Not reported	Not reported
Watanabe et al 2005 [34]	Urinary retention requiring urethral catheterization, n/N (%)	2/402 (0.5)		Not reported
Retrospective studies				
Szabo et al 2021a [37]	Acute urinary retention, n/N (%), Clavien grade	1/242 (0.4) Clavien I	Not reported	Not reported

Table 36 Urinary retention rates (LATP-any vs GATP grid and stepping device, decision question 1)

Study	Outcome	LATP-any	GATP biopsy grid & stepping device	Statistical significance
RCT				
Lv et al 2020 [38]	Retention of urine, n (%)	3 (2.78)	2 (1.85)	0.997

Table 37 Urinary retention rates (LATP-freehand vs LATRUS, decision question 2)

Study	Outcome	LATP-any	LATRUS	Statistical significance
Other prospective studies				
Chen et al 2021 [29]	Acute urinary retention, n/N (%)	8/212 (3.8)	8/178 (4.5)	0.8008
Hung et al 2020 (AB) [31]	Urinary retention rate	"No statistical significant difference"		Not reported
Kum et al 2018 (AB) [32]	Urinary retention (Clavien Dindo Grade II), n/N (%)	1/176 (0.6)	Not reported	Not reported
Retrospective studies				
Szabo et al 2021a [37]	Acute urinary retention, n/N (%), Clavien grade	1/242 (0.4) Clavien I	Not reported	Not reported

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)

4.9.5 Rates of erectile dysfunction

Only two studies in this systematic review reported assessing post-biopsy erectile dysfunction. [26] [31] 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 2020 [31] 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).

The RCT by Lam et al[26] reports a reduction in the IIEF-5 score that was "more significant in LATP arm" p<0.05. 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, [26] that a manuscript is being prepared for submission to a journal.

4.9.6 Survival

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

4.9.7 Progression free survival

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

4.9.8 Adverse events from treatment

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

4.10 Patient reported outcomes

4.10.1 Patient reported tolerability

A total of 12 studies reported data on the degree of pain and discomfort during prostate biopsy as rated by patients (
Table 38 and Table 39). 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.

Table 38 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 [23]	VAS pain level, mean (SD)	1.42 (1.37)	1.56 (1.73)	0.591
Guo et al 2015 [24]	Pain, VAS score, median (IQR)	4.0 (1.0–6.0)	2.0 (0.0–4.0)	< 0.001
	Most painful procedure, n (%) None Probe insertion Anaesthesia Sampling Others	 3 (1.7) 30 (14.5) 110 (63.6) 26 (15.0) 9 (5.2)	 37 (22.3) 67 (42.2) 29 (17.5) 25 (15.1) 5 (3.0)	 < 0.001 < 0.001 < 0.001 1.000 0.415
	Additional anaesthesia**,** number of times, (%)	26 (15.0)	2 (1.2)	< 0.001
Lam et al 2021 [26]	Patient tolerability comparison measured by VAS	"no statistically significant difference between both arms"		p=0.14
Other prospective studies				
Bojin (2019) [28]	Tolerability, VAS pain score 0-6, median	1.9	Not reported	Not reported
Chen et al 2021 [29]	VAS pain score for the entire procedure, mean (SD, range)	3.67 (2.57, 0-9)	Not reported	Not reported
Emiliozzi et al 2003 [30]	Mild post-biopsy perineal discomfort, n/N (%)	7/107 (6)		Not reported
Hung et al 2020 [31]	Overall pain scores	"no statistically significant difference"		0.527
Kum et al 2018 [32]	Procedure tolerability (100mm VAS score) during three stages of procedure: US probe insertion, 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 [33]	VAS scores, rated 0-9, for discomfort, median At probe insertion Probe presence Local anaesthetic injection Taking biopsy	 3 3 3 3	 4 3 2 3	 0.66 0.91 0.15 0.18
	VAS scores, rated 0-3, median Overall pain Embarrassment Describe to a friend	1 0 1	1 0 1	0.17 0.34 0.2
Retrospective studies				
Szabo et al I [37]	VAS pain ratings, 0-10, average, median (range and SD)	3.9, 4 (0-10, 1.9)[a]	Not reported	Not reported
Szabo I refers to the comparison of LATP using PrecisionPoint™ Transperineal Access System vs LATRUS from this study; VAS visual analogue scale				

Table 39 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 2020 [38]	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 2020 (AB) [41]	Participants tolerating the procedure, n (%)	72/72 (100)	Not reported	Not reported
VAS visual analogue scale				

4.11 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.

LATP vs. LATRUS. The multicentre UK study (TRANSLATE [48 49 50]) 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 will assist with both Decision Question 1 (LATP-any versus LATRUS) and Decision Question 2 (LATP-freehand versus LATRUS). This will be the first comparative evidence to become available for the UA1232 device. As well as clinically significant prostate cancer (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 four 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 [51] is a single centre study and will report on sexual function for which there is limited evidence in this review. 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 [52], 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 [53].

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 vs. GATP. One Australian study (LAPTProBE [54]), yet to start recruiting, will provide evidence for freehand LATP compared with GATP using a grid template. 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 [51]), the UK study is expected to complete the following year in October 2023 (TRANSLATE [48 49]), and one study has not yet started recruiting (LATProBE [54]). Details of all five studies are summarised in Table 40.

Table 40 Details of relevant ongoing studies

Study, design, country, completion date	Population	Intervention	Comparator	Outcomes
LATP vs. LATRUS				
Study: **TRANSLATE** [49 50] ISRCTN98159689 [48] **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 [51] 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: NCT04843566 [52a] **Country:** USA (multicentre RCT) **Estimated completion date:** June 2025	Men with elevated prostate-specific antigen 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 clinically significant disease; change in adverse events.
Study: NCT04815876 [53a] **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 clinically significant disease; change in adverse events.
LATP vs. GATP				
Study: LATProBE [54] 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.				

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. This includes a systematic review of cost-effectiveness studies of LATP prostate biopsies in people with suspected prostate cancer. And a systematic review of health-related quality of life (utility) for people with suspected or diagnosed prostate cancer.
2. An overview of evidence from company submissions.
3. An independent economic model developed by the EAG.

5.1 Systematic review of existing cost-effectiveness evidence

5.1.1 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.[55] 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. The relevant population, interventions and comparators are the same as for the systematic review of test performance and clinical effectiveness (see *section 3.2*) 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. All studies that report resource use, costs and health-related quality of life in the area of prostate cancer were excluded if they did not meet the inclusion criteria above but were considered separately as possible sources of evidence to inform model structure and inputs.

5.1.2 Methods for data extraction and assessment of economic studies

The EAG planned to extract data related with 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. This checklist was based on the Professional Society for Health Economics and Outcomes Research (ISPOR) [56] and Philips and colleagues' [57] checklists.

5.1.3 Results of the review of economic studies

Starting with 725 potentially relevant references identified in the original (704) and updated (21) searches, 11 studies appeared to provide information about economic studies based on title and abstract screening and were retrieved for full-text screening (see *Figure 14*). After inspection, 10 references were excluded: two are protocols for studies, two are not economic evaluations and five do not assess the interventions of interest. The excluded references and the reason for exclusion are shown in Appendix 7.

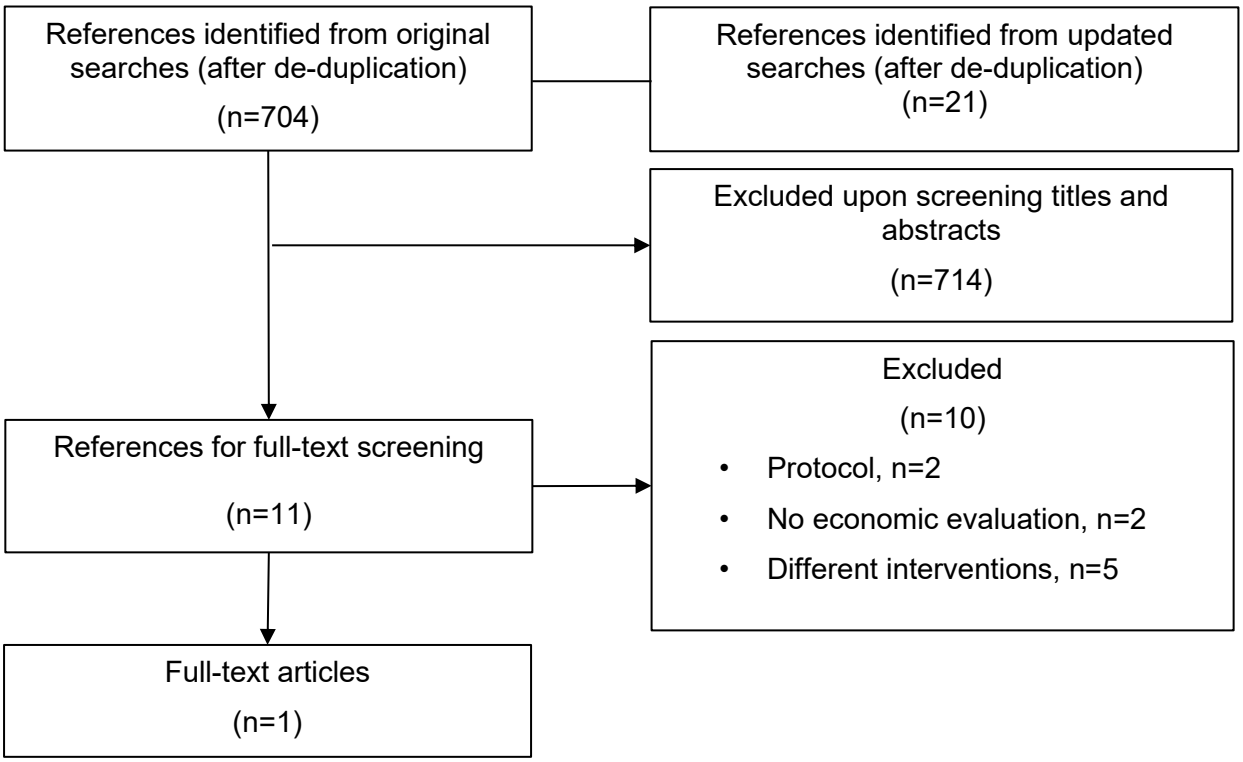


Figure 14 Flow chart for the identification of economic studies

Summary of included cost-effectiveness study: Wilson et al. (2021)

We identified one economic evaluation for inclusion within the scope of this assessment: Wilson et al. 2021.[58] Wilson and colleagues 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 is shown in Appendix 6, key characteristics and results are summarised in *Table 41* below, and further details including a list of the model inputs are shown in Appendix 8.

Wilson and colleagues 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 [42] 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 and colleagues.[59] [60] 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,[61] 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.

Costs were taken from routine NHS sources for the price year 2018/19. 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.

Base case results indicated that LATP (with the CamPROBE device at zero price) dominates LATRUS biopsy (*Table 41*). At a threshold of £20,000 per QALY gained, the estimated probability that LATP is cost-effective compared with LATRUS is 59% and the maximum cost-effective price for CamPROBE is £81.17 per procedure (or £40.59 per CamPROBE devices, as two are required per procedure). The maximum price at which CamPROBE is estimated to be cost-neutral is £40.82 per procedure. Two-way sensitivity analysis was used to explore uncertainty relating to the relative risk 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 and colleagues are subject to a high degree of uncertainty. They also exclude other relevant comparators, as specified in the two NICE decision problems.

Table 41 Characteristics of the included economic evaluation

Study	**Wilson and colleagues**
Publication Year	2021
Country	UK
Study type	Cost-effectiveness study
Population	Men with suspected localised prostate cancer
Intervention(s)	LATP biopsy (CamPROBE) versus LATRUS biopsy
Perspective of analysis	UK NHS
Time horizon	Lifetime
Model type	Decision tree + Markov model
Base case results	At zero price for CamPROBE biopsy device: Incremental costs: -£29.61 (95% CrI: -£501.54 to £441.68) Incremental QALYs: 0.0015 (95% CrI: -0.081 to 0.084) LATP dominates LATRUS
Abbreviations: CrI credible interval; For abbreviations see *List of Abbreviations*	

5.1.4 Overview of other published economic studies of interest

Table 42 presents an overview of other studies retrieved by the systematic review that were used to inform the EAG economic evaluation. These studies were not reported above as they do not meet the inclusion criteria of the systematic review. However, they are still considered possible sources of evidence to inform model structure and inputs.

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 evaluations assessed screening or other diagnostic tests and assays (versus 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 two 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 one-year

Markov cycle length. All the studies reported costs and utilities and estimated the cost/QALY.

Two economic studies in particular were very influential in the development of our model. Firstly, the cost-effectiveness analysis conducted alongside the PROMIS study reported in the Brown and colleagues HTA report (2018) and in the Faria and colleagues' paper (2018).[59 60] This 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 analysis by Wilson and colleagues, described above, relied heavily on the model structure and input parameters from the Faria and colleagues' model. We also use parameters from the PROMIS economic analysis to inform estimates of baseline prevalence of prostate cancer and diagnostic performance of TRUS biopsy in our model (see sections 5.7.1 and 5.7.2 below). This provides the baseline diagnostic outcomes for TRUS, against which other biopsy methods in the current scope are compared.

The second analysis that informed our model structure and parameters was that developed by the NICE Guideline Updates Team for the update of the NICE guideline on prostate cancer published in May 2019 (NG131).[62] Their model was designed to estimate the cost-effectiveness of follow up protocols for people with a raised PSA, negative mpMRI and/or negative biopsy. It includes a Markov model that predicts progression and diagnosis of prostate cancer for people with an initial 'true negative' (no or clinically non-significant disease) or 'false negative' diagnosis (intermediate or high risk localised or metastatic disease) and also for those with correctly diagnosed prostate cancer. We replicated this Markov model to predict long-term costs and outcomes based on diagnostic performance of the biopsy methods in the current decision problems. As well as the Health economic model report which is available on the NICE website,[62] we also had access to a copy of the NG131 economic model provided by the NICE Guideline Updates Team. See section 5.6.2 below for a description of the Markov model and 5.7.5 for the transition probabilities.

Table 42 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) [59]	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	-	-	Table 26, 35	Table 28, 35	Table 29, 35
Faria, 2018 (UK) [60]	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	-	Table 2, S9 and S11	Table S10	Table S11, S12
Mowatt, 2013 (UK) [63]	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	Table 16, 17, 18, 19	Table 25	Table 18, 22, 23, 24
Nicholson, 2015 (UK) [64]	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	Table 32, 34, 35
Cerantola, 2016 (Canada)	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	Table 1, 2

de Rooij, 2014 (The Netherlands) [65]	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	Table 1, 2
Dijkstra, 2017 (The Netherlands) [66]	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	Table 1, 3
Hao, 2021 (Sweden) [67]	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 organized quadrennial PSA screening among men aged 55 to 69 years	Microsimulation model	Lifetime	-	Table 1	Table 1, S4	Table S2
Pahwa, 2017 (USA) [68]	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) [69]	Cost-effectiveness of three active surveillance strategies (TRUS-guided biopsy, mpMRI followed by MRI-guided biopsy, mpMRI alone) for patients with low-risk prostate cancer	Markov model	Lifetime	1 year	Table 1	Table 2	Table 2
Sathianathen, 2018 (USA) [70]	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) [71]	Cost-effectiveness of three prostate biopsy approaches (TRUS-guided biopsy, direct in-bore MRI-guided biopsy and image fusion guided	Decision tree + Markov model	18 years	1 year	Table 1, 3	Table 3	Table 1, 2

	biopsy) for biopsy-naïve patients in whom clinically significant prostate cancer was suspected						
NG131 model, 2019 (UK) [62]	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	Table HE02, HE05, HE07, HE09, HE11	Table HE14	Table HE08, HE12, HE13
EPI, ExoDx™ Prostate [Intelli-Score]; PCA3, prostate cancer antigen 3; PHI, Prostate Health Index; MRS, magnetic resonance spectroscopy. For the remaining abbreviations see *List of Abbreviations.*							

5.2 Systematic review of health-related quality of life (HRQoL)

The EAG undertook searches to identify data on health-related quality of life (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 database searches for HRQoL studies (HRQoL 1) used the clinical effectiveness search strategies with the addition of the Canadian Agency for Drugs and Technologies in Health (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, search terms were used specifically for the EQ-5D utility measure (the CADTH search filter was not used), to reflect the NICE preferred method for utility assessment,[72] 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 ten years. The strategies for 'HRQoL 2' are shown in Appendix 1.

The inclusion and exclusion criteria for eligibility screening are given in *Table 43*. 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 is people who have undergone screening or diagnostic tests for prostate cancer and people who have diagnosed prostate cancer. The following HRQoL measures were eligible for inclusion in searches 'HRQoL 1': EQ-5D (3 or 5-level version), Short Form questionnaire-36 items (SF-36) (using all subscales), Short Form questionnaire-12 items (SF-12), Short Form questionnaire-6 items (SF-6D), Health Utilities Index (HUI) 1, 2 and 3 and 15D

questionnaire. All of these measures are generic, preference-based utility measures or can be mapped to the EQ-5D using published algorithms, in line with the NICE reference case.[72] However, in searches 'HRQoL 2', only studies assessing HRQoL with the EQ-5D instrument and using the UK tariff were eligible.

Table 43 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
Country 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 language
Others	-	Studies assessing the quality of life of specific treatments
For abbreviations see *List of Abbreviations.*		

The EAG planned to extract data related to the study design, country and sample size, HRQoL instruments used, and health states assessed.

5.2.1 Results of the review of HRQoL studies

We present the results of the systematic searches 'HRQoL 1' in Appendix 9.

The systematic searches 'HRQoL 2' identified 369 potentially relevant studies (see *Figure 15*). Of the 369 references, 21 were retrieved for full-text screening and six studies [73-78] were included after full text screening. Of the excluded studies, seven were based on HRQoL scores that did not fit the economic model, five on a different or unclear value set, two on the inclusion of a different population and one on the assessment of HRQoL associated with specific interventions. The excluded references and reasons for exclusion are shown in Appendix 10.

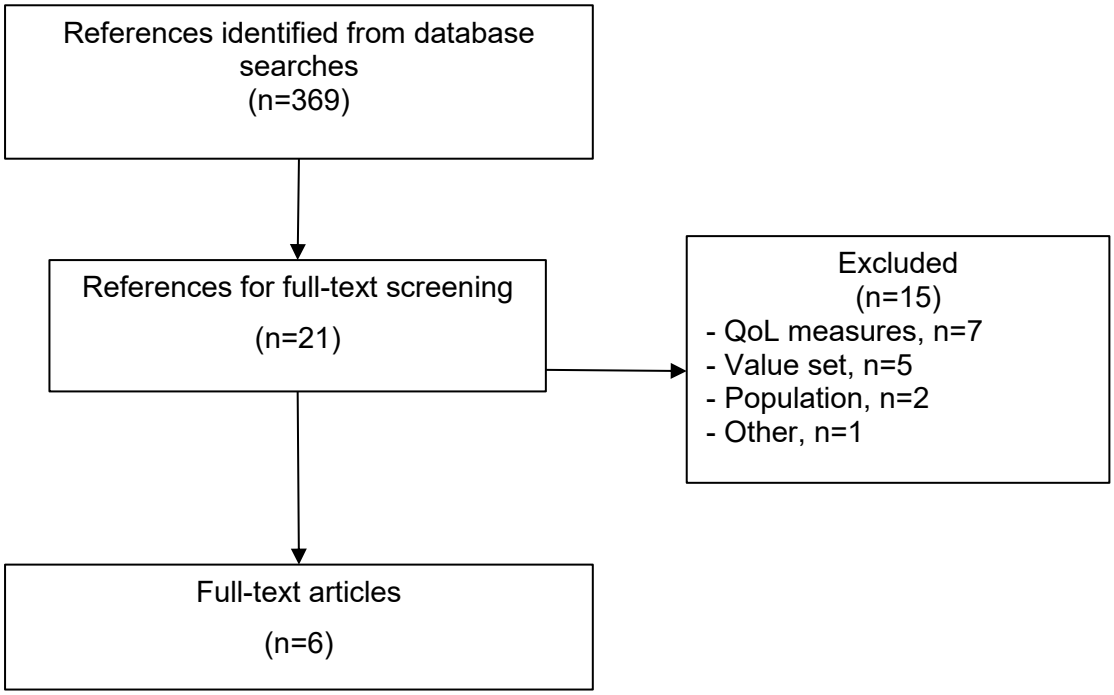


Figure 15 Flow chart for the identification of HRQoL studies (searches 'HRQoL 2')

The main characteristics of the six studies included in searches 'HRQoL 2' and the utility values reported by them are presented below (see *Table 44* and *Table 45).* Three studies were conducted in the UK and used the EQ-5D-5L version of the questionnaire and the remaining 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 greater than 300. These papers are discussed in relation to their applicability to the EAG economic model in section 5.7.8.

Further details can be found in Appendix 11.

Table 44 Characteristics of included HRQoL studies (searches 'HRQoL 2')

First Author, Year	N [a]	Country	Instrument	Health state(s) described
Booth et al. 2014 [73]	5,516	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 [74]	3,348	Republic of Ireland and Northern Ireland	EQ-5D-5L	Invasive prostate cancer (at least 20-month survivors)
Farkkila et al. 2014 [75]	30	Finland	EQ-5D-3L	End-stage prostate cancer
Gavin et al. 2016 [76]	3,348	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 [77]	621	Finland	EQ-5D-3L	Localised disease 6 months after diagnosis; localised disease in the following 12 months; remission; metastatic disease; palliative care
Watson et al. 2016 [78]	316	UK	EQ-5D-5L	No/mild and moderate/severe problems due to prostate cancer treatment in patients diagnosed at least 9 months before.

[a] Corresponds to the total number of participants who completed the HRQoL questionnaires.
For abbreviations see *List of Abbreviations.*

Table 45 Included HRQoL studies: summary of utility values (searches 'HRQoL 2')

Health states	Utility	Source
No prostate cancer		
No PC (screening programme)	0.83	Booth et al. 2014
No PC (no screening programme)	0.857	Booth et al. 2014
Prostate cancer		
Difference of PC vs. no PC (screening programme)	+0.005	Booth et al. 2014
Difference of PC vs. no PC (no screening programme)	-0.031	Booth et al. 2014
Early disease		
Difference of organ-confined PC vs. no PC (screening programme)	+0.01	Booth et al. 2014
Difference of organ-confined PC vs. no PC (no screening programme)	-0.031	Booth et al. 2014
Early disease PC (2-18 years post-treatment)	0.88	Gavin et al. 2016
Localised disease (6 months after diagnosis)	0.9 (0.84-0.96)	Torvinen et al. 2013
Difference vs. general Finish population	+0.103	Torvinen et al. 2013
Localised disease (18 months after diagnosis)	0.89 (0.86-0.92)	Torvinen et al. 2013
Difference vs. general Finish population	+0.089	Torvinen et al. 2013
Localised disease (remission)	0.87 (0.85-0.89)	Torvinen et al. 2013
Difference vs. general Finish population	+0.043	Torvinen et al. 2013
Advanced disease		
Difference of advanced PC vs. no PC (screening programme)	-0.039	Booth et al. 2014
Difference of advanced PC vs. no PC (no screening programme)	-0.051	Booth et al. 2014
Invasive PC (at least 20 months after diagnosis)	0.82	Drummond et al. 2015
Late disease PC (2-18 years post-treatment)	0.76	Gavin et al. 2016
Metastatic disease	0.74 (0.69-0.80)	Torvinen et al. 2013
Difference vs. general Finish population	-0.054	Torvinen et al. 2013
Palliative disease	0.59 (0.48-0.70)	Torvinen et al. 2013
Difference vs. general Finish population	-0.157	Torvinen et al. 2013

Health states	Utility	Source
End-stage PC	0.551 (0.405-0.664)	Farkkila et al. 2014
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
Urine Function (moderate/severe problems)	0.773 (0.222)	Watson et al. 2016
Bowel Function (no/mild problems)	0.862 (0.166)	Watson et al. 2016
Bowel Function (moderate/severe problems)	0.653 (0.195)	Watson et al. 2016
Sexual Function (no/mild problems)	0.861 (0.176)	Watson et al. 2016
Sexual Function (moderate/severe problems)	0.838 (0.17)	Watson et al. 2016
For abbreviations see *List of Abbreviations.*		

5.3 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 compares the costs of LATP (with the PrecisionPoint™ device) against different combinations of LATRUS and GATP for UK NHS Trusts.

This study 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 performance for transperineal biopsies compared with LATRUS. This suggests that the assumption of equal diagnostic performance may not be realistic.

The YHEC model includes costs associated with carrying out prostate biopsies and costs associated with biopsy complications from an HTA report by Ramsay et al. (2015) [79]. *Table 46* shows the costs for each type of biopsy, with the stepper apportioned across 250 cases. *Table 47* shows the annual costs of biopsy complications, based on an incidence over one year for 250 biopsies. According to this study, 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 stepper vary according to the number of cases. In addition, different NHS Trusts undertake different proportions of TRUS and GATP. Therefore, scenarios were conducted to estimate the economic impact of different combinations.

Table 46 YHEC cost minimisation study: input costs for each type of biopsy

	TRUS	GATP	LATP
Theatre session	-	£193.5	-
Outpatient room	£43	-	£43
Urologist	£57.33	£129	£57.33
Anaesthetist	-	£117.75	-
Grid	-	£78	-
Balloon/Probe cover	£4.6	£45.5	£4.6
Biopsy Gun	£25.96	£25.96	£25.96
Cassettes	-	£0.48	£0.48
Sponges	-	£0.16	£0.16
Drapes	-	£1.57	-
Spinal needles	£5.74	-	£5.74
Local anaesthetic normal dosage	£12.9	£100	£12.9
Antibiotics normal dosage	£0.25	-	-
PrecisionPoint™ device	-	-	£200
Stepper [a]	-	£88	-
Total cost per case	**£149.78**	**£779.92**	**£350.17**

Source: reproduced from YHEC study, Table 2.1.
[a] Unit cost of £22,000, apportioned across 250 cases.
For abbreviations see *List of Abbreviations.*

Table 47 YHEC cost minimisation study: annual costs of biopsy complications

Complication	Implication	Cost per case	TRUS (per year)		GATP (per year)		LATP (per year)	
			Cases	Cost	Cases	Cost	Cases	Cost
Sepsis [a]	Hospital stay	£8,570	1.25	£10,713	0	£0	0	£0
	Antibiotics	£210	1.25	£263	0	£0	0	£0
Infection	Hospital stay [b]	£963	8.75	£8,426	0.25	£241	0.25	£241
	Antibiotics [c]	£147	8.75	£1,286	0.25	£37	0.25	£37
Detection failure	Repeat MRI	£199	12.5	£2,488	-	-	-	-
	Repeat biopsy	£710	-	-	37.5	£26,607	-	-
Total annual cost			**£23,175**		**£26,885**		**£278**	

Source: reproduced from YHEC study, Table 2.2
[a] Ten-day hospital stay with antibiotics for sepsis.
[b] Three-day hospital stay for infection.
[c] Seven-day antibiotic treatment for infection.
For abbreviations see *List of Abbreviations.*

The results suggest 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 that 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 stepper or with another freehand device.

5.4 EAG independent economic evaluation approach and rationale

The EAG has 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 (section 2 above). 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 is provided in subsequent sections of this chapter.

5.4.1 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 metastatic disease 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 test the impact of including a proportion of people with pre-existing metastatic disease in scenario analysis.

5.4.2 The diagnostic pathway: decision tree

The structure of the decision tree is described in detail in *section 5.6.1* below. 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 and colleagues to estimate cost-effectiveness for LATP (as described in *sections 5.1.3 and 5.1.4* above).[58-60]

The cohort entering the decision tree is first stratified by baseline prevalence of low-, intermediate- and high-risk localised disease, and metastatic disease (if included). The tree

then models the diagnostic pathway and estimates complication and cancer detection rates for the cohort and associated costs and QALY loss with the alternative biopsy methods specified in the scope. The tree includes a second biopsy for a proportion of patients with a negative first biopsy, with the assumption that this second biopsy would be conducted with a LATRUS method. This is a simplification, in practice methods for repeat biopsies are likely to vary, but evidence for the diagnostic performance 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 conditional on prior, estimated from data reported by Faria and colleagues (*section 5.7.1* below).[59 60 80]
- Probabilities of detecting clinically significant (CS) and clinically non-significant (CNS) prostate cancer (*section 5.7.2 below)*. For LATRUS, these probabilities are also estimated from data reported by Faria and colleagues.[59 60 80] The TRUS cancer detection probabilities are adjusted for other biopsy methods using relative risk estimates from the EAG systematic reviews and meta-analyses (see *section 4.8* above).
- The probability of a repeat biopsy if the first biopsy is negative is estimated from a paper by Marenco Jimenez and colleagues (2021), identified from our clinical review.[81] Assumptions about how this probability differs according to the first biopsy method and result were tested in scenario analysis (see discussion in *section 5.7.2*).
- Probabilities of biopsy-related complications (see *section 5.7.4* below) were estimated from various sources.[61 82-86] Relevant papers were identified from our clinical review and the review of economic evaluations, with alternative sources tested in scenario analysis (see *sections 4.9, 5.1.3 and 5.1.4* above).
- The impact of biopsy-related complications on patient health-related quality of life (QALY loss) is based on assumptions as in the analysis by Wilson and colleagues (see *section 5.7.8* below).[58]
- Costs of the biopsy procedures and treatment for complications, see *section 5.7.6* below. We developed detailed cost estimates for different LATP approaches in decision question 2.

5.4.3 Long-term consequences: the Markov model

We considered two designs for the Markov model: 1) a model with three health states (progression free, metastatic disease and death), stratified by initial level of cancer risk and treatment, developed for the PROMIS economic evaluation by Faria and colleagues; and 2)

a model developed for 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.[59 60 62]

Key structural differences between the NG131 and Faria Markov models are that the NG131 model: predicts incidence of prostate cancer in members of the cohort who do not initially have it; it explicitly models progression between the different stages of localised disease (low-, intermediate- and high-risk); and it explicitly models subsequent diagnosis for people with false negative results after the biopsy pathway, based on estimated rates of symptomatic presentation and routine follow up in primary care. The latter feature is particularly important for the current decision problem as it enables quantification of the monetary and QALY costs of a biopsy failing to diagnose clinically significant 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 use 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.[62] We also had access to a copy of the model, which provided additional information about how the model was coded and detail to fit probabilistic distributions for some parameters. See *section 5.6.2* below for further description of the NG131 model and explanation of how we adapted it for use in the current decision problem. The NG131 model was designed to test alternative follow-up strategies for people with a negative diagnosis (true and false negatives), with up to three stages (screening, diagnostic imaging and prostate biopsy). This level of detail is not required for the current decision problem, so we replicated the NG131 model, rather than using it in its entirety. We align the input parameters and assumptions in our version of the Markov model with those in the NG131 model, except more recent or relevant sources were identified.

Our version of the NG131 model is intended to reflect the NICE recommendations for follow-up from the 2019 update, with flexibility to explore variations in clinical practice.[8] NICE guidance recommends consideration of a repeat biopsy for people with a negative biopsy and MRI Likert score of 3 or more (NG131 recommendation 1.2.10), which is integrated within our decision tree as described above. For people with an MRI Likert score of 1 or 2 and negative biopsy, NG131 recommendation 1.2.12 recommends a repeat PSA at 3 to 6 months followed by a prostate biopsy ‘if there is a strong suspicion of prostate cancer’ or discharge to primary care with PSA follow up every 2 years. In our version of the Markov

model we include parameters to specify a schedule of primary care follow up for people with one or more negative biopsy result (true or false negative). This includes a probability of follow up, the timing of a first PSA test, the frequency of subsequent tests, and a maximum duration of follow up. This gives flexibility to vary assumptions about follow up for the different subgroups and to reflect variations in practice. For our base case analysis we assume a test at 6 months then annual for a maximum of 10 years for everyone with a false negative biopsy result, but we vary this in sensitivity analysis.

The other difference between our version of the Markov model and the NG131 model is that we updated unit costs and included costs for some recently recommended treatments. The resource use assumptions in the NG131 model reflected NICE guidance at the time of the 2019 guideline update, including recommendations for follow-up, monitoring and treatment for localised and metastatic disease. For people with localised disease, included treatment options were active surveillance, radical prostatectomy, external radiotherapy, brachytherapy or hormone therapy (androgen deprivation therapy, ADT). People with metastatic disease were assumed to receive ADT and docetaxel with a proportion going on to abiraterone and docetaxel. We also included costs for enzalutamide and apalutamide as additional treatment options for metastatic disease, based on NICE technology appraisals TA712, TA740 and TA741.[87-89]

Parameters for the Markov model include:

- Transition probabilities (per 3-month cycle) between the 11 health states are the same as in the NG131 model (Table HE07 in the online model report).[62] See *section 5.7.5* below for details and explanation of how these probabilities were derived.
    - Prostate cancer incidence (true negative to undiagnosed low-risk).
    - Progression between the undiagnosed health states.
    - Progression between the diagnosed health states.
    - Diagnosis (transition from an undiagnosed to a diagnosed health state) due to onset of symptoms or periodic follow up in primary care.
    - Mortality, based on general population life tables, adjusted with relative risks of death for people with metastatic disease.
- Resource use and costs (see *section 5.7.7* below for details):
    - Follow up and monitoring costs are based on guidance from NG131, with some adjustments based on expert comments about use in clinical practice.
    - The distribution of treatments for localised disease differs by level of risk: estimated from information from Gnanapragasam (2016) and the National

Prostate Cancer Audit (NPCA 2020).[86 90] Treatment availability and use also differs for hormone-sensitive and hormone-relapsed metastatic disease. Other treatments included for metastatic disease include apalutamide and enzalutamide.

- Probabilities of complications related to radical treatments were obtained from the ProtecT trial (Donovan et al. 2003)[91] and adverse events related to ADT and docetaxel from STAMPEDE (James et al)[92], as in the NG131 model. We estimated adverse events related to apalutamide and enzalutamide from the TITAN and ARCHES trials, respectively.[93 94]

- Health outcomes are estimated in the form of QALYs, incorporating survival and the impact of symptoms and adverse effects on utility.[77 78 95] See *section 5.7.8* below.

5.4.4 Framework for economic analysis

Analysis follows the NICE reference case, as specified in section 15 of the Diagnostics Assessment Programme (DAP) manual.[72]

- 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 data with NICE-recommended UK general population values, if available.
- Costs are estimated from an NHS and personal social services (PSS) 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.[96 97] 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).

5.5 Modelled decision problem

5.5.1 Population and subgroups

The model is designed to estimate costs and health outcomes for the population specified in the NICE scope: people with suspected prostate cancer where prostate biopsy is indicated. We aim to reflect characteristics of this population in routine NHS practice, including age and probability of prostate cancer (stratified by risk) 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 or over (mean age at diagnosis was not reported) (NPCA 2020 Table 3).[86] 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 intermediate- and high-risk cancers was 64.9 and 66.8 respectively.[59] For the base case, we assume 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.[62] We test the effect of baseline age in scenario analysis.

For the purposes of the economic evaluation, we assume that the cohort have already had multiparametric MRI (mpMRI) as an investigation for suspected clinically localised prostate cancer, with results reported on a 5-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 performance of mpMRI from the PROMIS study, which we use to estimate the baseline prevalence of prostate cancer conditional on mpMRI results (see *section 5.7.1* below). 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 performance 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 *sections 4.2 to 4.6* above).

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 an 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 clinically significant prostate cancer than those with an 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:

A. People referred for a first biopsy with a Likert score of 3 or more (base case)
B. People referred for a first biopsy with a Likert score of 1 or 2

C. People referred after a previous negative biopsy with a Likert score of 3 or more
D. 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 performance for these groups.

The baseline prevalence of localised prostate cancer can be estimated for subgroups A to D using results from the PROMIS study, as reported by Faria and colleagues.[60] They categorised the study population by true disease status based on a combination of a template prostate mapping biopsy (TPMB) and TRUS biopsy (whichever was the most severe). No people with metastatic disease were included in the PROMIS study. Localised prostate cancer was classified into low, intermediate and high risk according to two sets of definitions.

For the economic model, we use results for the following definitions:

- Low-risk (LR): Gleason ≤ 6, PSA ≤10 ng/ml and clinical stage T1 to T2a
- Intermediate-risk (IR): Gleason 7, PSA 10-20 ng/ml and clinical stage T2b
- High-risk (HR): Gleason 8-10, PSA > 20 ng/ml and clinical stage T2c or higher

The Intermediate- and high-risk localised disease grouped together as clinically significant (CS) disease. Low-risk disease is classed as clinically non-significant (CNS).

We estimated the prevalence of LR, IR and HR localised prostate cancer in the four subgroups referred for TRUS biopsy, using the true disease status in the PROMIS cohort, diagnostic performance characteristics of mpMRI and TRUS biopsy reported by Faria and colleagues. See *section 5.7.1* below for details.

In our base case, we assume that the referred cohort does not include people with metastatic disease. 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). In the PROMIS study, which provides baseline estimates of prevalence for the model, 5 out of 740 men registered for the study were withdrawn due to having stage T4 or nodal disease (Brown et al. 2018 Table 6).[59]

The model has an option to include a proportion of people with metastatic disease in the cohort, with the assumption of the same cancer detection and complication rates as for people with high-risk localised disease.

5.5.2 Biopsy methods and devices

The model is designed to evaluate the decision questions defined in the NICE scope. We follow the naming conventions for interventions and comparators used in the pairwise and network meta-analyses in *section 4.8* above.

Decision question 1

- Intervention: Local anaesthetic transperineal prostate biopsy including use of grid and stepper unit, a coaxial needle or a freehand transperineal device (*LATP-all*)
- Comparators:
  - Local anaesthetic transrectal ultrasound biopsy (*LATRUS*)
  - General anaesthetic transperineal biopsy using a grid and stepping device (*GATP*)

Decision question 2

- Interventions: Local anaesthetic transperineal prostate biopsy with one of the following freehand transperineal biopsy devices: PrecisionPoint™ , UA1232, Trinity® Perine Grid, CamPROBE, SureFire or EZU-PA3U. Referred to collectively as *LATP-freehand*
- Comparators:
  - Local anaesthetic transrectal ultrasound biopsy (*LATRUS*)
  - Local anaesthetic transperineal prostate biopsy using a grid and stepping device. Referred to as *LATP-other*, because of the difficulty in identifying specific methods used in clinical studies.
  - General anaesthetic transperineal biopsy with a grid and stepping device (*GATP*)

5.6 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 *section 5.7* below for model input parameters and *section 5.8* for a list of model assumptions.

5.6.1 Decision tree

Overview

A simplified overview of the decision tree is shown in *Figure 16* below. Further detail is provided in the following sections.

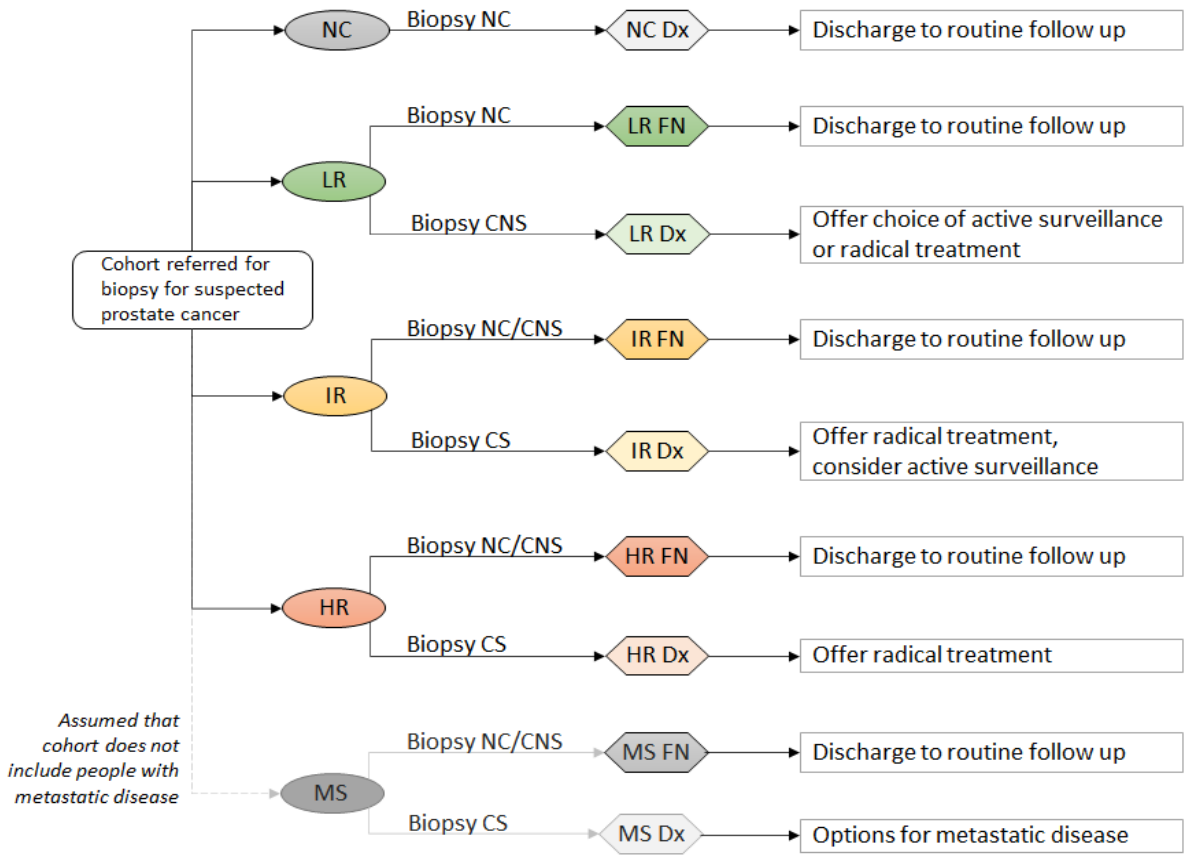


Figure 16 Overview of decision tree

CNS, clinically non-significant cancer; CS, clinically significant; 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, no cancer; NC Dx, no cancer correctly diagnosed.

The model starts with a cohort of interest, one of four subgroups A to D defined by mpMRI Likert score and history of previous biopsy. The cohort is stratified by true prostate cancer status (no cancer, low, intermediate or high risk localised or metastatic disease). The decision tree estimates diagnostic outcomes (the proportions of correct and false negative biopsy results) for LATRUS biopsy using cancer detection rates from the PROMIS study. Diagnostic outcomes for the other biopsy methods are calculated using relative risks from the network meta-analyses (base case) and pairwise meta-analyses (scenarios) reported above (see *section 4.8*). In addition to diagnostic outcomes, the decision tree estimates incidence of biopsy-related adverse events, including a small proportion of fatal events. The endpoints of the decision tree, comprising correct diagnoses (Dx) or false negatives (FN), represent the health states in the Markov model.

The tree divides the cohort according to the expected incidence of biopsy-related complications, categorised as:

- No AE: no or minor adverse events for which the patient does not seek treatment
- Mild AE: mild/moderate adverse events treated outside hospital
- Admission: overnight stay immediately after the biopsy or readmission within 28 days
- Mortality within 28 days of the biopsy

The following sections describe the structure of the decision tree for people with no cancer, LR, IR or HR localised, or metastatic disease in more detail.

No cancer decision tree (see Figure 17)

We assume that all biopsy methods are perfectly specific: there cannot be false positive results for people who truly do not have prostate cancer.

Complications may occur after the first and/or second biopsy, classified as above (no AE, mild AE, admission, mortality). Endpoints for the people without prostate cancer are correct diagnosis (NC Dx) and death from biopsy-related complications.

Clinically non-significant disease (see Figure 18)

For this population, the biopsy may give a correct diagnosis of CNS disease; a false positive result of CS disease; or a false negative result of no cancer. In practice, there were no cases of TRUS biopsy CS results for people with LR cancer in the PROMIS study.[59] Hence,

although we have included this false positive result as a possibility, the probability of this event in our model is zero.

If the biopsy result is negative (CNS or NC), 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 with a prior mpMRI Likert score of 3 or more than with first result NC and a Likert of 1 or 2. See *section 5.7.3* below for discussion of the source of estimates for re-biopsy rates.

A second biopsy can report a CS, CNS or NC result, although the estimated probability of a CS result for a second TRUS biopsy with LR cancer is zero (as in the Faria and colleagues' model, based on the systematic review and meta-analysis by Schoots and colleagues).[60 80]

Complications may occur after the first and/or second biopsy, classified as above (no AE, mild AE, admission, mortality). Endpoints for the people with low-risk disease are correct diagnosis (LR Dx), false positive (LR FP), false negative (LR FN) and death.

Clinically significant disease (see Figure 19 and Figure 20)

The structure of the decision tree is the same for intermediate- and high-risk as for low-risk, although the cancer detection and repeat biopsy probabilities differ for these groups. We assume that the incidence of complications does not differ by cancer risk group. Endpoints can only be correct diagnosis (IR Dx; HR Dx), false negative (IR FN; HR FN) and death.

The model also includes a decision tree for metastatic disease, which has the same structure as that for CS localised disease. This is not used in our analyses.

The trees are replicated for each intervention and comparator in decision question 1 and 2.

Input parameters for the decision tree are:

- True prevalence of LR, IR and HR prostate cancer by subgroup, estimated from published data from the PROMIS study (*section 5.7.1* below)
- Cancer detection rates for LR, IR and HR (*section 5.7.2* below)
    - Baseline rates for CS and CNS detection are estimated for first and second TRUS biopsy using published estimates from the PROMIS study
    - Relative accuracy of other biopsy methods is estimated from the NMA and pairwise meta-analyses reported in the clinical sections above
- Probability of a repeat biopsy after a negative first biopsy (*section 5.7.3* below)

- Incidence of biopsy related complications by biopsy method (*section 5.7.4* below)
- QALY loss for biopsy-related complications (*section 5.7.8* below)
- Costs for the biopsy procedure and treatment of complications (*section 5.7.6* below)

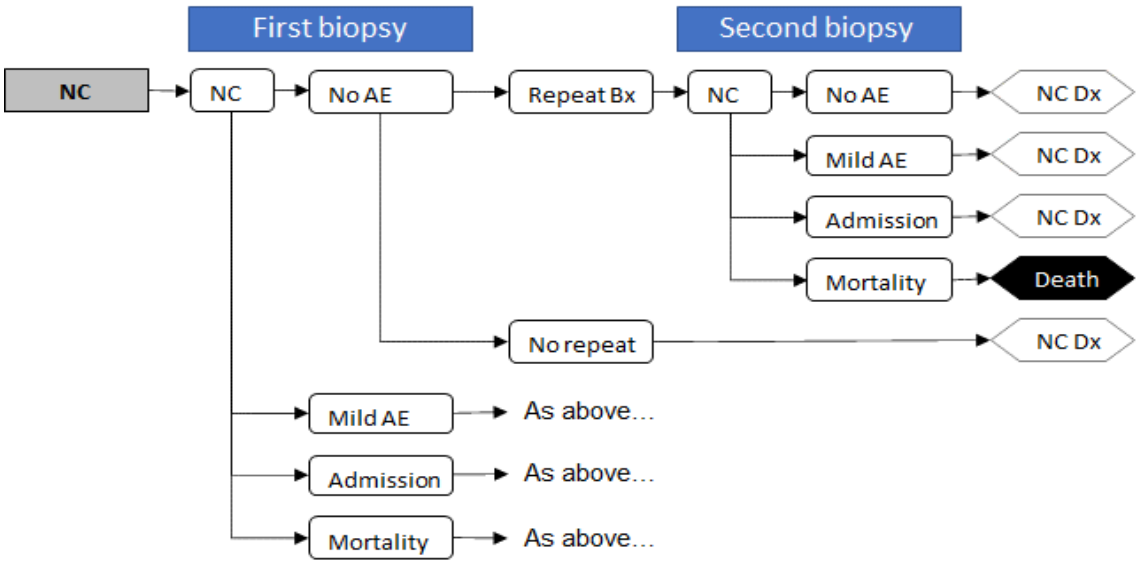


Figure 17 Illustration of decision tree for people without prostate cancer
NC, no cancer; LR, true low risk; NC Dx, no cancer correctly diagnosed; AE, adverse events.

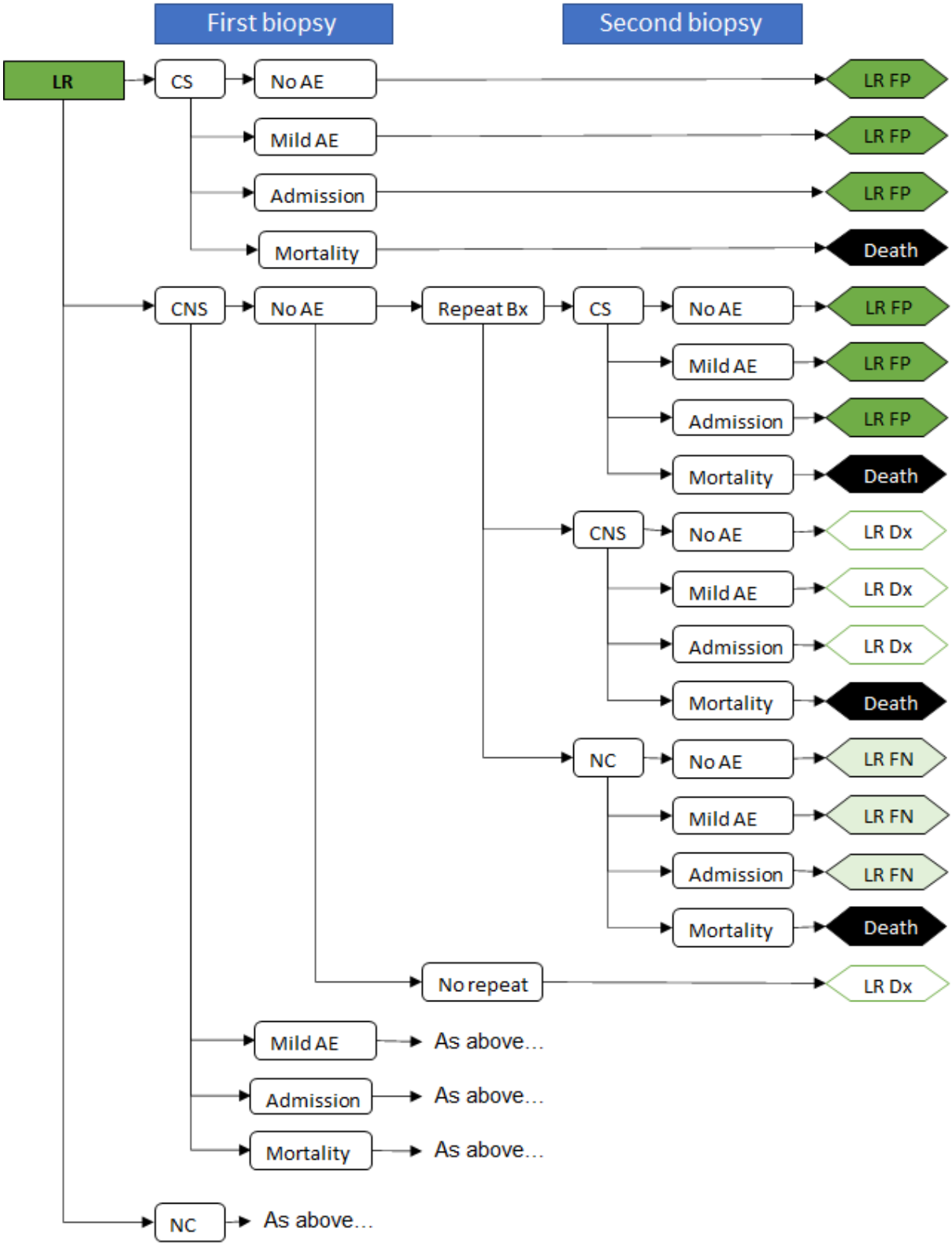


Figure 18 Illustration of decision tree for people with low-risk prostate cancer
CS, clinically significant; CNS, clinically non-significant; NC, no cancer; LR, true low-risk; LR Dx, low-risk correctly diagnosed (classified as clinically non-significant); LR FP, low-risk false positive (classified as clinically significant); LR FN, low risk false-negative (classified as no cancer); AE, adverse event; Bx, biopsy.

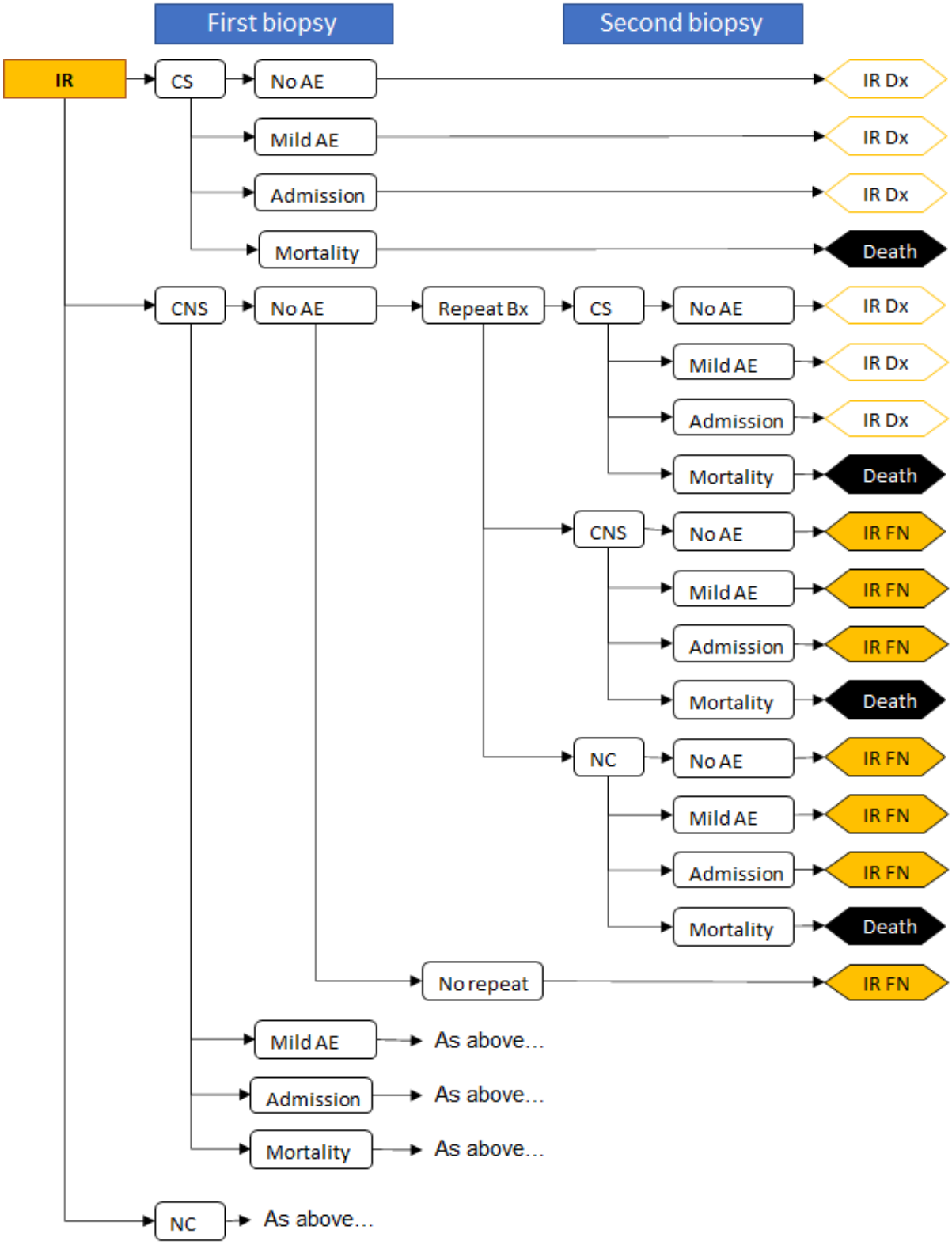


Figure 19 Illustration of decision tree for people with intermediate-risk prostate cancer
CS, clinically significant; CNS, clinically non-significant; NC, no cancer; IR, true intermediate-risk; IR Dx, intermediate-risk correctly diagnosed (classified as clinically significant); IR FN, intermediate-risk false negative (classified as clinically non-significant or no cancer); AE, adverse event; Bx, biopsy.

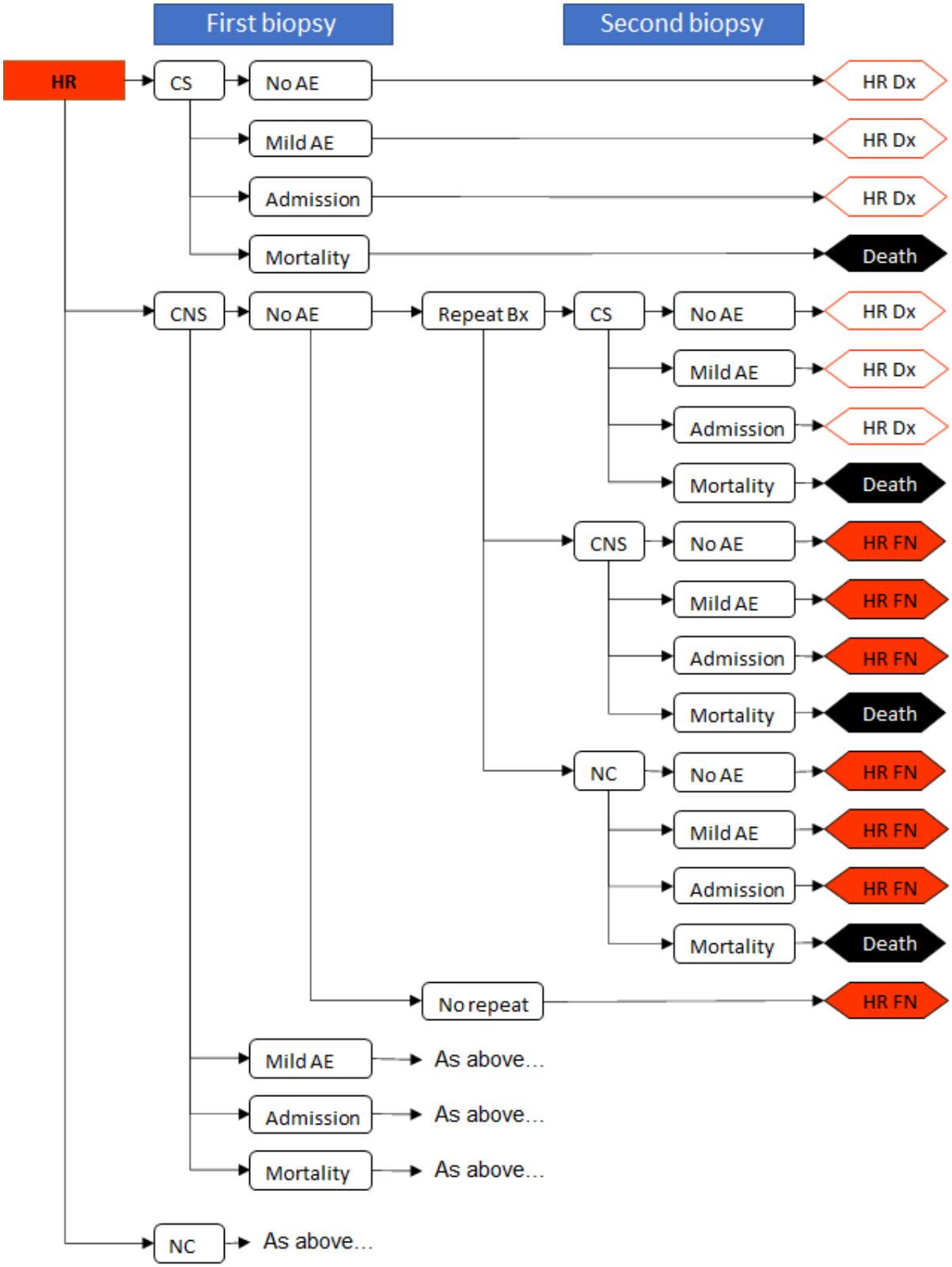


Figure 20 Illustration of decision tree for people with high-risk prostate cancer
CS, clinically significant; CNS, clinically non-significant; NC, no cancer; HR, true high-risk; HR Dx, high-risk correctly diagnosed (classified as clinically significant); HR FN, high-risk false negative (classified as clinically non-significant or no cancer); AE, adverse event; Bx, biopsy.

5.6.2 Markov model: long term outcomes

As discussed above (*section 5.4.3*), we considered two designs for the Markov model: the model developed for the economic evaluation of the PROMIS study by Faria and colleagues, later adapted by Wilson and colleagues to compare LATP using the CamPROBE device with TRUS (see *section 5.1.3*); and the model developed for the 2019 update of the NICE prostate cancer guideline (NG131) for evaluation of follow-up strategies for people with a negative mpMRI or biopsy result.[58-60 62]

Faria and colleagues' model

This three-state Markov model is illustrated in *Figure 21*. In reality, this model is more complicated than this, as the three-state Markov is replicated for patients with different true disease states and allocated treatments at the end of the diagnostic pathway. Faria and colleagues report five separate sets of transition probabilities for patients with low-risk cancer on 'watchful waiting' and intermediate- and high-risk cancer on either watchful waiting or with radical prostatectomy. The three-state model is replicated for each of these groups.

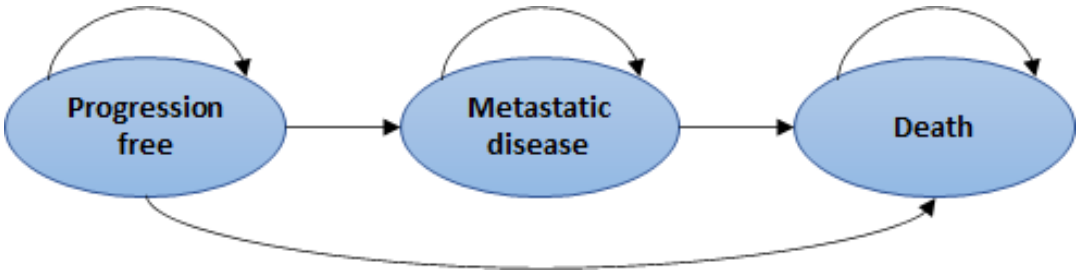


Figure 21 Illustration of the three-state Markov model from Faria and colleagues
Source: drawn by the ERG

NG131 model

The NG131 economic model was designed to evaluate the cost-effectiveness of alternative protocols for follow-up of people with raised PSA after a negative mpMRI and/or biopsy result.[62] It includes a Markov model with 11 health states grouped in four categories: 'true negatives' (no prostate cancer or undiagnosed low-risk disease); 'false negatives' (undiagnosed intermediate-, high-risk or metastatic disease); 'true positives' (diagnosed disease from low-risk to metastatic); and death related to prostate cancer or from other causes (see *Table 48*).

The schematic in *Figure 22* illustrates the transitions between these health states.

Table 48 Modelled health states in NG131 health economic model

Health States	
TN – no cancer	True negative, those truly diagnosed as having no cancer
TN – low-risk	Those who have clinically non-significant prostate cancer but diagnosed as no cancer. TN used to reflect that even if they were captured the treatment would not add benefits
FN – intermediate-risk	Cases with intermediate risk localised prostate cancer but were misclassified as having no cancer.
FN – high-risk	Cases with high-risk localised prostate cancer but were misclassified as having no cancer.
FN – metastatic	Cases where the disease spread outside the prostate and still not captured
T+ – low-risk	People with low-risk cancer and were truly captured
T+ – intermediate-risk	People with intermediate-risk cancer and were truly captured, receiving relevant treatments
T+ – high-risk	People with high-risk cancer and were truly captured, receiving relevant treatments
T+ – metastatic	People with metastases truly captured and receiving relevant treatments
Death from prostate cancer	Allowed only from diagnosed metastatic prostate cancer
Death from other causes	Allowed from any other alive states and sourced from life table data

Source: Adapted from Table HE03, Health economic report, NICE NG131, 2019.[62]
TN, true negative; FN, false negative; T+, true positive.

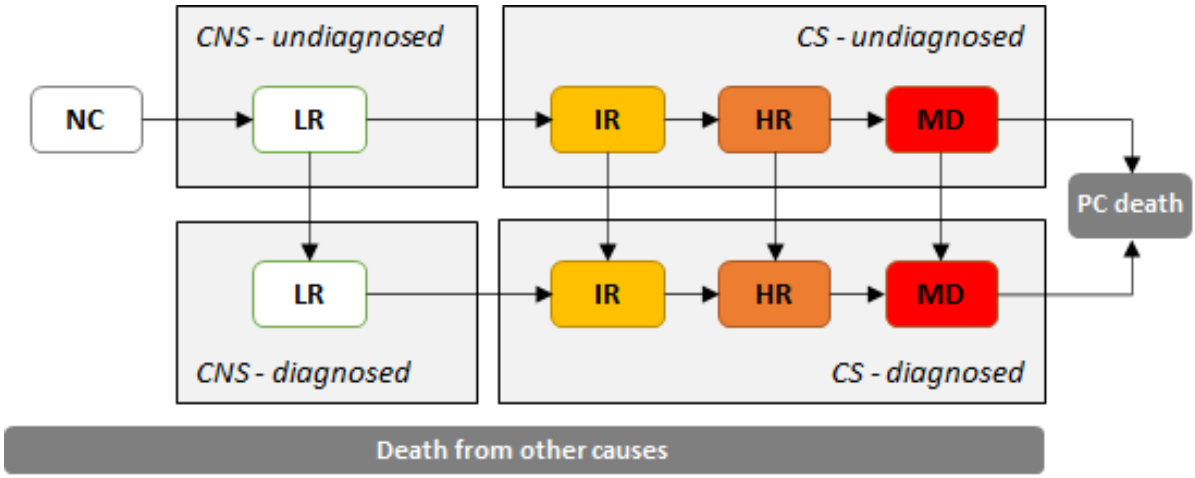


Figure 22 Illustration of guideline Markov model
Source: Drawn by EAG
MD, metastatic disease; For the remaining abbreviations see *List of Abbreviations*.

EAG approach

Unlike the Faria and colleagues' model, the NG131 model incorporates incidence of disease, as people without prostate cancer can develop low-risk localised disease. The NG131 model also models progression between low-, intermediate- and high-risk localised disease, whereas Faria and colleagues' group these states together into a single progression-free state. More importantly for our purposes, the NG131 model explicitly models the timing of diagnosis for false negative cases based on symptomatic presentation or routine monitoring as per NICE guidance following a negative biopsy result. This gives a direct method to model the downstream consequences of biopsy cancer detection failures, which is potentially important for comparison of the cost-effectiveness of alternative biopsy methods. We therefore chose to use a replicated version of the NG131 Markov model to estimate long-term costs and QALYs from the diagnostic outcomes from our decision tree.[62] We had access to the NG131 model, as well as the detailed report on the NICE website.[62]

Input parameters for the Markov model comprise:

- Transition probabilities are based on the NG131 model (*section 5.7.5* below). These comprise estimates of the incidence of prostate cancer, rates of progression for people with diagnosed and undiagnosed prostate cancer, diagnosis for people based on symptomatic presentation and follow-up PSA testing in primary care and mortality.
- Resource use and costs for active treatment, active surveillance or watchful waiting, follow-up and adverse events from treatment, and end-of-life care (*section 5.7.7*)
- Health state utilities and disutilities related to adverse events (*section 5.7.8*)

The Markov model is replicated for each intervention and comparator in decision question 1 and 2. Each version is identical, including input parameters, apart from the initial distribution of the cohort between the health states in the first model cycle, which is taken from the endpoints of the respective decision tree.

5.7 Model parameters

5.7.1 Baseline prevalence

We use results reported by the PROMIS economic evaluation to estimate the true prevalence of cancer (LR, IR and HR) for the subgroups with mpMRI Likert score ≤2 and Likert 3+, for first biopsy and previous negative biopsy. This provides the starting proportions of the cohort allocated to the decision trees illustrated in *Figure 17* to *Figure 20* above. Faria and colleagues report true disease status calculated from individual patient data with a reference standard combining template mapping biopsy and TRUS biopsy results (see *Table 49*).

Table 49 PROMIS economic evaluation, true disease status at referral for mpMRI

Group	Definition	N	%
No cancer	Men with no evidence of cancer at either TPMB or TRUSB.	159	27.9%
Low risk cancer	Men with Gleason score < 7 at either TRUSB or TPMB, and PSA<10.	91	16.0%
Intermediate risk cancer	Men with Gleason score=7 either TRUSB or TPMB, or PSA≥10.	301	52.9%
High risk cancer	Men with Gleason score ≥ 8 either TRUSB or TPMB.	18	3.2%
Total		596	100%

Source: Adapted from Faria et al. 2018, supplementary Table 5.
TPMB template prostate mapping biopsy

They calculated the probability of mpMRI results (NC, CS and CNS) conditional on true disease status from individual patient data. Results are reported for two definitions of 'clinically significant' for mpMRI results (see *Table 50*) and Likert cut-offs of 1 to 5. The PROMIS economic evaluation found that the optimal diagnostic strategies used mpMRI CS definition 2. We therefore use this definition in our analysis, with a Likert cut off of 3 (see *Table 51*).

We combined results from *Table 49,* Table 51*, and* Table 53 with Bayes formula to estimate the probability of prostate cancer by level of risk (NC, LR, IR and HR) conditional on previous mpMRI Likert score (1 or 2; and 3+) and history of previous biopsy. This provides prevalence estimates for our four subgroups A to D, see *Table 52* below.

Table 50 Definitions of CS cancer for mpMRI and TRUS diagnostic performance

	mpMRI diagnostic performance	TRUS diagnostic performance
Definition 1	Lesion volume of ≥ 0.5 ml and/or Gleason score of ≥ 4 + 3	Dominant Gleason pattern ≥ 4 and/or any Gleason pattern of ≥ 5 and/or a cancer core length of ≥ 6 mm.
Definition 2	Lesion volume of ≥ 0.2 ml and/or Gleason score of ≥ 3 + 4	Any Gleason pattern of ≥ 4 and/or a cancer core length of ≥ 4 mm
Source: Brown et al. 2018, Tables 18 and 19 For abbreviations see *List of Abbreviations.*		

Table 51 PROMIS economic evaluation, diagnostic performance of mpMRI

Disease status	**mpMRI classification**		
	No suspicion	**Suspicion of CNS**	**Suspicion of CS**
Definition 2 for mpMRI CS result; Likert cut-off ≥3			
No cancer	0.33 (0.26 to 0.40)	0.17 (0.11 to 0.23)	0.50 (0.43 to 0.58)
Low risk cancer	0.28 (0.19 to 0.38)	0.16 (0.08 to 0.24)	0.56 (0.46 to 0.67)
Intermediate risk cancer	0.08 (0.05 to 0.11)	0.05 (0.02 to 0.07)	0.87 (0.83 to 0.91)
High risk cancer	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	1.00 (1.00 to 1.00)
Source: Faria et al. 2018 Supplementary Table 7 For abbreviations see *List of Abbreviations.*			

Table 52 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 (NC)	19.4%	47.7%	40.0%	59.4%
Low-risk cancer (LR)	12.4%	25.7%	25.7%	32.0%
Intermediate-risk cancer (IR)	63.8%	26.6%	34.3%	8.6%
High-risk cancer (HR)	4.4%	0.0%	0.0%	0.0%
Source: Estimated by EAG from prevalence and diagnostic performance of mpMRI and TRUS biopsy from PROMIS (Faria et al. Supplementary Tables 5, 6 and 7). For abbreviations see *List of Abbreviations.*				

We note the reported zero probability of true HR localised prostate cancer for people with a Likert 1 or 2 result from mpMRI (*Table 51* above). We understand that such cases may occur in practice, although it is possible that this may reflect inaccurate mpMRI scoring.

5.7.2 Cancer detection rates

LATRUS biopsy

Estimates of diagnostic performance for LATRUS biopsy are taken from the PROMIS economic evaluation (see *Table 53* below). These results correspond with definition 2 for TRUS CS result, as defined in *Table 50* above, which reflects the definition in the optimal cost-effective strategy identified by Faria and colleagues. Methods of calculation for these results are reported in Supplementary Appendix section 2.2 of Faria et al. (2018).[60]

Table 53 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]			
Low risk cancer	0.79 (0.66 to 0.89)	0.21 (0.11 to 0.34)	
Intermediate risk cancer	0.15 (0.09 to 0.21)	0.11 (0.06 to 0.16)	0.74 (0.65 to 0.84)
High risk 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]			
Low risk cancer	0.68 (0.02 to 1.00)	0.32 (0.02 to 0.91)	
Intermediate risk cancer	0.05 (0.02 to 0.11)	0.08 (0.03 to 0.18)	0.87 (0.71 to 0.95)
High risk cancer	0.05 (0.02 to 0.11)	0.08 (0.03 to 0.18)	0.87 (0.71 to 0.95)

Source: Faria et al. 2018 Supplementary Table 6.
[a] Test 4, PROMIS data and Schoots et al. 2015; [b] Test 5 based on Schoots et al. 2015
For abbreviations see *List of Abbreviations.*

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 from the LATRUS rates adjusted using relative risks from EAG evidence synthesis (see *section 4.8* above). For our base case, we use results from the decision question 1 and 2 network meta-analyses which are based on the available RCTs (see *Figure 8* and *Figure 13* above). We also report a scenario using results from pairwise meta-analyses of observational data for comparison (see *Figure 4, Figure 5, Figure 6, Figure 9, Figure 10 and Figure 11* above. The values used in these analyses are shown in *Table 54* below.

Various assumptions and simplifications have been necessary to obtain the values required to model comparative detection rates for the interventions and comparators in the scope.

- The NMA value for 'LATP-freehand' is based on a single RCT (Lam et al. 2021), which used the PrecisionPoint™ device.[26] 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 in scenario analysis.
- 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 was poor, which has 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') in the economic analysis.
- The value for GATP is based on a single RCT (Lv 2020), which compared against LATP.[38] This means that relative risk estimates from the NMA compared with LATRUS differ for decision questions 1 and 2.

Table 54 Relative risks for cancer detection used in economic model

	Relative risk cancer detection versus LATRUS (95% CI)	
	Base case (NMA RCT)	**Scenario (observational MA)**
Decision question 1		
LATP-all	1.01 (0.85 to 1.18)	1.10 (1.01 to 1.21)
GATP	0.96 (0.64 to 1.44)	1.44 = 1.31 (0.58 to 2.94) x 1.10 [a]
Decision question 2		
LATP-freehand	1.40 (0.96 to 2.04)	1.21 (1.08 to 1.34)
LATP-other	0.94 (0.81 to 1.10)	1.01 (0.91 to 1.12)
GATP	0.90 (0.63 to 1.29)	1.32 = 1.31 (0.58 to 2.94) x 1.01 [a]
a Relative risk for GATP versus LATP adjusted for comparison with LATRUS		

5.7.3 Probability of a repeat biopsy

The probability of patients having a second biopsy after a negative first biopsy in the model is based on a prospective cohort study reported by Jimenez and colleagues (2021).[81] They assessed whether an initial GATP biopsy translates into a lower risk of rebiopsy compared with LATRUS. Repeat biopsy was indicated for 2 scores or greater despite initial negative biopsy, according to *Table 55* below. 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, 15.45% (95/615) and 5.36% (3/56) patients had repeat biopsies after LATRUS and GATP respectively. The study did not show statistically significant difference but a tendency for lower rebiopsy rates in the GATP group. For the

reasons above, we apply the LATRUS rebiopsy rate (15.45%) in our base case for all biopsy methods and vary this in scenario analyses.

Table 55 Rebiopsy protocol: rebiopsy was indicated for scores 2 or greater.

	Value	Score
PSA	>10 ng/ml	+1
PSA velocity	>1 ng/ml/year	+1
Prostate volume	<50 cc	+1
PSA free/PSA	<0.15	+1
PCA3	>35	+1
First degree familiar history of prostate cancer	Yes	+1
Prostatitis	Yes	-1
Source: reproduced from Jimenez et al. 2021, Table 1. For abbreviations see *List of Abbreviations.*		

5.7.4 Biopsy related complications

Tamhankar and colleagues 2020

For our base case analysis, we use comparative rates of admission based on an analysis of Hospital Episode Statistics (HES) to identify patients coded as M702 (TP needle biopsy of prostate) or M703 (TRUS needle biopsy of prostate) who were readmitted or attended accident and emergency within 28 days after the biopsy.[85] Patients were included if they had undergone either a TP or TRUS biopsy (under general or local anaesthetic) between April 2008 and March 2019. A separate evaluation of data between April 2017 and March 2019 was also conducted. For the analysis 2017-2019, 76,106 TRUS and 37,077 TP biopsies were evaluated. Outcomes included non-elective admissions, sepsis, infection, UTI and mortality within 28 days of biopsy. The authors also estimated the NHS expenses for non-elective admissions for TP versus TRUS biopsy (cost year 2013).

Results are summarised in *Table 56* below. Patients were more likely to have sepsis, infection or UTI after TRUS biopsy, with the difference reported as statistically significant. Non-elective admissions were higher for patients having TP biopsy, but the difference was not statistically significant for the two-year analysis. Infections were the main cause of non-elective admissions after TRUS biopsy while urinary retention was the main cause after TP biopsy. The estimated cost per patient of non-elective admission was higher for TRUS than for TP biopsy.

Table 56 Outcomes within 30 days of biopsy for the analysis 2017-2019 (Tamhankar et al. 2020)

Outcome	TRUS biopsy	TP biopsy
	n (%)	n (%)
N	76,106	37,077
Non-elective admission	2,845 (3.74)	1,314 (3.54)
Sepsis	850 (1.12)	155 (0.42)
Urinary retention (non-elective admission)	236 (0.31)	354 (0.95)
Haematuria (non-elective admission)	166 (0.22)	137 (0.37)
Mortality	53 (0.07)	19 (0.05)
Infection	1,139 (1.50)	248 (0.67)
UTI	848 (1.11)	266 (0.72)
Cost per patient of non-elective admission	£2,503.14	£1,894.63
Source: Tamhankar et al. 2020, Table 1, 3 and Figure 1 [85] For abbreviations see *List of Abbreviations*.[82] (49)		

National Prostate Cancer Audit (NPCA)

This comprises comparative rates of admission within 30 days of a transperineal or transrectal biopsy (anaesthesia type not reported) based on an analysis of data from the National Prostate Cancer Audit (NPCA) linked to HES by Berry and colleagues.[82] The audit data included all people newly diagnosed with prostate cancer between 1 April 2014 and 31 March 2017 identified from the English cancer registry (n=118,526). Of these, HES records for the most recent biopsy conducted between 1 January 2014 and the date of diagnosis were available for 75,464 patients, and data were available for analysis for 75,630 patients (62.1%). Patients who had a TRUS biopsy tended to be older but with a lower comorbidity score than patients who had a TP biopsy (see *Table 57*). Outcomes included overnight stay immediately after biopsy, readmissions for sepsis, urinary retention or haematuria within 30 days of biopsy, length of hospital stay and mortality within 30 days of biopsy. Differences between outcomes with TRUS and TP biopsies were adjusted for biopsy year, age, ethnicity, Charlson score and socio-economic status, except for mortality which was only adjusted for age. Results are summarised in *Table 58* and *Table 59* below. Patients were more likely to have an overnight stay after a TP biopsy (LATP or GATP) than after a TRUS biopsy: mean adjusted risk difference 9.7 percentage points (95% CI: 7.12 to 12.27). Readmissions for urinary retention were also more likely after a TP biopsy, but readmissions for sepsis were less likely. Length of stay for both sepsis and urinary retention were shorter after TP than TRUS biopsy.

Table 57 Patient characteristics: NPCA data (Berry et al. 2020)

	TRUS biopsy		TP biopsy		Total	
	n	%	*n*	%	*n*	%
N	59 907	81.4	13 723	18.6	73 630	100
Age group						
<60 years	7941	13.3	2534	18.5	10 475	14.2
60–69 years	22 898	38.2	6090	44.4	28 988	39.4
70–79 years	24 113	40.3	4676	34.1	28 789	39.1
≥80 years	4955	8.3	423	3.1	5378	7.3
Charlson comorbidity score						
0	46 744	78.0	9841	71.7	56 585	76.9
1	9152	15.3	2952	21.5	12 104	16.4
≥2	4011	6.7	930	6.8	4941	6.7
Socio-economic deprivation status (quintile of the national distribution)						
1 (least deprived)	14 169	22.7	4319	25.6	18 488	23.3
2	14 593	23.4	3874	23.0	18 467	23.3
3	13 453	21.5	3544	21.0	16 997	21.4
4	10 976	17.6	2883	17.1	13 859	17.5
5 (most deprived)	9286	14.9	2230	13.2	11 516	14.5
Ethnicity						
White	52 599	93.6	11 752	90.2	64 351	92.9
Asian	959	1.7	274	2.1	1233	1.8
Black	1896	3.4	708	5.4	2604	3.8
Other	765	1.4	292	2.2	1057	1.5
Missing	3688		697		4385	

Source: Berry et al. 2020, Table 1 [82]
For abbreviations see *List of Abbreviations*.

Table 58 Overnight stay and readmissions within 30 days of biopsy (Berry et al. 2020)

	TRUS biopsy	TP biopsy	Adjusted risk difference (% points)		
	n (%)	*n (%)*	Mean % [a]	95% CI	p
N	59,907	13,723			
Overnight stay [a]	1,415 (2.36)	1,681 (12.25)	9.70	7.12 to 12.27	<0.001
Sepsis [a]	806 (1.35)	142 (1.03)	−0.36	−0.56 to −0.15	0.001
Urinary retention [a]	571 (0.95)	265 (1.93)	1.06	0.71 to 1.41	<0.001
Urinary bleed [a]	396 (0.66)	97 (0.71)	0.07	−0.15 to 0.28	0.546
Mortality [b]	59 (0.10)	9 (0.07)	−0.03	−0.07 to 0.01	0.197

Source: Berry et al. 2020, Table 2 [82]
For abbreviations see *List of Abbreviations*. [a] Adjusted for biopsy year, age, ethnicity, Charlson score and socio-economic status
[b] Adjusted for age only

Table 59 Length of stay for readmissions within 30 days of biopsy (Berry et al. 2020)

	TRUS biopsy		TP biopsy		Adjusted mean difference (days)		
	n	*Mean*	n	*Mean*	Mean [a]	95% CI	p
Sepsis [a]	806	6.53	142	5.08	−1.10	−1.84 to −0.36	0.004
Urinary retention [a]	571	3.87	265	2.58	−1.32	−1.97 to −0.66	<0.001
Urinary bleed [a]	396	3.88	97	3.12	−0.70	−2.03 to 0.63	0.304

Source: Berry et al. 2020, Table 2 [82]
For abbreviations see *List of Abbreviations*. [a] Adjusted for biopsy year, age, ethnicity, Charlson score and socio-economic status

Other sources of data on biopsy complications

Wilson and colleagues used estimates of complication rates for LATRUS biopsy reported in the Cochrane review of antibiotic prophylaxis.[61] Reported rates of fever, urinary tract infection and sepsis from study arms with antibiotic treatment were used to represent rates of mild, moderate and severe adverse events with TRUS. They assumed no adverse events with LATP. We summarise these and other sources of data on complication rates with TRUS or TP biopsies in *Table 60* below.

Table 60 Biopsy complication rates

Biopsy		n	Mean	95% CI
Cochrane review, low risk with antibiotic prophylaxis (Zani et al. 2011)[61]				
TRUS	Bacteriuria	870	3.7%	2.2% to 6.2%
	Bacteraemia	494	12.7%	9.3% to 17.5%
	Fever	820	4.2%	2.5% to 6.9%
	Urinary tract infection	1077	3.3%	2.0% to 5.6%
	Hospitalisation	650	0.4%	0.1% to 1.8%
Rosario et al. 2012, prospective cohort study, ProBE [84]				
TRUS	Consultation with GP, nurse	1,147	10.4%	8.7% to 12.3%
	Hospital admission	1,147	1.3%	0.8% to 2.1%
Pepe and Aregona 2013, Italian cohort study [83]				
TP	One or more complication	3,000	40.2%	38.5% to 42.0%
	Emergency department visit	3,000	9.1%	8.1% to 10.2%
	Hospital admission	3,000	1.2%	0.9% to 1.7%

For abbreviations see *List of Abbreviations*.

Commentary on sources for biopsy complication rates

The analysis of Tamhankar and colleagues shows a higher rate of admissions and infections after TRUS but a higher rate of urinary retention and haematuria after TP biopsy. Mortality rates are also higher with TRUS biopsy but the difference is small. [85]

The analysis of NPCA data by Berry and colleagues suggests that overall complications requiring hospital stay or readmission are more common with TP biopsy than with TRUS biopsy, but the nature and severity of complications tends to be less severe.[82] The authors highlight the trade-off between admissions for sepsis and for urinary retention: noting that their estimates suggest that use of TP rather than TRUS biopsies would prevent one admission for sepsis at the cost of three additional admissions for urinary retention. The other notable results from the NPCA analysis are the much larger number of overnight stays after TP biopsy, but shorter length of stay for readmissions. The trend to reduced mortality with TP is also interesting, though the difference is small and not statistically significant.

Berry and colleagues suggest that the higher risk of urinary retention with TP rather than TRUS biopsy may be due to more common use of general anaesthetic and the larger number of cores taken.[82] If so, the results from their analysis may overestimate the risk of admission for urinary retention with LATP. Pepe and Aragona (2013) report similar complication rates (including admissions and emergency department visits) for LATP and GATP biopsies, although they did find a significant association between the number of cores taken and the incidence of complications.[83]

Strengths of both the Tamhankar and NPCA analysis are that they use a large, recent and nationally representative sample, and that it provides a direct comparison of complication rates for TP versus TRUS biopsies: unlike other data sources identified which only report results for TRUS (Zani et al. 2011, Rosario et al. 2012) or TP (Pepe and Aragona 2013) biopsies.[61 83 84] A potentially important limitation is that the NPCA data, contrary to Tamhankar, is restricted to people with a positive diagnosis of prostate cancer, so people with negative biopsy results are not included. It also only accounts for the last biopsy prior to diagnosis. Hence the study may not reflect complication rates in the population of interest for this assessment (people undergoing biopsy for suspected prostate cancer). However, Pepe and Aragona (2013) reported similar complication rates for TP biopsies in patients who received a positive or negative cancer diagnosis.[83] Another advantage of the Tamhankar analysis is that it reports a comparative cost per patient of non-elective admissions.[85]

Based on the rationale above, we used the rates of non-elective admission from Tamhankar and colleagues in our base case and the rates of admission from NPCA as a scenario analysis. Since Tamhankar does not report overnight stay rates, we used the ones from NPCA analysis in our base case.

Neither Tamhankar or Berry report on less severe complications, not requiring an overnight stay or hospital readmission. In our base case, we use estimates of outpatient treated complications from Rosario and colleagues for LATRUS and from Pepe and Aragona for LATP and GATP (see *section 4.9* above). We also conduct scenario analyses with these sources for rates of hospital admissions.

5.7.5 Long-term transition probabilities

Transition probabilities for the Markov model were based on values used in the NICE 2019 guideline update NG131. 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 (see *Table 61* below).[62]

The base case transition probabilities (per 3-month model cycle) are shown in *Table 62* below. The matrix differs for model cycles in which primary care follow up (PSA testing and LATRUS biopsy if indicted) is expected for people with a negative diagnosis because the probability of diagnosis for false negative cases is higher than in the other model cycles, when diagnosis is only related to symptomatic presentation.

Table 61 Transition probabilities for Markov model (NG131)

Parameter	Per 3-month cycle Mean (95% CI)	Source
Incidence		
Developing LR disease (not used in EAG analysis)	0.008 (0.0075 to 0.0088)	Andriol et al. (2010), Schoots et al (2015), Roehl et al 2002 and Brown et al (2018)[59]
Progression in undiagnosed cases		
From LR to IR	0.038 (0.028 to 0.052)	Calibrated to Watchful Waiting arm in SPCG4 study, Bill-Axelson et al. (2014)[17]
From IR to HR	0.085 (0.043 to 0.161)	
From HR to metastatic	0.014 (0.010 to 0.020)	
Progression in Diagnosed cases		
From LR to IR	0.035 (0.019 to 0.064)	Calibrated to data from Gnanapragasam (2016) and James et al. (2016)[90 92]
From IR to HR	0.031 (0.021 to 0.046)	
From HR to metastatic	0.008 (0.007 to 0.009)	
Mortality with metastases		
HR death not on docetaxel	13.38 (12.05 to 14.86)	Calibration. James et al. (2016)[92]
HR death on docetaxel	9.06 (7.67 to 10.71)	
Development of symptoms in undiagnosed cases		
NC or LR at one year	2.6% (1.1% to 4.8%)	Kirby (2003)[98]
IR or HR at five years	28.4% (24.5% to 32.5%)	Studer (2005)
Metastatic at 22 months	61.4% (56.5% to 66.2%)	James (2016)[92]
Diagnosis with follow up		
PSA velocity (0.75 ng/ml/year)	0.69 (0.57 to 0.79)	NG131 clinical review
Source: Table HE07 NICE NG131 Health economic model report[62]		

Table 62 Markov model transition probabilities (per 3 month model cycle)

Non-screening cycle (diagnosis through symptomatic presentation only)													
	Per cycle probability			Undiagnosed				Diagnosed				PCa death	Other death
	Progression	Diagnosis	NC	LR FN	IR FN	HR FN	MS FN	LR Dx	IR Dx	HR Dx	MS Dx		
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	13.38	
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	9.06	
Screening cycle (diagnosis through primary care follow up or symptomatic presentation)													
	Per cycle probability			Undiagnosed				Diagnosed				PCa death	Other death
	Progression	Diagnosis	NC	LR FN	IR FN	HR FN	MS FN	LR Dx	IR Dx	HR Dx	MS Dx		
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	13.38	
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	9.06	
Source: estimated by EAG base on parameter estimates reported by the NICE Guideline Update Team for the NG131 economic model For abbreviations, see footnotes to *Figure 6* above													

5.7.6 Costs of devices for prostate cancer biopsy

The following sections report resource use and cost parameters used in the model, including costs of devices for prostate cancer biopsy and costs of management of patients with suspected prostate cancer (follow up, treatment and adverse events). Resource use assumptions for costing biopsy methods, management strategies and biopsy and treatment complications are presented below. They are based on companies' submissions, published cost-effectiveness studies, the NICE Guideline (NG131) [8] and expert opinion.

The costs of each biopsy method were based on a micro-costing analysis developed by the EAG. We tested the impact of using the costs from NHS National Cost Collection Data Publication 2019/20 [97] as a scenario analysis. This reports the unit costs for the following type of biopsies:

- TP template biopsy, outpatient procedure: £328.81 (OPROC, LB77Z, 101, urology).
- TP template biopsy, day case procedure: £1,512.25 (DC, LB77Z).
- TRUS guided biopsy, outpatient procedure: £332.10 (OPROC, LB76Z, 101, urology).

Micro-costing analysis

The micro-costing used information provided by the companies to NICE (including the YHEC study), by clinical experts, and by the study of Wilson and colleagues [58]. Where information was unavailable for certain cost items, we made assumptions to inform our cost estimates.

For the cost of biopsy methods, we considered the following components:

- Cost of device (where applicable)
- Cost of general consumables (needles, antibiotics, anaesthesia, ultrasound 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 histopathologic analysis
- Urologist consultation to discuss biopsy results and disease management

For decision question 1 (LATP-all versus LATRUS and GATP), the cost of LATP-all is the average of the cost of each LATP device (CamPROBE, PrecisionPoint™ , EZY-PA3, UA1232, Trinity® Perine and SureFire Guide, LATP using grid and stepper unit and LATP using double freehand device), obtaining a cost of £460.83. For decision question 2, (LATP-freehand versus LATRUS, GATP and LATP using a grid and stepper unit), the cost of LATP

using a freehand device is the average cost of each freehand LATP device (CamPROBE, PrecisionPoint™ , EZY-PA3, UA1232, Trinity® Perine and SureFire Guide), obtaining a cost of £470.48.

More details on the assumptions used in the estimation of the costs of each biopsy method are shown in Appendix 12. The cost components and the total cost of the biopsy methods are shown in *Table 63*.

Table 63 Micro-costing analysis: cost components and total cost of biopsy methods

Cost component	Cost per biopsy									
	LATP								GATP	LATRUS
	CamPROBE	PrecisionPoint ™	EZU-PA3U	UA1232	Trinity ® Perine	SureFire Guide	Grid and Stepper	Double freehand		
Device	£70.00	£200.00	£19.13	£14.00	£7.54	£135	£79.95	-	£79.95	-
Consumables	£108.62	£108.62	£107.66	£107.84	£110.37	£108.62	£87.22	£108.62	£169.53	£81.07
Training	£2.38	£4.76	£0.60	£1.19	£0.60	£4.76	£4.76	£4.76	£4.76	£0.60
Staff										
Urologist	£48.79	£39.67	£44.23	£44.23	£44.23	£44.23	£44.23	£44.23	£119	£37.21
Nurse	£25.42	£20.67	£23.04	£23.04	£23.04	£23.04	£23.04	£23.04	£62	£19.38
Anaesthetist	-	-	-	-	-	-	-	-	£119	-
Place of biopsy	£52.89	£43.00	£47.95	£47.95	£47.95	£47.95	£47.95	£47.95	£193.50	£40.33
Reprocessing	-	-	£5	£5	£5	-	£5	-	£5	-
Histopathology	£107.50	£107.50	£107.50	£107.50	£107.50	£107.50	£107.50	£107.50	£107.50	£107.50
Urologist consultation	£59.5	£59.5	£59.5	£59.5	£59.5	£59.5	£59.5	£59.5	£59.5	£59.5
Total	**£475.10**	**£583.72**	**£414.60**	**£410.25**	**£405.72**	**£530.60**	**£459.15**	**£395.60**	**£919.75**	**£345.59**
For abbreviations see *List of Abbreviations.*										

5.7.7 Resource use and costs for management of suspected prostate cancer

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 NG131 [8] and the assumptions of the decision model that informs NG131 [62].

- A proportion of patients with a first biopsy result NC or CNS were assumed to repeat the biopsy.
    - MRI Likert score 3+: base case assumption is that 5% of patients with biopsy result NC and 15.45% of patients with CNS repeat the biopsy.
    - MRI Likert score 1 or 2: base case assumption is that 1.25% of patients with biopsy result NC and 5% of patients with CNS repeat the biopsy.
- Patients without cancer and a first biopsy result NC who have not repeated the biopsy and patients without cancer and a second biopsy result NC were assumed to be discharged and no additional costs were incurred.
- Patients with true disease (LR, IR, HR or metastatic) and a first biopsy result NC or CNS who have not repeated the biopsy and patients with true disease and a second biopsy result NC or CNS were assumed to be monitored as follows.
- Patients with low-risk prostate cancer and a biopsy result NC as well as patients with intermediate-, high-risk or metastatic and a biopsy result NC or CNS were assumed to be followed up in primary care. This consists of:
    - PSA velocity test measurement at 6 months after biopsy and yearly thereafter.
    - Patients with positive PSA (threshold 0.75mg/ml/year) 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 economic model that informs NG131 [62].
- Patients with low-risk prostate cancer and a biopsy result CNS were assumed to be offered a choice between radical treatment or active surveillance.
- Patients with intermediate-risk prostate cancer and a biopsy result CS were assumed to be offered radical treatment, but active surveillance can be considered as an option as well. A proportion of patients with no intent of curative treatment were assumed to have watchful waiting.
- Patients with high-risk prostate cancer and a biopsy result CS were assumed to be offered radical treatment. A proportion of patients with no intent of curative treatment were assumed to have watchful waiting.

- Patients with metastatic disease and a biopsy result CS were assumed to take drugs for metastatic disease.
- Active surveillance was assumed to include:
    - Year 1: PSA measurement every 3 months, DRE and mpMRI at 12 months.
    - Subsequent years: PSA measurement every 6 months and DRE every 12 months.
- Patients diagnosed with prostate cancer having radical treatment were assumed to measure PSA every six months for two 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 intermediate-risk, 70% diagnosed with high-risk and 100% diagnosed with metastatic prostate cancer were assumed to have a CT and a bone scan to monitor for metastases once.

Unit costs for repeat biopsy comes from the micro-costing analysis detailed above (see *Costs of devices for prostate cancer biopsy*). 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 lasting approximately 10 minutes. PSA as well as mpMRI, CT and bone scan costs were obtained from NHS National Cost Collection Data Publication 2019/20 [97]. 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 [96]. Details of costs are presented in *Table 65* below.

Treatment for diagnosed prostate cancer

Patients with low-/intermediate-risk localised prostate cancer will have one of the following treatments: active surveillance, radical prostatectomy or radical radiotherapy, while patients with high-risk localised prostate cancer will have radical prostatectomy or radical radiotherapy. Patients with no intent of curative treatment in the intermediate-/high-risk groups can have watchful waiting (see resource use above on *Monitoring of suspected and diagnosed prostate cancer*). The distribution of patients based on risk groups across treatments for localised disease were obtained from the NPCA Annual Report 2020 [86]. According to the report, around 5% of patients with low-risk and 79% of patients with high-risk localised disease have radical treatment. The distribution across radical treatments (radical prostatectomy and radical radiotherapy) were informed by Gnanapragasam and colleagues [90] (see *Table 64* below).

Radical prostatectomy was estimated as a robotic surgery [86]. Radical radiotherapy includes both brachytherapy and radical external beam radiotherapy (assumed as 20 fractions of hypofractionated radiotherapy using image-guided intensity modulated radiation therapy (IMRT)). During radical radiotherapy, patients were assumed to receive androgen deprivation therapy: bicalutamide 50mg for 21 days followed by leuprorelin/triptorelin 11.25mg or goserelin 3.6mg for 3 months to patients with low-risk prostate cancer, six months to patients with intermediate-risk prostate cancer and 2 years to patients with high-risk prostate cancer [62 63].

The management of metastatic disease, 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 recently recommended to be used for metastatic hormone sensitive prostate cancer – apalutamide plus ADT (ID1534 [87]) and enzalutamide plus ADT (TA712 [88]). The proportion of patients taking docetaxel for metastatic hormone-sensitive prostate cancer (36%) were obtained from the NPCA Annual Report 2020 [86] while the proportion of patients taking ADT alone were assumed to be 50% and the remaining treatment options were assumed to be taken by the remaining patients (7% 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 two 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 (TA) 712 [88] and is displayed in *Table 64* below. We considered that patients can only have abiraterone or enzalutamide at this stage if they have not received enzalutamide or apalutamide before.

The costs for radical treatment were obtained from NHS National Cost Collection Data Publication 2019/20 [97], while the costs for ADT and drugs for metastatic disease were

obtained from British National Formulary (BNF) 2020 and electronic market information tool (eMIT) 2020 [99] [100] (see *Table 65* below).

Managing adverse events of prostate biopsy, radical and metastatic treatment

Biopsy adverse events were categorised into mild (requiring a GP visit or something equivalent), requiring hospital admission (including haematuria, urinary retention, sepsis), and death. The proportion of patients with biopsy adverse events managed in the outpatient setting were obtained from Rosario and colleagues [84] for LATRUS biopsy and from Pepe and Aragona [83] for TP biopsies (both LATP and GATP). The rates of admission as well as the mortality rates were obtained from the study of Tamhankar and colleagues[82] [85](48, 49). The overnight stay rates were obtained from Berry and colleagues.[82]

We modelled the most common adverse events associated with radical treatment: sexual, urinary and bowel dysfunction. Incidence data were sourced from the ProtecT study [101]. For the metastatic treatment, we considered the adverse events from STAMPEDE [92] for ADT and docetaxel plus ADT, from TITAN for apalutamide plus ADT [102] and from ARCHES for enzalutamide plus ADT [93]. The whole list of adverse events is presented in *Table 64* below. The costs of adverse events from biopsy requiring admission come from the Tamhankar study (estimated cost per patient of non-elective admission) and were inflated to the cost year 2019/2020, based on the inflation indices from PSSRU 2020.[85] [96] Costs of the remaining adverse events come from NHS National Cost Collection Data Publication 2019/20 [97] and the decision model that informs NG131 [62] and are summarised in *Table 65* below.

We assume the same cost of adverse events for misdiagnosed patients (false negative 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 and colleagues in 2015 [103] (£14,859) and inflated the cost to the cost year 2019/2020, based on the inflation indices from PSSRU 2020 [96] (£16,052).

Table 64 Resource use inputs

Parameter	Input	Source	Notes
Distribution of LATP biopsy methods			
CamPROBE	7%	Assumption	
PrecisionPoint™	7%	Assumption	
EZU-PA3U	7%	Assumption	
UA1232	7%	Assumption	
Trinity® Perine	7%	Assumption	
SureFire Guide	7%	Assumption	
Grid and stepper unit	50%	Assumption	
Double freehand	7%	Assumption	
BSA	1.91	Sacco et al. 2010 (from NG131 model)	
Proportion of patients that repeat biopsy after a first biopsy result NC or CNS			
MRI Likert score 3+			
Result first biopsy: CNS	15.45%	Jimenez et al. 2021	
Result first biopsy: NC	5%	Assumption	Less patients with a biopsy result NC than CNS repeat biopsy
MRI Likert score 1 or 2			
Result first biopsy: CNS	5%	Assumption	Less patients with MRI score 1 or 2 than 3+ repeat biopsy
Result first biopsy: NC	1.25%	Assumption	Less patients with a biopsy result NC than CNS repeat biopsy
Frequency of follow-up (per year)			
False negative LR, IR, HR or metastatic that did not repeat biopsy or after repeat biopsy			
PSA	1	NG131 economic model	
Nurse appointment	1	NG131 economic model	
TRUS	1	NG131 economic model	
% having TRUS	69%	NG131 economic model	Sensitivity of PSA test
True positive low-risk (receiving active surveillance)			

Parameter	Input	Source	Notes
PSA (1st year)	4	NG131	
PSA (subs years)	2	NG131	
Nurse appointment (1st year)	4	NG131	
Nurse appointment (subs years)	2	NG131	
DRE	1	NG131	
mpMRI (1st year)	1	NG131	
True positive low-risk (receiving radical treatment)			
PSA (1st and 2nd year)	4	NG131	
PSA (subs years)	1	NG131	
Nurse appointment (1st year)	4	NG131	
Nurse appointment (subs years)	1	NG131	
True positive intermediate-risk (receiving active surveillance)			
PSA (1st year)	4	NG131	
PSA (subs years)	2	NG131	
Nurse appointment (1st year)	4	NG131	
Nurse appointment (subs years)	2	NG131	
DRE	1	NG131	
mpMRI (1st year)	1	NG131	
CT scan (1st year)	1	Clinical expert advice	
Bone scan (1st year)	1	Clinical expert advice	
% having CT and bone scan	50%	Clinical expert advice	
True positive intermediate-risk (receiving radical treatment)			
PSA (1st and 2nd year)	4	NG131	
PSA (subs years)	1	NG131	

Parameter	Input	Source	Notes
Nurse appointment (1st year)	4	NG131	
Nurse appointment (subs years)	1	NG131	
CT scan (1st year)	1	Clinical expert advice	
Bone scan (1st year)	1	Clinical expert advice	
% having CT and bone scan	50%	Clinical expert advice	
True positive intermediate-risk (receiving watchful waiting)			
PSA	1	NG131	
Nurse appointment	1	NG131	
CT scan (1st year)	1	Clinical expert advice	
Bone scan (1st year)	1	Clinical expert advice	
% having CT and bone scan	50%	Clinical expert advice	
True positive high-risk (receiving radical treatment)			
PSA (1st and 2nd year)	4	NG131	
PSA (subs years)	1	NG131	
Nurse appointment (1st year)	4	NG131	
Nurse appointment (subs years)	1	NG131	
CT scan (1st year)	1	Clinical expert advice	
Bone scan (1st year)	1	Clinical expert advice	
% having CT and bone scan	70%	Assumption	
True positive high-risk (receiving watchful waiting)			
PSA	1	NG131	
Nurse appointment	1	NG131	
CT scan (1st year)	1	Clinical expert advice	
Bone scan (1st year)	1	Clinical expert advice	

Parameter	Input	Source	Notes
% having CT and bone scan	70%	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%	Assumption	
Treatment distribution			
Localised disease (low-risk)			
Active surveillance	95%	NPCA Annual Report 2020	
Radical treatment	5%	NPCA Annual Report 2020	
Radical prostatectomy	2%	Gnanapragasam et al. 2016	
External radiotherapy	2.3%	Gnanapragasam et al. 2016	Weighted proportions based on Gnanapragasam et al. 2016
Brachytherapy	0.7%	Gnanapragasam et al. 2016	
Watchful waiting	0%	Assumption	Assume that no patients with LR have watchful waiting
ADT therapies	3%	Assumption	All patients on radical radiotherapy receive ADT
Localised disease (intermediate-risk)			
Active surveillance	12.7%	Gnanapragasam et al. 2016	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	
External radiotherapy	48.7%	Gnanapragasam et al. 2016	
Brachytherapy	4.1%	Gnanapragasam et al. 2016	
Watchful waiting	12.7%	Gnanapragasam et al. 2016	
ADT therapies	52.8%	Assumption	All patients on radical radiotherapy receive ADT
Localised disease (high-risk)			

Parameter	Input	Source	Notes
Active surveillance	0%	Assumption	Assume that no patients with HR have active surveillance
Radical treatment	71%	NPCA Annual Report 2020	
Radical prostatectomy	17.6%	Gnanapragasam et al. 2016	
External radiotherapy	52.5%	Gnanapragasam et al. 2016	Weighted proportions based on Gnanapragasam et al. 2016
Brachytherapy	0.9%	Gnanapragasam et al. 2016	
Watchful waiting	29%	NPCA Annual Report 2020	
ADT therapies	53.4%	Assumption	All patients on radical radiotherapy receive ADT
ADT market share (localised disease)			
Leuprorelin	33%	Assumption	
Triptorelin	33%	Assumption	Assumed that LHRH therapies are used at the same rate
Goserelin	33%	Assumption	
Bicalutamide	100%	Assumption	
Metastatic hormone-sensitive disease			
ADT alone	50%	Assumption	
Docetaxel + ADT	36%	NPCA Annual Report 2020	
Apalutamide + ADT	7%	Assumption	
Enzalutamide + ADT	7%	Assumption	
ADT market share (mHSPC)			
Leuprorelin	33%	Assumption	
Triptorelin	33%	Assumption	Assumed that LHRH therapies are used at the same rate
Goserelin	33%	Assumption	
Bicalutamide	50%	Assumption	
Metastatic hormone-relapsed disease			
Abiraterone	28%	NICE TA712	

Parameter	Input	Source	Notes
Docetaxel	22%	NICE TA712	Weighted proportions according to treatment for metastatic
Enzalutamide	30%	NICE TA712	hormone sensitive prostate cancer
Best supportive care	19%		
Duration of drug therapies			
Localised disease			
LHRH drugs			
Low-risk	3 months	NG131 model, Mowatt et al. 2013	
Intermediate-risk	6 months	NG131 model, Mowatt et al. 2013	
High-risk	2 years	NG131 model, Mowatt et al. 2013	
Bicalutamide	21 days	NG131 model, Mowatt et al. 2013	
Metastatic hormone-sensitive disease			
ADT alone	2 years	Assumption	
Docetaxel + ADT	6 cycles of chemo	STAMPEDE (from NG131 model)	Cycles of 3 weeks
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)	
Docetaxel	9.5 cycles of chemo	TAX327 (from NG131 model)	Cycles of 3 weeks
Enzalutamide	14 months	Pilon et al. 2017	
Adverse events			
Incidence of biopsy adverse events (TRUS)			
Mild AEs	1.31%	Rosario et al. 2012	

Parameter	Input	Source	Notes
AEs requiring admission	6.10%		
Non-elective admission	3.74%	Tamhankar et al. 2020	
Overnight stay	2.36%	Berry et al. 2020	
Mortality	0.07%	Tamhankar et al. 2020	
Incidence of biopsy adverse events (TP)			
Mild AEs	9.13%	Pepe & Aragona 2013	
AEs requiring admission	15.61%		
Non-elective admission	3.54%	Tamhankar et al. 2020	
Overnight stay	12.06%	Berry et al. 2020	
Mortality	0.05%	Tamhankar et al. 2020	
Incidence of radical treatment adverse events			
Active surveillance/ watchful waiting			
Erectile dysfunction	51%	ProtecT study	1-year FUP (Table 2; Table S2B, erect not firm f/ intercourse)
Urinary incontinence	4%	ProtecT study	1-year FUP (Table 2; Table S2A, one/more pads per day)
Bowel dysfunction	1.7%	ProtecT study	1-year FUP (Table S2C, mod/sev impact on QoL)
Radical prostatectomy			
Erectile dysfunction	85%	ProtecT study	1-year FUP (Table 2; Table S2B, erect not firm f/ intercourse)
Urinary incontinence	26%	ProtecT study	1-year FUP (Table 2; Table S2A, one/more pads per day)
Bowel dysfunction	2.5%	ProtecT study	1-year FUP (Table S2C, mod/sev impact on QoL)
Radical radiotherapy			
Erectile dysfunction	62%	ProtecT study	1-year FUP (Table 2; Table S2B, erect not firm f/ intercourse)
Urinary incontinence	4%	ProtecT study	1-year FUP (Table 2; Table S2A, one/more pads per day)
Bowel dysfunction	5.9%	ProtecT study	1-year FUP (Table S2C, mod/sev impact on QoL)
Incidence of metastatic treatment adverse events			

Parameter	Input	Source	Notes
ADT			
Cardiac disorder	3%	STAMPEDE (from NG131 model)	
Endocrine disorder	12.2%	STAMPEDE (from NG131 model)	
Gastrointestinal disorder	3%	STAMPEDE (from NG131 model)	
General disorder	3.9%	STAMPEDE (from NG131 model)	
Musculoskeletal disorder	5.8%	STAMPEDE (from NG131 model)	
Nervous system disorder	1.7%	STAMPEDE (from NG131 model)	
Neutropenia	1.8%	STAMPEDE (from NG131 model)	
Renal disorder	6%	STAMPEDE (from NG131 model)	
Respiratory disorders	2.3%	STAMPEDE (from NG131 model)	
Docetaxel + ADT			
Cardiac disorder	2.9%	STAMPEDE (from NG131 model)	
Endocrine disorder	10.4%	STAMPEDE (from NG131 model)	
Gastrointestinal disorder	8.2%	STAMPEDE (from NG131 model)	
General disorder	6.2%	STAMPEDE (from NG131 model)	
Musculoskeletal disorder	5.8%	STAMPEDE (from NG131 model)	
Nervous system disorder	3.5%	STAMPEDE (from NG131 model)	
Neutropenia	27.3%	STAMPEDE (from NG131 model)	
Renal disorder	4.2%	STAMPEDE (from NG131 model)	
Respiratory disorder	5.3%	STAMPEDE (from NG131 model)	
Apalutamide + ADT			
Blood disorder	2.1%	TITAN study (Kim et al. 2019)	Table 4
Cardiac disorder	8.4%	TITAN study (Kim et al. 2019)	Table 4
Gastrointestinal disorder	1.1%	TITAN study (Kim et al. 2019)	Table 4

Parameter	Input	Source	Notes
General disorder	3.4%	TITAN study (Kim et al. 2019)	Table 4
Musculoskeletal disorder	6.5%	TITAN study (Kim et al. 2019)	Table 4
Nervous system disorder	0.2%	TITAN study (Kim et al. 2019)	Table 4
Renal disorder	0.8%	TITAN study (Kim et al. 2019)	Table 4
Skin disorder	6.5%	TITAN study (Kim et al. 2019)	Table 4
Enzalutamide + ADT			
Cardiac disorder	4.9%	ARCHES study (Armstrong 2019)	Table 3
Endocrine disorder	0.3%	ARCHES study (Armstrong 2019)	Table 3
Gastrointestinal disorder	0.5%	ARCHES study (Armstrong 2019)	Table 3
General disorder	2.8%	ARCHES study (Armstrong 2019)	Table 3
Musculoskeletal disorder	4.4%	ARCHES study (Armstrong 2019)	Table 3
Nervous system disorder	2.1%	ARCHES study (Armstrong 2019)	Table 3
Neutropenia	0.3%	ARCHES study (Armstrong 2019)	Table 3
Skin disorder	0.3%	ARCHES study (Armstrong 2019)	Table 3

BSA, body surface area; LHRH, luteinizing hormone-releasing hormone; For the remaining abbreviations see *List of Abbreviations.*

Table 65 Costs used in the model

Parameter	Cost	Source	Notes
Follow up costs			
PSA	£1.20	NHS Cost Data 2019/20	DAPS: DAPS04
Primary care nurse	£9.83	PSSRU 2020	10-minute appointment with a Band 7 community-based nurse (p.129)
DRE	£78.46	PSSRU 2020	Assumed as a 20-minute GP appointment
mpMRI	£211.33	NHS Cost Data 2019/20	IMAG: RD03Z (outpatient)
CT scan	£126.47	NHS Cost Data 2019/20	IMAG: RD21A

Parameter	Cost	Source	Notes
Bone scan	£331.11	NHS Cost Data 2019/20	NM: RN15A
Treatment costs			
Localised disease			
Radical prostatectomy			
Surgery	£8,331.21	NHS Cost Data 2019/20	EL: LB69Z
First appointment	£246.86	NHS Cost Data 2019/20	OPROC: WF01B
Follow up appointment	£214.05	NHS Cost Data 2019/20	OPROC: WF01A
Number of follow up appointmnts	2	Wilson et al. 2021	
External radiotherapy	£3,113.54	NHS Cost Data 2019/20	RAD: weighted average of SC40Z and SC41Z (outpatient) plus SC21Z (outpatient) multiplied by 20 fractions
Brachytherapy	£3,106.02	NHS Cost Data 2019/20	RAD: SC55Z+SC30Z (weighted average of inpatient, day case and outpatient)
ADT therapies			
Low-risk	£245.93	BNF 2021, eMIT 2020	21-day course of bicalutamide + 1 injection of LHRH + admin costs
Intermediate-risk	£488.92	BNF 2021, eMIT 2020	21-day course of bicalutamide + 2 injection of LHRH + admin costs
High-risk	£1,946.84	BNF 2021, eMIT 2020	21-day course of bicalutamide + 8 injection of LHRH + admin costs
Metastatic hormone-sensitive disease			
ADT alone	£1,945.85	BNF 2021, eMIT 2020	28-day course of bicalutamide + 2-year LHRH drugs
Docetaxel + ADT	£4,075.69	eMIT 2020	Cost of ADT alone + 6 cycles of 75mg/m^2 docetaxel + admin costs
Apalutamide + ADT	£73,300.05	BNF 2021	Cost of ADT alone + 2-year apalutamide
Enzalutamide + ADT	£73,291.44	BNF 2021	Cost of ADT alone + 2-year enzalutamide
Metastatic hormone-relapsed disease			
Abiraterone	£23,784.73	BNF 2021	8 months (from NG131 model)
Docetaxel	£3,410.91	eMIT 2020	9.5 cycles of 75mg/m^2 docetaxel + admin costs

Parameter	Cost	Source	Notes
Enzalutamide	£41,618.26	BNF 2021	14 months
Best supportive care	£0	Assumption	Assumed no costs as they are negligible
Administration costs			
LHRH drugs	£12.92	PSSRU 2020	15.5 min with a Band 6 hospital-based nurse (p.155)
Docetaxel (IV, 1st attendance)	£299.61	NHS Cost Data 2019/20	CHEM: SB12Z
Docetaxel (IV, subs attendances)	£365.91	NHS Cost Data 2019/20	CHEM: SB15Z
Adverse event costs			
Biopsy adverse events			
Mild AEs (Urinary infection)	£47.55	Wilson et al. 2021	GP visit + urinalysis + 7-day trimethoprim
GP visit	£39.23	PSSRU 2020	10.3b General practitioner (unit costs per patient contact lasting 9.22 min)
Urinalysis	£8.09	NHS Cost Data 2019/20	DAPS: DAPS07
7-day trimethoprim	£0.23	eMIT 2020	200mg x 14 tablets
Non-elective admission (TRUS)	£2,503.14	Tamhankar et al. 2020	Inflated to 2019/20
Non-elective admission (TP)	£1,894.63	Tamhankar et al. 2020	Inflated to 2019/20
Overnight stay	£602	PSSRU 2020	7.1 NHS reference costs for hospital services - average cost per episode of non-elective short stay (less than two days)
Mortality	£9,739.48	NHS Cost Data 2019/20	NE: WJ06A (weighted average of short and long stay)
Radical treatment adverse events			
Erectile dysfunction	£174.29	NHS Cost Data 2019/20	OPROC: LB43Z (weighted average)
Urinary incontinence	£308.05	NG131 model	Managed by containment pads. Inflated to 2019/20
Bowel dysfunction	£1,883.19	NG131 model	Mean weighted cost including costs associated with sigmoidoscopy, laser therapy, enemas and blood transfusion. Inflated to 2019/20
Metastatic treatment adverse events			

Parameter	Cost	Source	Notes
Blood disorder	£1,831.00	NHS Cost Data 2019/20	NE: SA03G-SA03H, SA08G-SA08J, SA12G-SA12K (weighted average of short and long stay)
Cardiac disorder	£1,592.17	NHS Cost Data 2019/20	NE: EB10 (weighted average of short and long stay)
Endocrine disorder	£174.29	Assumption	Same as erectile dysfunction
Gastrointestinal disorder	£1,491.68	NHS Cost Data 2019/20	NE: FD10 (weighted average of short and long stay)
General disorder	£39.87	Assumption	Same as fever
Musculoskeletal disorder	£1,061.24	NHS Cost Data 2019/20	NE: HD26 (weighted average of short and long stay)
Nervous system disorder	£1,512.84	NHS Cost Data 2019/20	NE: AA26 (weighted average of short and long stay)
Neutropenia	£6,605.17	NHS Cost Data 2019/20	NE: PM45 (weighted average of short and long stay)
Renal disorder	£47.55	Assumption	Same as urinary infection
Respiratory disorders	£657.49	NHS Cost Data 2019/20	NE: DZ19 (weighted average of short and long stay)
Skin disorder	£1,615.18	NHS Cost Data 2019/20	NE: JD07 (weighted average of short and long stay)
Other costs			
End of life	£16,052	Round et al. 2015	From initiation of strong opioids until death (expected survival 243 days); inflated to 2019/20
Abbreviations: IV, intravenous; For the remaining abbreviations see *List of Abbreviations.*			

5.7.8 Utilities

We considered that the studies retrieved by the systematic searches 'HRQoL 1' do not provide any utility score that fits our decision model. None of the studies reported a utility decrement for the biopsy procedure itself (compared to a baseline value) nor utility decrements associated with biopsy complications. In addition, none of the studies reported utilities related to localised and metastatic disease.

From the six studies retrieved by the systematic searches 'HRQoL 2', we used data from two to inform our decision model: Torvinen and colleagues [77] and Watson and colleagues [78].

The reasons we didn't use the other four are described below:

- Booth and colleagues [73] reported a utility decrement of patients with prostate cancer (organ-confined and advanced disease) compared to a separate group of patients without prostate cancer. The decrement is therefore informed by different groups of patients, which is not optimal. In addition, patients with localised disease show better utilities than patients without prostate cancer, which seems unlikely.
- Drummond and colleagues [74] reported a slightly higher utility for people with invasive prostate cancer as compared to the general population (0.82 vs. 0.8104 for base case population of 66 years), which again seems unlikely.
- Farkkila and colleagues (33) assessed the HRQoL of end-stage cancer patients (prostate, breast and colo-rectal cancers). The utility associated with the 30 prostate cancer patients that completed the questionnaires was 0.551. This is a Finnish study with a small sample size of patients. In addition, it does not report a utility decrement suitable to include in the model.
- Gavin and colleagues [76] reported a higher utility for patients with localised disease as compared to general population (0.88 vs. 0.8104 at age 66). This supports the use of general population utilities for the localised disease health states.

To fill in data gaps left after using the utilities from the systematic searches, we have considered the utility inputs used by Faria and colleagues [60], Wilson and colleagues [58] and the decision model that informs NG131 [62]. In addition, we reviewed the studies of interest retrieved by the cost-effectiveness searches for completeness (see *section 5.1.4*).
Table 66 presents the utilities used in our base case model. The baseline utilities of the cohort were based on the age-related utilities from Ara and Brazier [95].

Table 66 Base case utilities

Health states	Input	Duration	Source	Notes
Baseline	Age-related utilities	-	Ara and Brazier, 2010	
Decision tree				
Biopsy disutilities				
LATRUS	0	-	Faria et al. 2018	The assumption made by Faria et al. 2018 was based on Essink-Bot et al. 1998
LATP	0	-	Assumption	No difference between
GATP	0	-	Assumption	biopsy methods
Biopsy complications disutilities				
Mild AEs/ Overnight stay	-0.29	3 days	Wilson et al. 2021 Lee et al. 2018	Assumed as the decrement for UTI
AEs requiring admission	-0.49	30 days	Wilson et al. 2021 Lee et al. 2018	
Death from complications	-0.49	30 days	Assumption	Assumed the same decrement as for sepsis
Markov model				
Health state disutilities				
Localised disease	Age-related utilities	-	Ara and Brazier, 2010	Assumed same as general population
Metastatic	-0.137	-	Torvinen et al. 2013	Calculated as the difference between EQ-5D score reported for metastatic disease and the average score reported for localised disease
Radical treatment adverse events disutilities				
Sexual dysfunction	-0.023	-	Watson et al. 2016	Calculated as the difference between the utility for patients with no/mild complications and patients with moderate/severe complications
Urinary dysfunction	-0.095	-	Watson et al. 2016	
Bowel dysfunction	-0.209	-	Watson et al. 2016	
For abbreviations see *List of Abbreviations.*				

Decision tree

- We considered that the performance of a prostate biopsy impacts HRQoL in a similar way regardless of the method used (LATP, GATP or LATRUS). In addition, as no better data are available and the utilities will cancel out across comparators, we assumed that the performance of a prostate biopsy itself has no impact on HRQoL, as assumed in the Faria and colleagues model[60].
- However, we accounted for the differences between biopsy methods by considering the variable occurrence of biopsy adverse events and the corresponding utility decrements from each event.
    - The utility decrement for mild adverse events and adverse events requiring admission was based on the estimates used by Wilson and colleagues [58] and Lee and colleagues[104] for UTI (-0.29 for 3 days) and sepsis (-0.49 for 30 days) respectively. We assumed a utility decrement of -0.49 for 30 days for patients who died due to biopsy adverse events as well.
    - For patients staying overnight after the biopsy procedure, we assumed the same estimates as for UTI (-0.29 for 3 days).
    - We assumed that the QALY loss reported by Wilson and colleagues [58] for UTI and sepsis were based on the utility decrements used by Lee and colleagues [104]. The decrement applied to UTI is based on a study from 1997 [105], which assessed suspected UTI in healthy adult women and measured the utilities using the Index of Well-Being. The decrement applied to sepsis is based on a study from 2001 [106], which assessed the change in health status among sepsis survivors over a 6-month period (mean age 60 years, 48% female).

Markov model

- For the localised disease health states (including LR, IR and HR), we assumed that the reduction in HRQoL is a consequence of age (based on Ara and Brazier[95]), since there is no evidence of worse HRQoL than the general population in this health state.[76],[77] We have however considered the utility decrement due to treatment adverse events.
- The utility decrement for treatment adverse events was calculated as the difference between the EQ-5D utilities reported for no/mild complications and moderate/severe complications in the study of Watson and colleagues [78]. A utility decrement of 0.023, 0.095 and 0.209 was applied to sexual, urinary, and bowel dysfunction, respectively.
- For the metastatic health state, we applied a utility decrement of 0.137 obtained from the Torvinen and colleagues study.[77] This decrement was calculated as the

difference between the average EQ-5D score reported for localised cancer and the EQ-5D score reported for metastatic cancer.

- For patients with undiagnosed disease (false negative LR, IR, HR or metastatic), we assumed the same disutility as for patients on active surveillance. This assumption results in patients with undiagnosed metastatic disease (-0.019) having a much lower disutility value than patients with diagnosed metastatic disease (-0.137). This can be explained by the following:
    - Undiagnosed patients are not receiving treatment, and therefore they are not experiencing treatment disutility as opposed to diagnosed patients.
    - We do not expect undiagnosed patients to have severe symptoms, otherwise they are likely to be diagnosed. Therefore, these patients are not experiencing disutility due to severe symptoms as opposed to diagnosed patients.
    - We have tested the impact of this assumption in scenario analysis, applying the disutility of diagnosed metastatic patients (-0.137) to undiagnosed metastatic patients.

5.8 Model assumptions

Table 67 lists the key assumptions in the *de novo* economic model.

Table 67 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 metastatic disease.
	Initial cohort does not include people for whom active treatment would not be appropriate – they would not be referred for biopsy.
	Mean age of the initial cohort of 66 years.
Diagnostic accuracy	All biopsies are assumed to be perfectly specific – if the biopsy result is positive (CNS or CS) means that 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 the our model is 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 level of risk of 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 false negative states, starting on low-risk, before moving to true positive states. People with true disease (diagnosed or undiagnosed) are at continuous risk of progression. Progression occurs from low-risk to intermediate- to high- and then to metastatic. Prostate cancer specific death occurs only among metastatic patients, i.e., cases with localised prostate cancer are not at risk of prostate cancer death.
Utilities	Utility for localised disease is assumed equal to that of the general population plus disutilities from radical treatment adverse events.
	False negative patients (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 (5-15.45%) than with a score of 1 or 2 (1.25-5%).
	Patients without cancer and a biopsy result NC are discharged and no additional costs are incurred.
	Patients with low-risk prostate cancer and a biopsy result NC as well as patients with intermediate-, high-risk or metastatic and a biopsy result NC or CNS are followed up in primary care.
	Patients with low-risk prostate cancer and a biopsy result CNS as well as patients with intermediate-risk and a biopsy result CS are offered a choice between radical treatment or active surveillance, while patients with high-risk and a biopsy result CS are not offered active surveillance. A proportion of patients with no intent of curative treatment were assumed to have watchful waiting. Patients with metastatic disease are offered with drugs for metastatic disease.
	Primary care follow-up consists of a PSA velocity test measurement at 6 months and yearly thereafter. Patients with a positive PSA (threshold 0.75mg/ml/year) have a LATRUS biopsy for disease confirmation.
Follow up resource use	Active surveillance costs consists 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 six months for two 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% of the patients with HR disease and 100% of the patients with metastatic disease have one CT and bone scan.

Prostate cancer treatment	The proportion of patients taking ADT alone for metastatic hormone sensitive prostate cancer are assumed to be 50% and the proportion of patients taking apalutamide plus ADT and enzalutamide plus ADT are assumed to be 7% each.
	ADT alone, apalutamide plus ADT and enzalutamide plus ADT were taken until disease progression, which we assumed to occur after two 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 androgen deprivation therapy (ADT).
Micro-costing analysis	The cost of SureFire Guide is an average of the other two disposable LATP devices (CamPROBE and PrecisionPoint™).
	Co-axial needle was assumed to be used for biopsies using both freehand and double freehand devices.
	Antibiotic prophylaxis for TP biopsies is one prophylactic dose of ciprofloxacin (500mg), while for LATRUS biopsies is a course of ciprofloxacin 500mg 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 have a given amount of 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 stepper unit, LATP using double freehand devices and GATP. For LATRUS, we assumed that this would only require one hour of training.
	We assumed that all biopsies are carried out by one urologist and that there are two nurses in the room for assistance.
	Due to lack of data, we assumed athe average procedure time between CamPROBE and PrecisionPoint™ of 0.37h for the remaining LATP devices and 1h for GATP.
	The cost of reprocessing was assumed to be £5, as advised by a Specialist Committee Member.
	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.
For abbreviations see *List of Abbreviations*.	

5.9 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 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, which we had access to.

5.10 Economic analysis results

5.10.1 Base case: decision question 1

Deterministic results

Deterministic cost effectiveness results for decision question 1 are shown in *Table 68*. LATP-all is more costly but yields more QALYs than LATRUS for all subgroups. The ICER for LATP-all versus LATRUS increases from £72,503 per QALY gained in subgroup A up to £81,246 per QALY gained for subgroup D. LATP-all dominates GATP in all subgroups.

Table 68 Base case cost effectiveness (deterministic): decision question 1

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	£19,472	9.2991					
LATP-all	£19,620	9.3011	£148	0.0020	-0.005	-0.003	£72,503
GATP	£20,089	9.2993	£469	-0.0018	-0.031	-0.020	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,314	9.4783					
LATP-all	£15,462	9.4802	£148	0.0019	-0.006	-0.003	£78,130
GATP	£15,927	9.4793	£464	-0.0009	-0.030	-0.019	Dominated
Subgroup C: MRI Likert 3+ previous negative biopsy							
LATRUS	£16,236	9.4565					
LATP-all	£16,384	9.4584	£148	0.0019	-0.006	-0.003	£77,970
GATP	£16,849	9.4574	£465	-0.0010	-0.030	-0.019	Dominated
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	£13,632	9.5474					
LATP-all	£13,780	9.5493	£148	0.0018	-0.006	-0.003	£81,246
GATP	£14,243	9.5488	£462	-0.0005	-0.029	-0.019	Dominated

ICER incremental cost effectiveness ratio (fully incremental)
INHB incremental net health benefit versus LATRUS, at thresholds £20,000-£30,000/QALY gained
For abbreviations see *List of Abbreviations*

Probabilistic results

Results for the probabilistic sensitivity analysis for decision question 1 are shown in *Table 69*. The results are similar to the deterministic results shown above, with slightly higher ICERs for LATP-all compared with LATRUS. The ICERs for LATP-all are well above the upper £30,000 per QALY threshold and GATP is dominated in all subgroups.

The distribution of incremental costs and QALYs (compared with LATRUS) from the probabilistic sensitivity analysis for subgroup A decision problem 1 are shown in *Figure 23* below. This shows that LATP-all is associated with a higher expected cost and high uncertainty over the QALY gain compared with LATRUS or GATP. The cost-effectiveness acceptability curve (CEAC) for subgroup A decision problem 1 are shown in *Figure 24*. This shows LATRUS is predicted to be the most cost-effective option at cost-effectiveness thresholds below around £75,000 per QALY gained. Above this threshold, LATP-all is predicted to be more cost-effective than the other comparators.

Table 69 Base case cost effectiveness (probabilistic): decision question 1

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	£19,517	9.2974					
LATP-all	£19,667	9.2994	£149	0.0020	-0.006	-0.003	£76,288
GATP	£20,140	9.2966	£623	-0.0008	-0.032	-0.022	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,283	9.4787					
LATP-all	£15,431	9.4806	£148	0.0019	-0.006	-0.003	£79,575
GATP	£15,900	9.4792	£617	0.0005	-0.030	-0.020	Dominated
Subgroup C: MRI Likert 3+ previous negative biopsy							
LATRUS	£16,188	9.4539					
LATP-all	£16,335	9.4557	£147	0.0018	-0.006	-0.003	£82,326
GATP	£16,803	9.4539	£615	0.0000	-0.031	-0.021	Dominated
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	£13,625	9.5426					
LATP-all	£13,775	9.5444	£150	0.0018	-0.006	-0.003	£82,940
GATP	£14,238	9.5437	£613	0.0011	-0.030	-0.019	Dominated

ICER incremental cost effectiveness ratio (fully incremental)
INHB incremental net health benefit versus LATRUS, at thresholds £20,000-£30,000/QALY gained

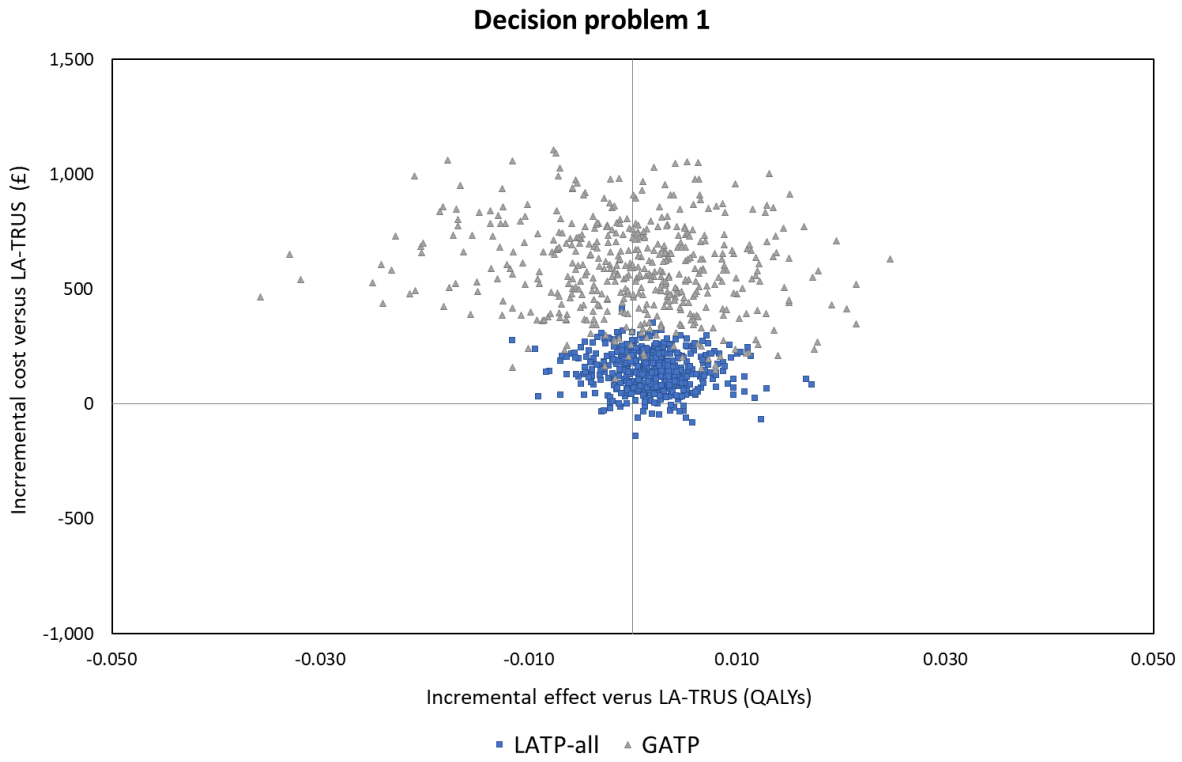


Figure 23 Cost effectiveness scatterplot: subgroup A (decision question 1)

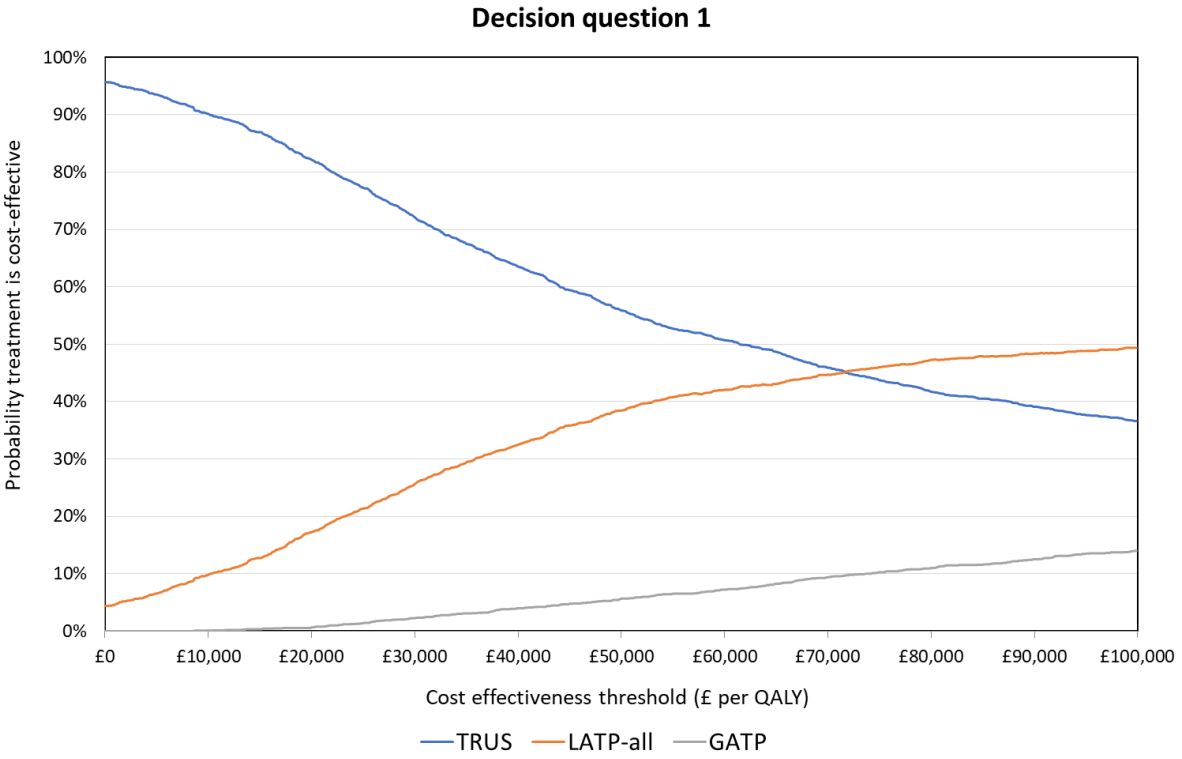


Figure 24 Cost effectiveness acceptability curve: subgroup A (decision question 1)

Intermediate outcomes

Intermediate outcomes related to the decision tree biopsy pathway are shown in *Table 70* below. 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 (NC or CNS) first biopsy 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 clinically significant (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 (false negatives) are due to small, non-statistically significant differences in cancer detection estimates from the decision question 1 NMA (see *Figure 8* above). We note that these parameters are highly uncertain, see *section 5.10.3* below for scenario analysis using alternative sources for these relative risks.

Base case estimates of biopsy-related adverse events result in a higher proportion of people with ‘mild’ AEs (not requiring hospital admission) with the transperineal methods (LATP-all and GATP) than with LATRUS. The estimated rate of admissions is over 15% for the transperineal methods, although rates are much lower if overnight stays immediately after the biopsy are excluded (approximately 3.5%). There is high uncertainty over differences in AE rates and also the impact on patient’s health-related quality of life between the biopsy methods, see scenario analyses in *section 5.10.3* below.

Outcomes from the Markov model are summarised in *Table 71* below. Deaths from prostate cancer decline and mean life years (LYs) and quality adjusted life years (QALYs) increase for the subgroups with lower baseline prevalence of clinically significant prostate cancer. There are small differences in these outcomes between the biopsy methods, driven by the proportions of the cohort with false negative biopsy results estimated from the decision tree. *Table 72* summarises costs estimated from the decision tree and Markov models. 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 alternative estimates of biopsy costs in section 5.10.3 below.

Table 70 Base case decision tree intermediate outcomes (deterministic): decision question 1

Biopsy method	Mean biopsies	Undiagnosed		Biopsy related adverse events (AE)			AE QALY loss
		CNS	CS	Mild	Admissions	Deaths	
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	1.034	9.92%	15.22%	1.4%	6.3%	0.07%	-0.0016
LATP-all	1.034	9.90%	15.01%	9.2%	15.8%	0.05%	-0.0018
GATP	1.034	10.00%	16.13%	9.2%	15.8%	0.05%	-0.0018
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	1.013	20.40%	6.73%	1.3%	6.2%	0.07%	-0.0016
LATP-all	1.013	20.35%	6.64%	9.2%	15.7%	0.05%	-0.0018
GATP	1.013	20.58%	7.12%	9.2%	15.7%	0.05%	-0.0018
Subgroup C: MRI Likert 3+ previous negative biopsy							
LATRUS	1.000	17.44%	4.45%	1.3%	6.1%	0.07%	-0.0016
LATP-all	1.000	17.38%	4.37%	9.1%	15.6%	0.05%	-0.0018
GATP	1.000	17.72%	4.83%	9.1%	15.6%	0.05%	-0.0018
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	1.000	21.74%	1.12%	1.3%	6.1%	0.07%	-0.0016
LATP-all	1.000	21.66%	1.09%	9.1%	15.6%	0.05%	-0.0018
GATP	1.000	22.09%	1.21%	9.1%	15.6%	0.05%	-0.0018

CNS clinically non-significant prostate cancer (low-risk localised); CS clinically significant prostate cancer (intermediate or high-risk localised disease)
For abbreviations see *List of Abbreviations*

Table 71 Base case health outcomes from Markov model (deterministic): decision question 1

Biopsy method	Deaths (% of whole cohort)			Undiscounted		Discounted	
	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-all	19.59%	80.33%	99.92%	16.014	12.581	11.720	9.303
GATP	19.62%	80.30%	99.92%	16.011	12.578	11.718	9.301
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-all	10.86%	89.05%	99.91%	16.784	12.963	12.140	9.482
GATP	10.88%	89.04%	99.91%	16.782	12.962	12.139	9.481
Subgroup C: MRI Likert 3+ previous negative biopsy							
LATRUS	12.64%	87.26%	99.90%	16.638	12.903	12.063	9.458
LATP-all	12.64%	87.28%	99.92%	16.642	12.906	12.066	9.460
GATP	12.65%	87.26%	99.92%	16.640	12.904	12.064	9.459
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-all	7.32%	92.59%	99.91%	17.091	13.113	12.307	9.551
GATP	7.33%	92.58%	99.91%	17.090	13.113	12.306	9.551

LY life years; QALY quality adjusted life years
For abbreviations see *List of Abbreviations*

Table 72 Base case intermediate costs from decision tree and Markov model (deterministic): decision question 1

Biopsy method	Decision tree costs			Markov model, undiscounted costs					Discounted Total costs
	Biopsies	AEs	Total cost	Treatment	AE	Follow up	End of life	Total	
Subgroup A: MRI Likert 3+ first biopsy									
LATRUS	£357	£119	£477	£8,965	£2,709	£587	£16,042	£28,304	£18,996
LATP-all	£471	£153	£624	£8,965	£2,710	£587	£16,043	£28,306	£18,996
GATP	£932	£153	£1,085	£8,975	£2,708	£589	£16,043	£28,315	£19,005
Subgroup B: MRI Likert 1 or 2 first biopsy									
LATRUS	£350	£117	£467	£5,118	£1,715	£521	£16,040	£23,395	£14,847
LATP-all	£464	£150	£614	£5,119	£1,716	£521	£16,042	£23,397	£14,848
GATP	£924	£150	£1,075	£5,123	£1,715	£522	£16,042	£23,402	£14,852
Subgroup C: MRI Likert 3+ previous negative biopsy									
LATRUS	£346	£115	£461	£5,953	£1,987	£555	£16,041	£24,535	£15,775
LATP-all	£459	£149	£608	£5,953	£1,987	£555	£16,042	£24,538	£15,776
GATP	£920	£149	£1,069	£5,958	£1,986	£556	£16,042	£24,543	£15,780
Subgroup D: MRI Likert 1 or 2 previous negative biopsy									
LATRUS	£346	£115	£461	£3,568	£1,303	£490	£16,039	£21,399	£13,171
LATP-all	£459	£149	£608	£3,568	£1,303	£490	£16,041	£21,401	£13,172
GATP	£920	£149	£1,069	£3,570	£1,302	£491	£16,041	£21,404	£13,174

AE biopsy related adverse events
For abbreviations see *List of Abbreviations*

5.10.2 Base case: decision question 2

Deterministic results

For decision question 2, LATP-freehand dominates both LATP-other and GATP, yielding lower costs and more QALYs. The ICER for LATP-freehand versus LATRUS is below £20,000 per QALY gained for both subgroups undergoing a first biopsy (A and B), but above £30,000 per QALY gained for the subgroups with a previous negative biopsy (C and D). The QALY advantage for LATP-freehand in this analysis is driven by the favourable relative risk of cancer detection estimated from our NMA (see *Table 54* above). We note uncertainties over the evidence base that underlies these results and test the impact of estimates of cancer detection rates in section 5.10.3.

Table 73 Base case cost effectiveness (deterministic): decision question 2

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	£19,472	9.2991					
LATP-freehand	£19,582	9.3121	£110	0.0130	0.007	0.009	£8,447
LATP-other	£19,632	9.2985	£50	-0.0135	-0.009	-0.006	Dominated
GATP	£20,100	9.2969	£468	-0.0016	-0.034	-0.023	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,314	9.4783					
LATP-freehand	£15,448	9.4857	£134	0.0074	0.001	0.003	£18,196
LATP-other	£15,468	9.4789	£19	-0.0067	-0.007	-0.004	Dominated
GATP	£15,932	9.4782	£464	-0.0008	-0.031	-0.021	Dominated
Subgroup C: MRI Likert 3+ previous negative biopsy							
LATRUS	£16,236	9.4565					
LATP-freehand	£16,382	9.4611	£146	0.0047	-0.003	0.000	£31,311
LATP-other	£16,390	9.4570	£8	-0.0041	-0.007	-0.005	Dominated
GATP	£16,854	9.4562	£464	-0.0009	-0.031	-0.021	Dominated
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	£13,632	9.5474					
LATP-freehand	£13,781	9.5515	£148	0.0040	-0.003	-0.001	£36,665
LATP-other	£13,783	9.5486	£3	-0.0029	-0.006	-0.004	Dominated
GATP	£14,246	9.5482	£462	-0.0004	-0.030	-0.020	Dominated

ICER incremental cost effectiveness ratio (fully incremental)
INHB incremental net health benefit versus LATRUS, at thresholds £20,000-£30,000/QALY gained
For abbreviations see *List of Abbreviations*

Probabilistic results

Table 74 shows probabilistic results for decision question 2. As with question 1, these are similar to the deterministic results shown above, with slightly higher ICERs for LATP-freehand compared with LATRUS in all subgroups. The ICER for LATP-freehand in subgroup A remains under £20,000 per QALY gained. The ICERs for subgroups C and D are above the £30,000 per QALY threshold. LATP-other and GATP are dominated in all subgroups. The probabilistic results for this decision question are illustrated for subgroup A in *Figure 25* and *Figure 26* below.

Table 74 Base case cost effectiveness (deterministic): decision question 2

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	£19,517	9.2974					
LATP-freehand	£19,641	9.3074	£124	0.0100	0.004	0.006	£12,456
LATP-other	£19,680	9.2966	£163	-0.0008	-0.009	-0.006	Dominated
GATP	£20,150	9.2944	£633	-0.0030	-0.035	-0.024	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,283	9.4787					
LATP-freehand	£15,422	9.4849	£139	0.0062	-0.001	0.002	£22,320
LATP-other	£15,441	9.4792	£157	0.0005	-0.007	-0.005	Dominated
GATP	£15,904	9.4782	£621	-0.0005	-0.032	-0.021	Dominated
Subgroup C: MRI Likert 3+ previous negative biopsy							
LATRUS	£16,188	9.4539					
LATP-freehand	£16,335	9.4580	£147	0.0041	-0.003	-0.001	£35,674
LATP-other	£16,342	9.4544	£154	0.0005	-0.007	-0.005	Dominated
GATP	£16,807	9.4530	£619	-0.0009	-0.032	-0.022	Dominated
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	£13,625	9.5426					
LATP-freehand	£13,777	9.5464	£152	0.0038	-0.004	-0.001	£39,966
LATP-other	£13,777	9.5438	£152	0.0012	-0.006	-0.004	Dominated
GATP	£14,240	9.5433	£615	0.0007	-0.030	-0.020	Dominated

ICER incremental cost effectiveness ratio (fully incremental)
INHB incremental net health benefit versus LATRUS, at thresholds £20,000-£30,000/QALY gained
For abbreviations see *List of Abbreviations*

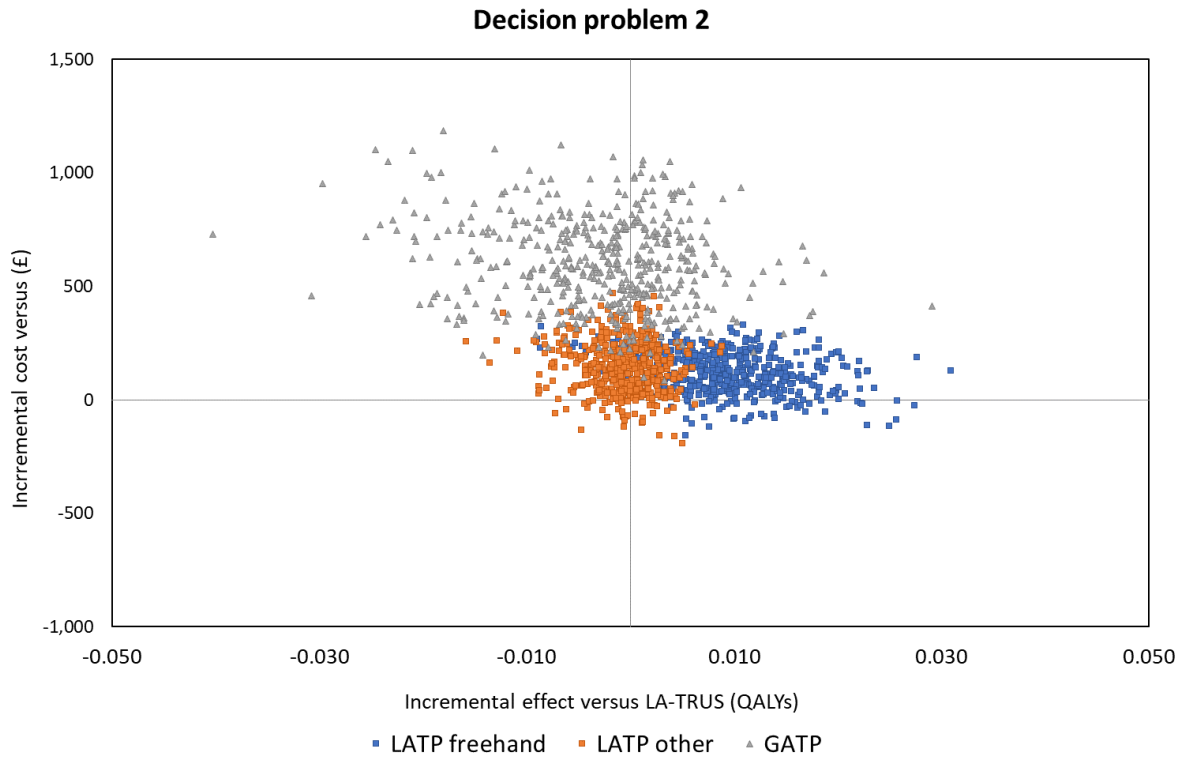


Figure 25 Cost effectiveness scatterplot: subgroup A (decision question 2)

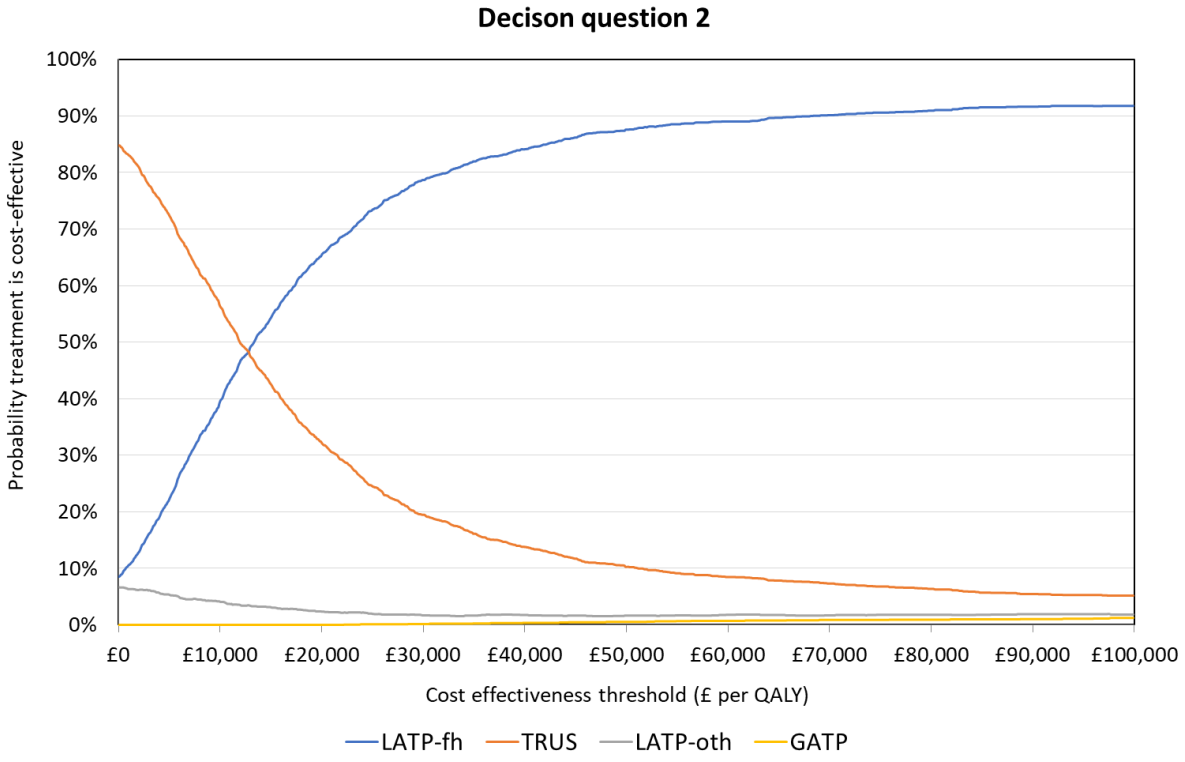


Figure 26 Cost effectiveness acceptability curve: : subgroup A (decision question 2)

Intermediate outcomes

Intermediate outcomes and costs for decision question 2 are shown below in *Table 75*, *Table 76* and *Table 77* below. Cancer detection estimates for LATP-freehand are more favourable than for LATP-all in decision question 1 and LATP-other in decision question 2 (*Table 70* and *Table 75* respectively) – driven by the more favourable relative risk estimates from the NMA. Other decision tree results are similar, as we use the same estimates of probability of repeat biopsy and adverse event rates for the different transperineal methods in our base case. This might not be realistic, and we explore alternative scenarios in 5.10.3 below.

The Markov outcomes for decision question 2 (*Table 76* below) show the impact of the more favourable estimate of 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. 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 TRUS or LATP-other (*Table 77*). We investigate alternative sources of cost estimates in 5.10.3 below.

Table 75 Base case decision tree intermediate outcomes (deterministic): decision question 2

Biopsy method	Mean biopsies	Undiagnosed		Biopsy related adverse events (AE)			AE QALY loss
		CNS	CS	Mild	Admissions	Deaths	
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	1.034	9.92%	15.22%	1.4%	6.3%	0.07%	-0.0016
LATP-freehand	1.034	9.15%	8.38%	9.2%	15.8%	0.05%	-0.0018
LATP-other	1.034	10.05%	16.60%	9.2%	15.8%	0.05%	-0.0018
GATP	1.034	10.13%	17.57%	9.2%	15.8%	0.05%	-0.0018
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	1.013	20.40%	6.73%	1.3%	6.2%	0.07%	-0.0016
LATP-freehand	1.014	18.64%	3.85%	9.2%	15.7%	0.05%	-0.0018
LATP-other	1.013	20.68%	7.32%	9.2%	15.7%	0.05%	-0.0018
GATP	1.013	20.87%	7.73%	9.2%	15.7%	0.05%	-0.0018
Subgroup C: MRI Likert 3+ previous negative biopsy							
LATRUS	1.000	17.44%	4.45%	1.3%	6.1%	0.07%	-0.0016
LATP-freehand	1.000	14.95%	3.59%	9.1%	15.6%	0.05%	-0.0018
LATP-other	1.000	17.85%	5.04%	9.1%	15.6%	0.05%	-0.0018
GATP	1.000	18.13%	5.46%	9.1%	15.6%	0.05%	-0.0018
Subgroup D: MRI Likert 1 or 2 previous negative biopsy							
LATRUS	1.000	21.74%	1.12%	1.3%	6.1%	0.07%	-0.0016
LATP-freehand	1.000	18.64%	0.90%	9.1%	15.6%	0.05%	-0.0018
LATP-other	1.000	22.26%	1.26%	9.1%	15.6%	0.05%	-0.0018
GATP	1.000	22.60%	1.37%	9.1%	15.6%	0.05%	-0.0018

CNS clinically non-significant prostate cancer (low-risk localised); CS clinically significant prostate cancer (intermediate or high-risk localised disease)

Table 76 Base case health outcomes from Markov model (deterministic): decision question 2

Biopsy method	Deaths (% of whole cohort)			Undiscounted		Discounted	
	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-freehand	19.41%	80.51%	99.92%	16.037	12.599	11.734	9.314
LATP-other	19.64%	80.29%	99.92%	16.009	12.577	11.717	9.300
GATP	19.66%	80.26%	99.92%	16.006	12.575	11.715	9.299
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	10.88%	89.03%	99.91%	16.781	12.961	12.139	9.481
GATP	10.90%	89.02%	99.91%	16.779	12.960	12.138	9.480
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	12.66%	87.26%	99.92%	16.639	12.904	12.064	9.459
GATP	12.68%	87.24%	99.92%	16.637	12.902	12.063	9.458
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	7.33%	92.58%	99.91%	17.089	13.112	12.306	9.550
GATP	7.34%	92.57%	99.91%	17.089	13.112	12.306	9.550

LY life years; QALY quality adjusted life years

Table 77 Base case intermediate costs from decision tree and Markov model (deterministic): decision question 2

Biopsy method	Decision tree costs			Markov model, undiscounted costs					Discounted Total costs
	Biopsies	AEs	Total	Treatment	AE	Follow up	End of life	Total	
Subgroup A: MRI Likert 3+ first biopsy									
LATRUS	£357	£119	£477	£8,965	£2,709	£587	£16,042	£28,304	£18,996
LATP-freehand	£482	£153	£635	£8,909	£2,721	£576	£16,043	£28,249	£18,947
LATP-other	£471	£153	£624	£8,979	£2,708	£590	£16,043	£28,319	£19,008
GATP	£932	£153	£1,085	£8,987	£2,706	£591	£16,043	£28,328	£19,015
Subgroup B: MRI Likert 1 or 2 first biopsy									
LATRUS	£350	£117	£467	£5,118	£1,715	£521	£16,040	£23,395	£14,847
LATP-freehand	£475	£151	£625	£5,092	£1,721	£513	£16,042	£23,368	£14,823
LATP-other	£464	£150	£614	£5,125	£1,715	£523	£16,042	£23,404	£14,853
GATP	£924	£150	£1,075	£5,129	£1,714	£524	£16,042	£23,408	£14,857
Subgroup C: MRI Likert 3+ previous negative biopsy									
LATRUS	£346	£115	£461	£5,953	£1,987	£555	£16,041	£24,535	£15,775
LATP-freehand	£470	£149	£619	£5,942	£1,990	£548	£16,042	£24,522	£15,763
LATP-other	£459	£149	£608	£5,960	£1,986	£557	£16,042	£24,545	£15,782
GATP	£920	£149	£1,069	£5,964	£1,985	£558	£16,042	£24,549	£15,786
Subgroup D: MRI Likert 1 or 2 previous negative biopsy									
LATRUS	£346	£115	£461	£3,568	£1,303	£490	£16,039	£21,399	£13,171
LATP-freehand	£470	£149	£619	£3,560	£1,305	£482	£16,041	£21,389	£13,162
LATP-other	£459	£149	£608	£3,571	£1,302	£491	£16,041	£21,405	£13,175
GATP	£920	£149	£1,069	£3,572	£1,302	£492	£16,041	£21,407	£13,177
For abbreviations see *List of Abbreviations*									

5.10.3 Scenario analyses

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 and colleagues (see *section 5.7.3*).[81] Jimenez and colleagues also reported the rate of re-biopsy after a first GATP biopsy (5.26%), 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 and colleagues 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 other side, 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.

In this scenario we test the impact of using a re-biopsy probability of 5.26% for LATP (all methods) and GATP, retaining the base case probability of 15.45% for LATRUS, for subgroup A (Likert 3+ first biopsy). *Table 78* below shows a large increase in the ICER for LATP versus LATRUS (increment of £45,830 per QALY compared with the base case) for decision question 1 and a slight increase for decision question 2 (increment of £708 per QALY). For both decision questions, LATP dominates GATP.

This scenario does not change overall conclusions in subgroup A: for decision question 1 the ICER for LATP-all versus LATRUS increases further above a £30,000 per QALY threshold; and in decision question 2 the ICER for LATP-freehand increases but remains below a £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 increased this probability to 15.45% for LATP (the same as if the biopsy had detected clinically non-significant disease) but left the probability at 5% for other comparators.

Table 78 Scenario: probability of repeat biopsy 5.26% for LATP and GATP, and 15.45% for LATRUS (subgroup A, deterministic)

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Decision question 1							
LATRUS	£19,472	9.2991					
LATP all	£19,620	9.3003	£148	0.0012	-0.006	-0.004	£118,333
GATP	£20,089	9.2985	£469	-0.0018	-0.031	-0.021	Dominated
Decision question 2							
LATRUS	£19,472	9.2991					
LATP-freehand	£19,581	9.3110	£109	0.0119	0.006	0.008	£9,155
LATP-other	£19,631	9.2978	£50	-0.0132	-0.009	-0.007	Dominated
GATP	£20,099	9.2962	£468	-0.0016	-0.034	-0.024	Dominated
For abbreviations see *List of Abbreviations*							

Cancer detection rates

Relative risk of cancer detection from observational data

The base case source for the relative risks of cancer detection is the EAG network meta-analyses based on RCT data. In this scenario we test the effect of using estimates from observational studies included in our clinical review for the comparisons between LATP-all, LATP-freehand and LATP-other versus LATRUS, as summarised in EAG pairwise meta-analyses (see *section 4.8* above). See *Table 54* above for the relative risk values used in the base case and scenario.

Observational data for GATP is only available in comparison with LATP. Therefore the estimated relative risk for GATP versus LATRUS has to be adjusted by the relative risk for LATP versus LATRUS for use in the model. This yields different estimates for the effectiveness of GATP in decision question 1 and 2: 1.44 (1.31 x 1.10) or 1.32 (1.31 x 1.01) respectively. We also test the effect of assuming the same relative risk for GATP versus TRUS in decision question 2 as in decision question 1 (1.44).

Table 79 shows the results for decision question 1. This analysis has the effect of reducing the estimated cost-effectiveness of LATP and improving cost-effectiveness for GATP. In decision question 1, the ICER for LATP-all compared with LA-TRUS is below £30,000 per

QALY gained in subgroup A, but higher for the other subgroups. Although GATP is no longer dominated in this analysis, its ICERs are well above £30,000 per QALY for all subgroups.

Table 79 Scenario: relative risk of cancer detection from observational studies – decision question 1

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	£19,472	9.2991					
LATP-all	£19,607	9.3041	£134	0.0051	-0.002	0.001	£26,550
GATP	£20,032	9.3120	£425	0.0079	-0.015	-0.006	£54,052
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,3[illegible]	9.4[illegible]					
LATP-all	£15,455	9.4817	£141	0.0034	-0.004	-0.001	£41,833
GATP	£15,898	9.4857	£442	0.0041	-0.022	-0.012	£109,055
Subgroup C: MRI Likert 3+ negative biopsy							
LATRUS	£16,236	9.4565					
LATP-all	£16,377	9.4599	£141	0.0034	-0.004	-0.001	£41,150
GATP	£16,831	9.4612	£454	0.0013	-0.025	-0.015	£358,421
Subgroup D: MRI Likert 1 or 2 negative biopsy							
LATRUS	£13,632	9.5474					
LATP-all	£13,777	9.5500	£145	0.0026	-0.005	-0.002	£56,031
GATP	£14,230	9.5516	£453	0.0016	-0.026	-0.016	£279,175

Table 80 shows the scenario results for decision question 2. These are less favourable for LATP-freehand than the base case, reducing the ICERs compared with LATRUS, although they remain below £30,000 per QALY for subgroups A and B. Although this scenario is more favourable for GATP than the base case, the ICERs compared with LATP-freehand are well above £30,000 per QALY in all subgroups. This remains the case if we use the same relative risk for GATP versus TRUS as in decision question 1.

Table 80 Scenario: relative risk of cancer detection from observational studies – decision question 2 (deterministic)

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	£19,472	9.2991					
LATP-freehand	£19,603	9.3074	£130	0.0083	0.002	0.004	£15,687
LATP-other	£19,620	9.3011	£17	-0.0063	-0.005	-0.003	Dominated
GATP	£20,040	9.3103	£419	0.0092	-0.017	-0.008	£150,206
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,314	9.4783					
LATP-freehand	£15,459	9.4833	£145	0.0050	-0.002	0.000	£28,955
LATP-other	£15,462	9.4802	£3	-0.0031	-0.005	-0.003	Dominated
GATP	£15,902	9.4848	£440	0.0046	-0.023	-0.013	£301,071
Subgroup C: MRI Likert 3+ negative biopsy							
LATRUS	£16,236	9.4565					
LATP-freehand	£16,383	9.4610	£147	0.0045	-0.003	0.000	£32,877
LATP-other	£16,384	9.4584	£1	-0.0026	-0.005	-0.003	Dominated
GATP	£16,832	9.4611	£448	0.0027	-0.025	-0.015	£3,735,400
Subgroup D: MRI Likert 1 or 2 negative biopsy							
LATRUS	£13,632	9.5474					
LATP-other	£13,780	9.5493	£148	0.0018	-0.006	-0.003	Dominated
LATP-freehand	£13,784	9.5507	£4	0.0015	-0.004	-0.002	£46,314
GATP	£14,232	9.5512	£448	0.0005	-0.026	-0.016	£966,685

Relative risks of CS versus CNS cancer detection for LATP and GATP

We also run an exploratory scenario analysis in which we assume that LATP and GATP are more likely to detect CS disease than LATRUS. We apply a relative risk of 1.05 to the relative risk of LATP/GATP vs. LATRUS to detect CS disease.

Table 81 presents the results for decision question 1 and shows lower ICERs for LATP versus LATRUS than in the base case (£38,273 per QALY for subgroup A). GATP is dominated. The results for decision question 2 are very similar to the base case results (see *Table 82* below).

Table 81 Scenario analysis: increased relative risk of cancer detection rates for CS for LATP and GATP – decision question 1 (deterministic)

Biopsy method	Total		Incremental		Incr. NHB		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	£19,472	9.2991					
LATP all	£19,613	9.3028	£141	0.0037	-0.003	-0.001	£38,273
GATP	£20,081	9.3010	£469	-0.0018	-0.029	-0.018	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,314	9.4783					
LATP all	£15,459	9.4809	£145	0.0026	-0.005	-0.002	£55,831
GATP	£15,923	9.4800	£464	-0.0009	-0.029	-0.019	Dominated
Subgroup C: MRI Likert 3+ negative biopsy							
LATRUS	£16,236	9.4565					
LATP all	£16,381	9.4591	£145	0.0026	-0.005	-0.002	£56,363
GATP	£16,846	9.4581	£465	-0.0009	-0.029	-0.019	Dominated
Subgroup D: MRI Likert 1 or 2 negative biopsy							
LATRUS	£13,632	9.5474					
LATP all	£13,780	9.5494	£147	0.0020	-0.005	-0.003	£73,962
GATP	£14,242	9.5490	£462	-0.0004	-0.029	-0.019	Dominated

Table 82 Scenario analysis: increased relative risk of cancer detection rates for CS for LATP and GATP – decision question 2 (deterministic)

Biopsy method	Total		Incremental		Incr. NHB		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	£19,472	9.2991					
LATP-freehand	£19,581	9.3123	£108	0.0133	0.008	0.010	£8,172
LATP-other	£19,624	9.3002	£44	-0.0121	-0.006	-0.004	Dominated
GATP	£20,092	9.2986	£468	-0.0016	-0.031	-0.021	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,314	9.4783					
LATP-freehand	£15,448	9.4858	£134	0.0075	0.001	0.003	£17,823
LATP-other	£15,464	9.4797	£17	-0.0062	-0.006	-0.004	Dominated
GATP	£15,928	9.4789	£464	-0.0008	-0.030	-0.020	Dominated
Subgroup C: MRI Likert 3+ negative biopsy							
LATRUS	£16,236	9.4565					
LATP-freehand	£16,382	9.4612	£146	0.0047	-0.003	0.000	£31,001
LATP-other	£16,387	9.4577	£5	-0.0034	-0.006	-0.004	Dominated
GATP	£16,851	9.4569	£464	-0.0008	-0.030	-0.020	Dominated
Subgroup D: MRI Likert 1 or 2 negative biopsy							
LATRUS	£13,632	9.5474					
LATP-freehand	£13,781	9.5515	£148	0.0041	-0.003	-0.001	£36,561
LATP-other	£13,782	9.5488	£2	-0.0027	-0.006	-0.004	Dominated
GATP	£14,245	9.5484	£462	-0.0004	-0.030	-0.019	Dominated

Probability of biopsy complications

The rationale for choosing the sources for the probabilities of biopsy complications is described in section 5.7.4 above. The sources for mild AEs were Rosario and colleagues for LATRUS and Pepe and Aragona for transperineal biopsies.[83 84] For admissions and death, we used data from the Tamhankar and colleagues' study.[85] We also included data on overnight stay from Berry and colleagues as part of the admission probability.[82] As discussed above, the sources for mild AEs do not compare transrectal with transperineal biopsies. In addition, the sources that report admission and death for transrectal versus transperineal biopsies do not distinguish between LATP and GATP biopsies. Therefore,

although the above observational studies are of a reasonable quality, considerable uncertainty remains over comparative complication rates for the biopsy methods of interest.

We conducted a range of scenario analyses to test the effect of using different sources to inform estimates of the probability of complications associated with an overnight stay after the biopsy, admissions and death. We focus on these more serious complications because of their impact on patients and costs for the health service.

- Rosario and colleagues as a source of admission for LATRUS (increasing the number of admissions for LATRUS compared to base case)[84]
- Pepe and Aragona as a source of admission for TP biopsies (reducing the number of admissions for TP biopsies compared to base case (about 14% less))[83]
- Tamhankar and colleagues as a source of admission for LATRUS and TP biopsies (without the inclusion of overnight stay from Berry and colleagues) (reducing admissions for TP biopsies compared to base case due to the exclusion of the probability of overnight stay from Berry and colleagues, which is much higher for TP biopsies than LATRUS).[82 85]
- Berry and colleagues as a source of admission for LATRUS and TP biopsies (includes overnight stay) (reducing admissions for LATRUS compared to base case).[82]

Table 83 (decision question 1) and *Table 84* (decision question 2) show the results of these scenarios for subgroup A (MRI Likert score 3+ at first biopsy).

For decision question 1, using estimates from Berry and colleagues is the only scenario that benefits LATRUS versus LATP, since they report lower admissions associated with transrectal biopsies. The other scenarios favour the cost-effectiveness of transperineal biopsies, although the ICER of LATP versus LATRUS remains above £20,000 per QALY gained unless estimates from Pepe and Aragona are used. This study reports a probability of admission of 1.23% which is much lower than the base case assumption (15.61%). The Pepe and Aragona study, from 2013, included around 3,000 patients and was conducted in Italy. Both Tamhankar and colleagues and Berry and colleagues were conducted more recently in the UK and have a representative sample size of >70,000 patients, and also provide a comparison between transrectal and transperineal biopsies. Tamhankar and colleagues assessed the population of interest in the current assessment (patients with suspected prostate cancer undergoing a prostate biopsy) while Berry and colleagues reported results for patients already diagnosed with prostate cancer. This was the reason why we chose to use the Tamhankar study in our base case. Berry and colleagues reported

the frequency of overnight stay directly after the biopsy, which is much higher in the group of patients having a TP biopsy than LATRUS. However, it is possible that a proportion of these overnight stays might be attributable to the use of general anaesthetics and not due to the transperineal route and therefore should not be applied to LATP. If that is true, using the data from Tamhankar and colleagues alone might be the best option (yielding an ICER of £31,109 per QALY for LATP versus LATRUS). GATP is dominated in all scenarios.

Table 83 Scenario: alternative sources for serious biopsy complications, subgroup A (deterministic) – decision question 1

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Rosario and colleagues 2012 – increase admissions for LATRUS							
LATRUS	£19,550	9.2980					
LATP all	£19,623	9.3011	£73	0.0031	-0.001	0.001	£23,321
GATP	£20,092	9.2993	£469	-0.0018	-0.026	-0.017	Dominated
Pepe and Aragona 2013 – reduce admissions for TP							
LATRUS	£19,472	9.2991					
LATP all	£19,492	9.3025	£19	0.0034	0.002	0.003	£5,621
GATP	£19,960	9.3007	£469	-0.0018	-0.023	-0.015	Dominated
Tamhankar and colleagues 2020 – reduce admissions for TP							
LATRUS	£19,429	9.2997					
LATP all	£19,511	9.3023	£82	0.0026	-0.001	0.000	£31,109
GATP	£19,980	9.3005	£469	-0.0018	-0.027	-0.018	Dominated
Berry and colleagues 2020 – reduce admissions for LATRUS							
LATRUS	£19,415	9.2971					
LATP all	£19,620	9.2993	£205	0.0022	-0.008	-0.005	£94,454
GATP	£20,089	9.2975	£469	-0.0018	-0.033	-0.022	Dominated

For decision question 2, LATP using freehand devices either dominates the other options or has an ICER lower than £12,733 per QALY compared to LATRUS (*Table 84*). Results follow the same trends for the other subgroups. For example, the ICER for LATP-freehand versus LATRUS is estimated at £17,713 per QALY in the lowest risk subgroup (subgroup D, Likert 1 or 2 and previous negative biopsy) if we only use data on admissions from Tamhankar and colleagues (excluding the overnight stays estimated by Berry and colleagues). With overnight stays, admissions and deaths reported by Berry and colleagues, the ICER in subgroup D increases to £48,794.

Table 84 Scenario: alternative sources for serious biopsy complications, subgroup A (deterministic) – decision question 2

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Rosario and colleagues 2012 – increase admissions for LATRUS							
LATRUS	£19,550	9.2980					
LATP-freehand	£19,585	9.3120	£34	0.0140	0.012	0.013	£2,430
LATP-other	£19,635	9.2985	£50	-0.0135	-0.004	-0.002	Dominated
GATP	£20,102	9.2969	£468	-0.0016	-0.029	-0.019	Dominated
Pepe and Aragona 2013 – reduce admissions for TP							
LATP-freehand	£19,453	9.3135					
LATRUS	£19,472	9.2991	£19	-0.0144	-0.015	-0.015	Dominated
LATP-other	£19,503	9.2999	£31	0.0008	-0.016	-0.015	Dominated
GATP	£19,971	9.2983	£468	-0.0016	-0.041	-0.032	Dominated
Tamhankar and colleagues 2020 – reduce admissions for TP							
LATRUS	£19,429	9.2997					
LATP-freehand	£19,473	9.3133	£43	0.0136	0.011	0.012	£3,196
LATP-other	£19,523	9.2997	£50	-0.0135	-0.005	-0.003	Dominated
GATP	£19,990	9.2981	£468	-0.0016	-0.030	-0.020	Dominated
Berry and colleagues 2020 – reduce admissions for LATRUS							
LATRUS	£19,415	9.2971					
LATP-freehand	£19,582	9.3103	£167	0.0131	0.005	0.008	£12,733
LATP-other	£19,632	9.2967	£50	-0.0135	-0.011	-0.008	Dominated
GATP	£20,099	9.2951	£468	-0.0016	-0.036	-0.025	Dominated

Biopsy costs

Source of biopsy costs: decision question 1

For decision question 1, we use the costs obtained from our micro-costing analysis as our base case and the costs reported in the NHS cost collection data 2019/20 as a scenario analysis (see *Table 85* below). The unit costs from the NHS source are: £332 for LATRUS, £329 for LATP and £1,512 for GATP. This reduction of about £100 in the estimated cost of LATP (compared with our base case) produces a low incremental cost of £31 versus LATRUS and therefore a large reduction in the ICER: from £15,196 in subgroup A to £17,043 per QALY in subgroup D.

Table 85 Scenario: biopsy costs from NHS Costs (deterministic) – decision question 1

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	£19,458	9.2991					
LATP all	£19,489	9.3011	£31	0.0020	0.000	0.001	£15,196
GATP	£20,681	9.2993	£1,192	-0.0018	-0.061	-0.042	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,300	9.4783					
LATP all	£15,331	9.4802	£31	0.0019	0.000	0.001	£16,374
GATP	£16,519	9.4793	£1,187	-0.0009	-0.060	-0.040	Dominated
Subgroup C: MRI Likert 3+ negative biopsy							
LATRUS	£16,222	9.4565					
LATP all	£16,253	9.4584	£31	0.0019	0.000	0.001	£16,395
GATP	£17,441	9.4574	£1,188	-0.0010	-0.060	-0.041	Dominated
Subgroup D: MRI Likert 1 or 2 negative biopsy							
LATRUS	£13,619	9.5474					
LATP all	£13,650	9.5493	£31	0.0018	0.000	0.001	£17,043
GATP	£14,835	9.5488	£1,186	-0.0005	-0.059	-0.039	Dominated

This means that the cost of LATP drives the model conclusions. Of course, the NHS estimates might be more in line with real practice in terms of including all the relevant item costs and measuring them more accurately. However, we question whether these national NHS costs are including the cost of the freehand devices. For that reason, our micro-costing analysis might be a better source although there are some important uncertainties:

- Cost of SureFire Guide device, as we have not been provided with its cost and therefore assumed an average of the other two disposable LATP freehand devices (CamPROBE and PrecisionPoint™). This might be different from the real price.
- The number of cores taken, as there is no evidence available on the differences between devices. Therefore, we assumed the same number of cores for every method (12 cores), which may well not be realistic.

Proportion of use of LATP methods and devices: decision question 1

The base case assumption for decision question 1 is equal use of all the LATP methods (including all included freehand devices, grid and stepper and coaxial), in the absence of data on current and likely future use of each device in practice. According to the information provided by some clinical experts and specialist committee members, it seems that there are

three devices that are more frequently used: CamPROBE, PrecisionPoint™ and UA1232. We were also informed that LATP using grid and stepper unit are used in some hospitals but not a majority. We understand that the other LATP devices are not currently being used in UK practice. We test another scenario assuming 10% use of a grid and stepper unit, and 30% market share each for CamPROBE, PrecisionPoint™ and UA1232. This results in a weighted average cost of LATP-all of £462 compared to the simple average of £459 in our base case (see *Table 86*). This results in a moderate increase in the ICERs for LATP-all versus LATRUS for decision question 1. If all hospitals were using the least expensive options (LATP using double freehand device or Trinity® Perine), the ICER will still be higher than £40,000 per QALY for LATP-all versus LATRUS.

Table 86 Scenario: use of LATP devices (10% grid and stepper; 30% each for CamPROBE, PrecisionPoint™ and UA1232) (deterministic) – decision question 1

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	£19,472	9.2991					
LATP all	£19,648	9.3011	£175	0.0020	-0.007	-0.004	£85,866
GATP	£20,089	9.2993	£441	-0.0018	-0.031	-0.020	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,314	9.4783					
LATP all	£15,489	9.4802	£175	0.0019	-0.007	-0.004	£92,530
GATP	£15,927	9.4793	£437	-0.0009	-0.030	-0.019	Dominated
Subgroup C: MRI Likert 3+ negative biopsy							
LATRUS	£16,236	9.4565					
LATP all	£16,411	9.4584	£175	0.0019	-0.007	-0.004	£92,329
GATP	£16,849	9.4574	£437	-0.0010	-0.030	-0.019	Dominated
Subgroup D: MRI Likert 1 or 2 negative biopsy							
LATRUS	£13,632	9.5474					
LATP all	£13,808	9.5493	£175	0.0018	-0.007	-0.004	£96,218
GATP	£14,243	9.5488	£435	-0.0005	-0.029	-0.019	Dominated

Cost of transperineal biopsy freehand devices – decision question 2

For decision question 2, we use a simple average of the cost of each LATP freehand device in our base case to obtain the cost for the LATP-freehand arm. In this scenario, we use the cost of the individual device PrecisionPoint™ , which was used in the clinical trial that provided the evidence on diagnostic performance for LATP-freehand (Lam et al. 2021).[26]

This means that the cost of LATP-freehand (£584) is higher than the cost of LATP with a grid and stepper unit (£459). *Table 87* shows that this increase of about £114 in the cost of LATP-freehand compared to base case has an impact on the model conclusions, as the ICER for LATP-freehand versus LATRUS in subgroup B rises above £30,000 per QALY.

Conversely, if we assume the cost of Trinity® Perine (£406), the ICER for LATP-freehand versus LATRUS is £20,779 per QALY or lower for all subgroups.

Table 87 Scenario: cost of PrecisionPoint™ device (deterministic) – decision question 2

Biopsy method	Total		Incremental		INHB (QALYs)		ICERs
	Cost	QALYs	Cost	QALYs	£20k	£30k	£/QALY
Subgroup A: MRI Likert 3+ first biopsy							
LATRUS	£19,472	9.2991					
LATP-other	£19,632	9.2985	£160	-0.0006	-0.009	-0.006	Dominated
LATP-freehand	£19,696	9.3121	£64	0.0135	0.002	0.006	£17,208
GATP	£20,100	9.2969	£404	-0.0151	-0.034	-0.023	Dominated
Subgroup B: MRI Likert 1 or 2 first biopsy							
LATRUS	£15,314	9.4783					
LATP-other	£15,468	9.4789	£154	0.0006	-0.007	-0.004	Dominated
LATP-freehand	£15,562	9.4857	£94	0.0067	-0.005	-0.001	£33,615
GATP	£15,932	9.4782	£370	-0.0075	-0.031	-0.021	Dominated
Subgroup C: MRI Likert 3+ negative biopsy							
LATRUS	£16,236	9.4565					
LATP-other	£16,390	9.4570	£154	0.0005	-0.007	-0.005	Dominated
LATP-freehand	£16,496	9.4611	£106	0.0041	-0.008	-0.004	£55,683
GATP	£16,854	9.4562	£359	-0.0050	-0.031	-0.021	Dominated
Subgroup D: MRI Likert 1 or 2 negative biopsy							
LATRUS	£13,632	9.5474					
LATP-other	£13,783	9.5486	£151	0.0012	-0.006	-0.004	Dominated
LATP-freehand	£13,894	9.5515	£111	0.0029	-0.009	-0.005	£64,771
GATP	£14,246	9.5482	£351	-0.0033	-0.030	-0.020	Dominated

Disutility from the biopsy procedure

The EAG model includes estimated impact on health-related quality of life (disutility) from biopsy-related complications, but no disutility from the procedure itself. This follows the approach in previous economic analyses of diagnostic strategies for people with suspected

prostate cancer.[58 60 62 107] We are conscious that the modelled QALY loss for 'mild' adverse effects (associated with a consultation with a healthcare professional but not hospital admission) may not reflect pain, discomfort or anxiety associated with a biopsy for some patients. There are differences in the types and severity of adverse effects associated with the different biopsy procedures, numbers of cores taken and anaesthetic approach.[82] We therefore wanted to test the sensitivity of the cost-effectiveness results to changes in assumptions about the QALY loss associated with more and less serious adverse events.

The base case assumed a disutility of -0.29 for 3 days for mild adverse events and 1 day for overnight stay after the biopsy. We tested the impact of increasing this duration to 5 days. This further increased the ICERs for LATP-all compared with LATRUS in decision question 1 (ICER £91,937 per QALY gained for subgroup A), because the incidence of mild adverse events is higher for LATP. However, this had little effect on the results for decision question 2: ICER £8,738 per QALY gained for LATP-freehand versus LATRUS in subgroup A. Increasing the duration of disutility to 30 days only increased this ICER to £12,083 per QALY gained. This is because the small absolute QALY reduction does not offset the QALY gain from increased cancer detection with LATP-freehand in the decision question 2 analysis.

Similarly, increasing the duration and disutility associated with serious adverse events, which have a higher incidence with LATRUS, reduced ICERs for LATP-all in decision question 1, but not sufficiently to change the cost-effectiveness conclusion. For example, assuming a very large disutility of -0.7 for 100 days per hospital admission reduced the ICER for LATP-all versus LATRUS in subgroup A to £61,559 per QALY gained.

Other scenarios

Table 88 presents other scenario analyses conducted for decision questions 1 and 2 in subgroup A. This table presents the scenario analyses 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 *Table 88* below.

Table 88 Scenario analyses' results for the subgroup of patients with an MRI Likert score 3+ having first biopsy

	Element	Base case	Scenario analysis	Justification	ICER/QALY – DQ1		ICER/QALY – DQ2		
					LATP vs. LATRUS	LATP vs. GATP	LATP fh vs. LATRUS	LATP fh vs. LATP other	LATP fh vs. GATP
1	Time horizon	40 years	20 years	Test the impact of an alternative time horizon	£77,679	Dominates	£8,895	Dominates	Dominates
2	Discount rate	3.5%	0%	Test the impact of alternative discount rates, as recommended by NICE	£51,347	Dominates	£4,972	Dominates	Dominates
3			1.5% QALYs 1.5% costs		£59,90	Dominates	£6,226	Dominates	Dominates
4			1.5% QALYs 3.5% costs		£59,619	Dominates	£6,563	Dominates	Dominates
5	Initial age of the cohort	66 years	55 years	Test the impact of a younger cohort	£53,299	Dominates	£6,835	Dominates	Dominates
6			63 years	Mean age at referral for a first prostate biopsy in PROMIS trial	£65,563	Dominates	£7,684	Dominates	Dominates
7			69 years	Test the impact of an older cohort	£81,443	Dominates	£9,569	Dominates	Dominates
8	Proportion of the cohort initially diagnosed with metastatic disease	0%	5%	It is likely that a small proportion of patients with metastatic disease undergoes biopsy	£75,142	Dominates	£9,093	Dominates	Dominates
9	Probability of a false positive result of CS for patients	0%	5%	As advised by SCM, it's unlikely that there are no false positive results of CS for	£69,282	Dominates	£8,214	Dominates	Dominates

	with low-risk disease (for first and second biopsies)			patients with low-risk disease.					
10	Probability of CNS and NC for patients with high-risk and metastatic disease	0%	CNS: 8% NC: 5%	Test the impact of false negative results by using the probabilities of CNS and NC from second biopsy.	£65,574	Dominates	£8,392	Dominates	Dominates
11	Incidence of prostate cancer in people without the disease	0%	0.8%	Assume some incident cases, as it happens in clinical practice	£72,567	Dominates	£8,453	Dominates	Dominates
12	Proportion of patients in primary care follow-up having a PSA test yearly	100%	50%	It is unlikely that all patients comply and measure their PSA every year.	£60,698	Dominates	£4,618	Dominates	Dominates
13	Distribution of patients across treatments for localised disease	NPCA data 2020 + Gnanapragasam 2016 adjusted data	Gnanapragasam 2016	In line with the distribution of treatment used in the model that informed NG131	£73,491	Dominates	£8,880	Dominates	Dominates
14	Radical treatment	AS/WW: 50.9% RP: 85.4%	AS/WW: 70% RP: 90%	As suggested by SCM David	£72,290	Dominates	£8,446	Dominates	Dominates

	adverse events: probability of erectile dysfunction	RT: 62.4%	RT: 80%	Wakefield, the probability of erectile dysfunction is likely to be higher an441approximately 100% of patients lack libido.					
15	Distribution of patients across treatments for mHSPC	ADT alone: 50% DOX+ADT: 36% APA+ADT: 7% ENZA+ADT: 7%	ADT alone: 25% DOX+ADT: 36% APA+ADT: 7% ENZA+ADT: 32%	According to a SCM, the proportion of patients using enzalutamide is growing while the proportion of patients receiving ADT alone is reducing and it's likely to be less than 25%.	£72,342	Dominates	£6,952	Dominates	Dominates
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.	£72,593	Dominates	£9,287	Dominates	Dominates
17	Duration of ADT alone, APA+ADT and ENZA+ADT for mHSPC	2 years	3 years	According to a SCM	£72,435	Dominates	£7,898	Dominates	Dominates
18	Disutility for patients with FN result and true	-0.019	-0.137	Apply the same disutility as for patients diagnosed with metastatic disease	£72,575	Dominates	£8,490	Dominates	Dominates

	metastatic disease								

5.10.4 Three-way sensitivity analyses

There are three assumptions that are driving the model conclusions: the cost of LATP, the probability of biopsy-related serious adverse events and the relative risk of cancer detection rates for LATP versus LA-TRUS. To test the impact of different combinations of these three factors, we conducted threshold analyses as follows.

- Cost of LATP
    - Cost of LATP-all (applicable to decision question 1)
        - Average cost of all biopsy methods and devices (base case)
        - Cost of CamPROBE
        - Cost of PrecisionPoint™
        - Cost of EZU-PA3
        - Cost of UA1232
        - Cost of Trinity® Perine
        - Cost of SureFire Guide
        - Cost of LATP using grid and stepper unit
        - Cost of LATP using double freehand device
    - Cost of LATP-freehand (applicable to decision question 2)
        - Average cost of all biopsy devices (base case)
        - Cost of CamPROBE
        - Cost of PrecisionPoint™
        - Cost of EZU-PA3
        - Cost of UA1232
        - Cost of Trinity® Perine
        - Cost of SureFire Guide
- Probability of biopsy-related serious adverse events
    - Based on the study of Tamhankar and colleagues (including the probability of overnight stay; applicable to both LA-TRUS and LATP) (base case)
    - Based on the study of Tamhankar and colleagues (excluding the probability of overnight stay; applicable to both LA-TRUS and LATP biopsies)
    - Based on the study of Berry and colleagues (including the probability of overnight stay; applicable to both LA-TRUS and LATP biopsies)
    - Based on the study of Rosario and colleagues (only applicable to LA-TRUS biopsy)
    - Based on the study of Pepe and Aragona (only applicable to LATP biopsies)
- Relative risk of cancer detection rates of LATP versus LA-TRUS

- Based on the EAG NMA (base case)
- Based on the pairwise meta-analysis including observational studies only
- Relative risk increased by 20% for decision question 1 and 10% for decision question 2
- Relative risk reduced by 10% for decision question 1 and 20% for decision question 1

The tables below show the results of each combination of the previous model parameters for subgroup A (patients with an MRI Likert score 3+ having a first biopsy). *Table 89* to *Table 92* refer to decision question 1 and *Table 93* to *Table 96* refer to decision question 2.

Decision question 1

Table 89 shows the results for the base case relative risk of cancer detection. LATP-all is above £30,000 per QALY when the probability of biopsy-related serious adverse events includes the probability of overnight stay or is based on Tamhankar and colleagues (without including overnight stay), except when the latter is combined with the cost of EZU-PA3, UA1232, Trinity® Perine or double freehand device. LATP-all is below £30,000 per QALY when the probability of biopsy-related serious adverse events is based on the studies from Rosario and colleagues or Pepe and Aragona, except when this is combined with the cost of PrecisionPoint™ or SureFire Guide.

Table 90 shows the results for the relative risks based on the pairwise meta-analysis including observational studies only. LATP-all is generally below £30,000 per QALY but it is above this threshold for every scenario using the cost of PrecisionPoint™ or for the scenarios that combined the cost of SureFire Guide and the probability of biopsy-related serious adverse events including the probability of overnight stay.

Table 91 shows the results with a 20% increase in the relative risks. In this case, LATP-all is below £30,000 in all scenarios expect for the combination of the cost of PrecisionPoint™ and the probability of biopsy-related serious adverse events from Berry and colleagues.

LATP-all is dominated or above £30,000 per QALY when the relative risk of cancer detection is reduced by 10%. The only exception is for the combination of the cost of EZU-PA3 and the probability of biopsy-related serious adverse events from Pepe and Aragona.

Table 89 Threshold analysis: base case relative risk of cancer detection for LATP versus LA-TRUS (ICER for LATP-all versus LA-TRUS, subgroup A)

		Probability of biopsy-related serious AEs				
		Tamhankar + overnight stay	Tamhankar	Berry	Rosario	Pepe and Aragona
Cost of LATP-all	Average	£72,503	£31,109	£94,454	£23,321	£5,621
	CamPROBE	£80,220	£37,103	£101,703	£28,388	£10,195
	PrecisionPoint	£133,400	£78,413	£151,659	£63,307	£41,724
	EZU-PA3	£50,595	£14,091	£73,874	£8,937	Dominates
	UA1232	£48,465	£12,436	£71,873	£7,538	Dominates
	Trinity Perine	£46,249	£10,715	£69,792	£6,083	Dominates
	SureFire Guide	£107,393	£58,211	£127,228	£46,230	£26,305
	LA TP Grid/Stepper	£72,409	£31,036	£94,366	£23,260	£5,565
	LA TP Double freehand	£41,292	£6,865	£65,136	£2,828	Dominates

Legend: green cells refer to ICERs < £20,000 per QALY; yellow cells refer to ICERs between £20,000 and £30,000 per QALY.
For abbreviations, see *List of Abbreviations*.

Table 90 Threshold analysis: relative risk of cancer detection from observational studies (ICER for LATP-all versus LA-TRUS, subgroup A)

		Probability of biopsy-related serious AEs				
		Tamhankar + overnight stay	Tamhankar	Berry	Rosario	Pepe and Aragona
Cost of LATP-all	Average	£26,550	£12,065	£36,905	£9,607	£888
	CamPROBE	£29,662	£14,854	£39,938	£12,177	£3,325
	PrecisionPoint	£51,109	£34,073	£60,842	£29,888	£20,121
	EZU-PA3	£17,715	£4,147	£28,293	£2,311	Dominates
	UA1232	£16,856	£3,377	£27,456	£1,602	Dominates
	Trinity Perine	£15,962	£2,576	£26,585	£864	Dominates
	SureFire Guide	£40,620	£24,674	£50,619	£21,226	£11,907
	LA TP Grid/Stepper	£26,512	£12,031	£36,868	£9,576	£859
	LA TP Double freehand	£13,963	£785	£24,637	Dominates	Dominates

Legend: green cells refer to ICERs < £20,000 per QALY; yellow cells refer to ICERs between £20,000 and £30,000 per QALY.
For abbreviations, see *List of Abbreviations*.

Table 91 Threshold analysis: relative risk of cancer detection increased by 20% (ICER for LATP-all versus LA-TRUS, subgroup A)

		Probability of biopsy-related serious AEs				
		Tamhankar + overnight stay	Tamhankar	Berry	Rosario	Pepe and Aragona
Cost of LATP-all	Average	£14,282	£5,950	£20,799	£4,665	Dominates
	CamPROBE	£16,164	£7,709	£22,652	£6,334	£679
	PrecisionPoint	£29,135	£19,830	£35,423	£17,838	£11,789
	EZU-PA3	£8,939	£956	£15,538	Dominates	Dominates
	UA1232	£8,419	£471	£15,026	Dominates	Dominates
	Trinity Perine	£7,878	Dominates	£14,494	Dominates	Dominates
	SureFire Guide	£22,791	£13,902	£29,178	£12,212	£6,356
	LA TP Grid/Stepper	£14,259	£5,928	£20,777	£4,645	Dominates
	LA TP Double freehand	£6,670	Dominates	£13,304	Dominates	Dominates

Legend: green cells refer to ICERs < £20,000 per QALY; yellow cells refer to ICERs between £20,000 and £30,000 per QALY.
For abbreviations, see *List of Abbreviations*.

Table 92 Threshold analysis: relative risk of cancer detection reduced by 10% (ICER for LATP-all versus LA-TRUS, subgroup A)

		Probability of biopsy-related serious AEs				
		Tamhankar + overnight stay	Tamhankar	Berry	Rosario	Pepe and Aragona
Cost of LATP-all	Average	Dominated	Dominated	Dominated	Dominated	Dominated
	CamPROBE	Dominated	Dominated	Dominated	Dominated	Dominated
	PrecisionPoint	Dominated	Dominated	Dominated	Dominated	Dominated
	EZU-PA3	Dominated	Dominated	Dominated	Dominated	£20,862
	UA1232	Dominated	Dominated	Dominated	Dominated	£32,108
	Trinity Perine	Dominated	Dominated	Dominated	Dominated	£43,808
	SureFire Guide	Dominated	Dominated	Dominated	Dominated	Dominated
	LA TP Grid/Stepper	Dominated	Dominated	Dominated	Dominated	Dominated
	LA TP Double freehand	Dominated	Dominated	Dominated	Dominated	£69,977

Legend: green cells refer to ICERs < £20,000 per QALY; yellow cells refer to ICERs between £20,000 and £30,000 per QALY.
For abbreviations, see *List of Abbreviations*.

Decision question 2

LATP-freehand remains below £30,000 per QALY in almost all combinations of LATP costs, probability of biopsy-related serious adverse events and relative risk of cancer detection rates. The exceptions are combinations of:

- Cost of PrecisionPoint™ plus adverse events from Berry and colleagues plus relative risk from pairwise meta-analysis including observational studies only (*Table 94*).
- Cost of PrecisionPoint™ or SureFire Guide plus adverse events from Tamhankar and colleagues (both including and excluding overnight stay) plus relative risk reduced by 20% (*Table 96*).
- Cost of Camprobe, PrecisionPoint™ or SureFire Guide plus adverse events from Berry and colleagues plus relative risk reduced by 20% (*Table 96*).

Table 93 Threshold analysis: base case relative risk of cancer detection rates for LATP versus LA-TRUS (ICER for LATP-freehand versus LA-TRUS, subgroup A)

		Probability of biopsy-related serious AEs				
		Tamhankar + overnight stay	Tamhankar	Berry	Rosario	Pepe and Aragona
Cost of LATP-freehand	Average	£8,447	£3,196	£12,733	£2,430	Dominates
	CamPROBE	£8,841	£3,572	£13,123	£2,793	Dominates
	PrecisionPoint	£17,208	£11,577	£21,407	£10,524	£6,581
	EZU-PA3	£4,180	Dominates	£8,508	Dominates	Dominates
	UA1232	£3,845	Dominates	£8,176	Dominates	Dominates
	Trinity Perine	£3,496	Dominates	£7,831	Dominates	Dominates
	SureFire Guide	£13,116	£7,663	£17,356	£6,743	£2,888

Legend: green cells refer to ICERs < £20,000 per QALY; yellow cells refer to ICERs between £20,000 and £30,000 per QALY.
For abbreviations, see *List of Abbreviations*.

Table 94 Threshold analysis: relative risk of cancer detection from observational studies (ICER for LATP-freehand versus LA-TRUS, subgroup A)

		Probability of biopsy-related serious AEs				
		Tamhankar + overnight stay	Tamhankar	Berry	Rosario	Pepe and Aragona
Cost of LATP-freehand	Average	£15,687	£7,211	£22,225	£5,854	£183
	CamPROBE	£16,301	£7,784	£22,829	£6,398	£708
	PrecisionPoint	£29,357	£19,980	£35,684	£17,969	£11,881
	EZU-PA3	£9,027	£990	£15,668	Dominates	Dominates
	UA1232	£8,504	£501	£15,154	Dominates	Dominates
	Trinity Perine	£7,960	Dominates	£14,618	Dominates	Dominates
	SureFire Guide	£22,972	£14,016	£29,397	£12,310	£6,417

Legend: green cells refer to ICERs < £20,000 per QALY; yellow cells refer to ICERs between £20,000 and £30,000 per QALY.
For abbreviations, see *List of Abbreviations*.

Table 95 Threshold analysis: relative risk of cancer detection increased by 10% (ICER for LATP-freehand versus LA-TRUS, subgroup A)

		Probability of biopsy-related serious AEs				
		Tamhankar + overnight stay	Tamhankar	Berry	Rosario	Pepe and Aragona
Cost of LATP-freehand	Average	£8,890	£3,456	£13,304	£2,667	Dominates
	CamPROBE	£9,296	£3,844	£13,706	£3,041	Dominates
	PrecisionPoint	£17,930	£12,092	£22,253	£11,000	£6,926
	EZU-PA3	£4,486	Dominates	£8,945	Dominates	Dominates
	UA1232	£4,141	Dominates	£8,602	Dominates	Dominates
	Trinity Perine	£3,781	Dominates	£8,246	Dominates	Dominates
	SureFire Guide	£13,707	£8,058	£18,073	£7,108	£3,127

Legend: green cells refer to ICERs < £20,000 per QALY; yellow cells refer to ICERs between £20,000 and £30,000 per QALY.
For abbreviations, see *List of Abbreviations*.

Table 96 Threshold analysis: relative risk of cancer detection rates reduced by 20% (ICER for LATP-freehand versus LA-TRUS, subgroup A)

		Probability of biopsy-related serious AEs				
		Tamhankar + overnight stay	Tamhankar	Berry	Rosario	Pepe and Aragona
Cost of LATP-freehand	Average	£25,008	£12,111	£34,285	£9,877	£1,915
	CamPROBE	£25,905	£12,924	£35,162	£10,633	£2,635
	PrecisionPoint	£44,992	£30,227	£53,819	£26,703	£17,948
	EZU-PA3	£15,272	£3,285	£24,769	£1,680	Dominates
	UA1232	£14,507	£2,592	£24,021	£1,037	Dominates
	Trinity Perine	£13,712	£1,871	£23,244	£367	Dominates
	SureFire Guide	£35,658	£21,765	£44,695	£18,844	£10,459

Legend: green cells refer to ICERs < £20,000 per QALY; yellow cells refer to ICERs between £20,000 and £30,000 per QALY.
For abbreviations, see *List of Abbreviations*.

6 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

We do not have any additional factors to report.

7 DISCUSSION

7.1 Clinical effectiveness evidence

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

We included 23 studies which we grouped into five pairwise comparisons of LATP prostate biopsy vs and an alternative biopsy modality relevant to the decision problem (Table 97). Each pairwise comparison was of primary relevance to one of two decision questions regarding the clinical and cost effectiveness of LATP prostate biopsy.

Table 97 Number of included studies by comparison and decision question

Comparison (Intervention vs comparator)	Number of studies	DQ1	DQ2
1. LATP-any vs LATRUS	15	✓	
2. LATP-any vs GATP grid and stepping device	4	✓	
3. LATP-freehand vs LATRUS	7		✓
4. LATP-freehand vs GATP grid and stepping device	1		✓
5. LATP-freehand vs LATP grid and stepping device	0		✓
DQ Decision question; ✓ the comparison is primarily relevant to this decision question			

The largest volume of available evidence is for comparison 1.LATP-any vs LATRUS. By virtue of its title, this comparison incorporates the spectrum of LATP biopsy methods and hence, has a diverse evidence base. The majority of the available LATP prostate-biopsy 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 to be 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 heterogenous 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 relative risks around 1 for cancer detection rates, indicating similar effects. Confidence intervals were narrow, indicating good precision around effect estimates. Our overall interpretation of decision question 1 evidence is that LATP biopsy, overall, is similar to LATRUS biopsy in diagnostic performance, 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 just 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 datasets often provide more certain estimates of rare events, hence why we use these to inform our cost effectiveness analysis.

Generalisability

The transperineal 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 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 as a whole."

The studies were typically single centre, conducted by clinical investigators using local biopsy protocols to evaluate different biopsy modalities with the purpose of establishing which modality is most optimum (in their centre) on a range of factors such as in terms of use of general or local anaesthesia protocols, procedure time and related resources, biopsy complications and patient's ability to tolerate pain and discomfort during and after the biopsy. Few studies reported use of pre-biopsy mpMRI, some studies pre-date the introduction of mpMRI into prostate biopsy protocols and given the preponderance of studies done in East Asia use of mpMRI worldwide may differ from practice in the UK.

The multicentre UK study (TRANSLATE [48] [49] [50]) 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 future consideration of both Decision Question 1 (LATP-any versus

LATRUS) and Decision Question 2 (LATP-freehand versus LATRUS). This will be the first comparative evidence to become available for the UA1232 device, and is expected to provide information on cancer detection, infection rates and other outcomes including cost.

7.2 Cost effectiveness evidence

We developed an economic model to assess the cost-effectiveness of LATP prostate biopsies and freehand transperineal biopsy devices for LATP prostate biopsies. 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 clinically significant 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.

We estimated cost-effectiveness for four subgroups of patients with suspected prostate cancer. The subgroups vary by prior likelihood of having clinically significant 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 performance or adverse event rates of LATP with different freehand transperineal biopsy devices or with a grid and stepping device. Cancer detection rates for the different biopsy methods are estimated from the EAG network meta-analyses in the base case, with scenarios using relative risks from pairwise meta-analysis of observational evidence.

Relative rates of complications associated with the different biopsy methods are difficult to assess. There is good evidence from NHS practice, based on hospital episode statistics and data from the National Prostate Cancer Audit, and observational cohort studies from other countries. However, this does not reliably distinguish between type of anaesthesia as well as biopsy route (transrectal versus 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 randomised controlled trial reporting on the diagnostic performance of GATP compared with LATP. The ICER for LATP based on pooled evidence for all LATP methods compared with LA-TRUS was above

£70,000 per QALY gained in all subgroups, well above the usual £20,000 to £30,000 per QALY threshold used for decision-making by NICE advisory committees. This conclusion was supported by probabilistic sensitivity analysis, although scenario analysis based on different assumptions and sources of evidence indicates that results are sensitive to uncertainties over the relative costs and rate of hospital admissions associated with LATP and LA-TRUS.

With decision question 2, the economic analysis indicated that LATP with a freehand device was the most cost-effective strategy, with an ICER of £8,447 per QALY for the highest risk subgroup with MRI Likert score of 3 or more at first biopsy, and £18,196 per QALY for the subgroup with an MRI Likert score 1 or 2 at first biopsy. For the subgroups with a previous negative biopsy, the ICER is higher than £30,000 per QALY. The more favourable ICER estimates for LATP with a freehand device, compared with the pooled LATP analysis in decision question 1, is mostly driven by the cancer detection rates. We note that this rests on a single randomised controlled trial 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 below £20,000 per QALY for the highest-risk subgroup. Similarly, increasing the cost of LATP with a freehand device by assuming the cost of the most expensive device (£584), the ICER remained below £20,000 per QALY for the highest-risk subgroup but not for the other subgroups (with ICERs above £30,000 per QALY).

The LATP-other comparator (pooled evidence from studies that did not specify a freehand device) and GATP were not cost-effective in any situation, being dominated or with high ICERs.

7.3 Strengths and limitations of the assessment

7.3.1 Strengths

We conducted a systematic review of evidence related to the decision questions specified in the NICE scope, with pairwise and network meta-analysis 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 and colleagues, the

adaptation of the PROMIS analysis by Wilson and colleagues and the economic model that informed the update of the NICE guideline (NG131). The decision tree is based on prevalence and diagnostic performance 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 performance 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 relative risk 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.

7.3.2 Limitations

The economic model has several limitations. The definition of patient subgroups 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 the subgroups according to site of lesions or prostate volume, due to lack of data to differentiate prognosis or diagnostic performance of the biopsy methods under assessment.

We extrapolated data on repeat biopsy from LA-TRUS and GATP (based on the Jimenez and colleagues' study) to LATP, in the absence of specific evidence for LATP. Moreover, the Jimenez and colleagues' study assesses a Spanish cohort that may not be generalisable to UK practice. A scenario analyses on the probability of repeat biopsy showed that the model results are quite sensitive to the variation in these assumptions, although it didn't change the direction of the model conclusions.

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. Anyway, 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 include costs for recently recommended treatments for mHSPC (apalutamide and enzalutamide), we did not adjust survival to take their use into account. Our scenario analysis showed that excluding apalutamide and enzalutamide from the treatment options for mHSPC has a low impact in the model results.

7.4 Uncertainties

Uncertainties in the clinical evidence base contribute to uncertainties over cost-effectiveness. In particular, the relative risk for cancer detection for LATP-freehand is based on a single RCT which used the PrecisionPoint™ device. The relative risk 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 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) corresponds 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. There are two main uncertainties: the cost of SureFire Guide, which we assumed was an average of the other two disposable LATP freehand devices in the absence of an official price; and the number of cores taken, which we assume to be 12 cores 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 over-sampling 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.

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 and colleagues [58], 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 for patients undergoing active surveillance, although it is uncertain if that reflects real practice.

7.5 Other relevant factors

We do not have any suggestions for additional factors to consider.

8 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 transrectal ultrasound-guided prostate biopsy under local anaesthetic. One randomised controlled trial estimated a non-significant improvement in the cancer detection rate for transperineal prostate biopsy using a freehand device under local anaesthetic compared with transrectal ultrasound-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 under review 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 local anaesthetic transperineal prostate biopsy is associated with more urinary retention whereas local anaesthetic transrectal ultrasound-guided prostate biopsy has higher infection rates.

Based on pooled evidence for all types of LATP biopsy (with or without a specified freehand device), it is unlikely to be a cost-effective option for any of the patient subgroups that we considered: LATP has an estimated incremental cost of over £70,000 per QALY gained compared with LATRUS biopsy. However, we found that LATP with a freehand device is likely to be the most cost-effective option for patients with no previous biopsy at high risk of having prostate cancer as indicted by mpMRI results. In this analysis, LATP with freehand device was less expensive and more effective than GATP, and it had an incremental cost per QALY gained compared with LATRUS below £30,000 for patients who had not had a previous prostate biopsy. These results are sensitive to the estimated cost of the freehand device and the sources for cancer detection rates and biopsy complication rates.

8.1 Implications for service provision

This analysis suggests that the use of LATP freehand transperineal biopsy devices is potentially cost effective. However, this conclusion is uncertain, as it is based on limited data. The comparative cost-effectiveness of different freehand transperineal biopsy devices is unknown. Our study also suggests that the additional cost 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).

8.2 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 randomised controlled trial 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 multi-centre randomised study across 9 NHS Trusts in England.

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10 APPENDICES

Appendix 1 Literature search strategies for the systematic reviews of clinical effectiveness, cost effectiveness and HRQoL

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, the databases were searched from inception, and only an English language limit was applied. In order to be sensitive and retrieve all relevant studies, no study design search filters were used. *Table 98* below details the search strategies for the databases and the conference hand searches. See also section 3.1 of this report.

Table 98 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 to July 08, 2021 Date of original search: 09/07/2021 Date of update search: 19/10/2021	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
Embase Classic+Embase 1947 to 2021 July 08 Date of original search: 09/07/2021	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.	Original search: 1348 Update search: 17

Date of update search: 19/10/2021	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").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 (CDSR and CENTRAL) Date of original search: 09/07/2021 Date of update search: 19/10/2021	#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) #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)	Original search: Reviews: 2 Trials: 122 Update search: Reviews: 0 Trials: 2

	#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: 09/07/2021 Date of update search: 19/10/2021	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")) 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"))	Original search: 491 Update search: 34

	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 Date of original search: 09/07/2021 Date of update search: 19/10/2021	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 Date of original search: 09/07/2021 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 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	Original search: 2

	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	
International HTA Database (INAHTA) Date of original search: 09/07/2021 Date of update search: 19/10/2021	(((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 Date of original search: 09/07/2021	Prostate and biops* - only useful search terms 82 results: 71 in French, 14 in English, 1 in German 0 relevant	Original search: 0
PROSPERO Date of original search: 09/07/2021	#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	Original search: 73

	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	
ClinicalTrials.gov Date of original search: 10/06/2021	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 Date of original search: 10/06/2021	Search terms: prostate cancer, biopsy, biopsies, prostate biopsy, transperineal, perineal, transrectal, TRUS	Original search: 0
NIHR CRN Portfolio Search Date of original search: 10/06/2021	272 results for prostate cancer. Title screen = 0 relevant/biopsy related.	Original search: 0
American Society of Clinical Oncology (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 2018-2021 Keywords: prostat*, biopsy, biopsies, transperineal, TRUS, etc.	Original search: 16
American Urologic Association (AUA) Annual Meeting Date of original search: June 2021 Date of update search: 19/10/2021	Hand search proceedings published in *The Journal of Urology* supplements for 2018-2021 Keywords: prostat*, biopsy, biopsies, transperineal, TRUS, etc.	Original search: 54 Update search: 3
British Association of Urological Surgeons has an Annual Scientific meeting Date of original search: June 2021	Hand search proceedings published in the *Journal of Clinical Oncology* supplements for 2018-2021 Keywords: prostat*, biopsy, biopsies, transperineal, TRUS, etc.	Original search: 9 Update search: 2

Date of update search: 19/10/2021		
European Association of Urology (EAU) Annual Meeting Date of original search: June 2021 Date of update search: 19/10/2021	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

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 Canadian Agency for Drugs and Technologies in Health (CADTH) filter for Economic Evaluations/Cost/Economic Models [55] 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 99*, below.

Table 99 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 to June 16, 2021 Date of original search: 17/06/2021 Date of update search: 02/11/2021	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: 144 Update search: 10

	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 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	
Embase **Classic+Embase** 1947 to 2021 Week 23 Date of original search: 17/06/2021 Date of update search: 02/11/2021	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.	Original search: 378 Update search: 8

	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 Update search: 71 limit 70 to dd=20210618-20211102	
Cochrane Library for CDSR and CENTRAL Date of original search: 17/06/2021 Date of update search: 02/11/2021	#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)	Original search: Reviews: 1 Trials: 69 Update search: Reviews: 0 Trials: 3

	#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: [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 Date of original search: 17/06/2021	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*	Original search: 4 Update search: 0

Date of update search: 02/11/2021	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	
Web of Science ***Indexes=SCI-EXPANDED, CPCI-S Timespan=1970-2021*** Date of original search: 17/06/2021 Date of update search: 02/11/2021	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"))	Original search: 86 Update search: 21

	#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*))	
DARE and NHS EED Date of original search: 07/06/2021 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	Original search: 6

	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	

International HTA Database (INAHTA) Date of original search: 07/06/2021 Date of update search: 02/11/2021	(((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 Date of original search: 07/06/2021 Date of update search: 02/11/2021	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

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 ten years. The strategies are in *Table 100* and *Table 101* below.

Table 100 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 June 17, 2021 Date of original search: 17/06/2021	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.	Original search: 75

	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 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,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 shortform12 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 shortform20 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. 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	
Embase **Classic+Embase** 1947 to 2021 Week 23 Date of original search: 17/06/2021	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.	Original search: 138

	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 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 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.	

	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 shortform12 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 shortform20 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	
Web of Science – Science Citation Index Expanded (SCI-EXPANDED, Conference Proceedings Citation Index – Science (CPCI-S) *Timespan=1970-2021* Date of original search: 16/09/2021	#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)	Original search:

	#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 "shortform 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") #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 Date of original search: 18/06/2021	#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)	Original search: 35

	#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) #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 101 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 to September 14, 2021 Date of original search: 15/09/2021 Date of update search: 29/01/29	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:
Embase Classic+Embase 1947 to 2021 Week 36 Date of original search: 15/09/2021 Date of update search: 29/01/29	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:

Web of Science – Science Citation Index Expanded (SCI-EXPANDED, Conference Proceedings Citation Index – Science (CPCI-S) Date of original search: 16/09/2021 Date of update search: 29/01/29	(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: 2011-01-01 to **2021-09-16** Refine by English language	Original search: 133 Update search:
Cochrane Library Date of original search: 16/09/2021 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 Extended inclusion/exclusion criteria for the systematic review of diagnostic test evaluation and clinical effectiveness

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	*Exclusion criteria*
• People with clinical suspicion of prostate cancer • People who have had a previous prostate biopsy that was negative for prostate cancer	• 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)

- Local anaesthetic transperineal prostate biopsy (LATP) by any of these methods:
  - Grid and stepper unit
  - Coaxial needle (double freehand)
  - Freehand transperineal biopsy device

- The following freehand transperineal biopsy 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)

- Local anaesthetic transrectal ultrasound prostate biopsy (LATRUS)
- General anaesthetic transperineal prostate (GATP) biopsy using a grid and stepper unit

Inclusion criteria	*Exclusion criteria*
• Systematic and/or targeted biopsies • Cognitive/visual registration fusion biopsy	• Software-based fusion biopsy • Sedation

Interventions – relevant diagnostic procedures (Decision question 2)

- The following freehand transperineal biopsy 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)

- Local anaesthetic transrectal ultrasound prostate biopsy (LATRUS)
- General anaesthetic transperineal prostate (GATP) biopsy using a grid and stepper unit
- Local anaesthetic transperineal prostate (LATP) biopsy using a grid and stepper unit

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: o Measures of diagnostic accuracy o Cancer detection rates o Clinically significant cancer detection rates o Clinically insignificant cancer detection rates o Low, medium, high risk cancer detection rates o Biopsy sample suitability/quality o Number of biopsy samples taken o Procedure completion rates o Re-biopsy events within 6 months • Clinical outcomes: o Hospitalisation events after biopsy o Rates of biopsy related complications, including infection, sepsis and haematuria. o Rates of urinary retention o Rates of erectile dysfunction o Survival o Progression free survival o Adverse events from treatment • Patient reported outcomes o Health related quality of life o 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.

Appendix 3 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 102* below. 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 103* below.

Table 102 Studies excluded at full text screening

Study	Publication type	Exclusion reason
ACTRN12620001145998 / LATProBE 2020 [54]	Trial register record	Ongoing study (no results)
ISRCTN98159689 / TRANSLATE 2021 [48]	Trial register record	Ongoing study (no results)
Adshead 2019 [108]	Conference abstract	Intervention
Berry 2020 [82]	Journal article	Population
Berry 2020 [109]	Conference abstract	Population
Chae 2009 [110]	Journal article	Language
Eldred-Evans 2018 [111]	Conference abstract	Intervention
Han 2008 [112]	Journal article	Intervention
Israel 2021 [113]	Conference abstract	Comparator
Kasivisvanathan 2015 [114]	Letter	Intervention
Kawakami 2007 [115]	Journal article	Intervention
Lavoipierre 2008 [116]	Letter	Outcomes
Lim 2018 [117]	Conference abstract	Intervention
Lim 2020 [118]	Journal article	Intervention
Lo 2019 [119]	Journal article	Comparator
NCT03496142 2018 [120]	Trial register record	Intervention
NCT04108871 2019 [121]	Trial register record	Ongoing study (no results)
NCT04815876 2021 [53]	Trial register record	Ongoing study (no results)
NCT04843566 2021 [52]	Trial register record	Ongoing study (no results)
Neale 2020 [122]	Journal article	Intervention
Pahwa 2017 [68]	Journal article	Outcomes
Pal 2018 [123]	Journal article	Intervention
Pepe 2017 [124]	Journal article	Design
Postema 2017 [125]	Journal article	Intervention
Presti 2000 [126]	Journal article	Design
Ristau 2018 [127]	Journal article	Comparator
Roberts 2020 [128]	Conference abstract	Intervention
Roberts 2021 [129]	Journal article	Intervention
Rochester 2009 [130]	Journal article	Comparator
Rodriguez Socarras 2020 [131]	Journal article	Intervention
Roethke 2014 [132]	Journal article	Intervention
Rojas Claros 2019 [133]	Conference abstract	Intervention

Salagierski 2019 [134]	Journal article	Intervention
Satoh 2005 [135]	Journal article	Comparator
Self 2018 [136]	Conference abstract	Design
Shigemura 2007 [137]	Journal article	Intervention
Sivaraman 2015 [138]	Journal article	Intervention
Song 2019 [139]	Journal article	Intervention
Stabile 2018 [140]	Journal article	Intervention
Suga 1999 [141]	Journal article	Population
Sulaiman 2019 [142]	Conference abstract	Design
Taira 2010 [143]	Journal article	Intervention
Tamhankar 2020 [144]	Conference abstract	Intervention
Taverna 2016 [145]	Journal article	Intervention
Taverna 2016 [146]	Conference abstract	Intervention
Teoh 2015 [147]	Journal article	Intervention
Tilak 2015 [148]	Journal article	Comparator
Tschirdewahn 2020 [149]	Journal article	Intervention
Valerio 2015 [150]	Journal article	Intervention
Vanni 2004 [151]	Journal article	Intervention
Vezelis 2021 [152]	Journal article	Intervention
Wang 2019 [153]	Journal article	Comparator
Westhoff 2019 [154]	Journal article	Intervention
Williams 2018 [155]	Conference abstract	Comparator
Williams 2018 [156]	Conference abstract	Comparator
Yamada 2020 [157]	Journal article	Intervention
Yang 2019 [158]	Conference abstract	Intervention
Yaxley 2017 [159]	Journal article	Intervention
Yunkai 2010 [160]	Journal article	Comparator
Zhang 2020 [161]	Journal article	Intervention
Zhang 2019 [162]	Conference abstract	Intervention
Zhang 2017 [163]	Journal article	Intervention
Zhang 2015 [164]	Journal article	Intervention
Zhao 2012 [165]	Journal article	Intervention
Zhou 2020 [166]	Journal article	Intervention

Table 103 Studies where eligibility for inclusion remains unclear (after full-text screening and contacting authors)

Study	Publication type	Reason unclear	Notes
Al-Dahir 2019 [167]	Conference abstract	Unclear Comparator	No author contact details; no response via ResearchGate
Chan 2020 [168]	Conference abstract	Unclear Population	No author response
Chan 2020 [169]	Conference abstract	Unclear Population	No author response
Cole 2019 [170]	Conference abstract	Unclear Population and Comparator	Invalid author contact details
Cole 2020 [171]	Conference abstract	Unclear intervention	Invalid author contact details
Demozzi 2018 [172]	Conference abstract	Unclear Comparator	No author response
Di Franco 2017 [173]	Journal article	Unclear Population	No author response

Elkhoury 2020 [174]	Conference abstract	Unclear Population	No author contact details
Ferrante 2020 [175]	Conference abstract	Unclear Comparator	No author response
Ferriero 2019 [176]	Conference abstract	Unclear Population	No author response
Islam 2020 [177]	Conference abstract	Unclear Population	No author response
Islam 2021 [178]	Conference abstract	Unclear Population	No author response
Lai 2021 [179]	Conference abstract	Unclear Intervention	No author response
Lovegrove 2019 [180]	Conference abstract	Unstratified data	Not data owner[a]
Lovegrove 2019 [181]	Conference abstract	Unstratified data	Not data owner[a]
Marra 2015 [182]	Conference abstract	Unclear Intervention and Comparator	No author response
Maruf 2020 [183]	Conference abstract	Unclear Population	No author response
Newman 2020 [184]	Conference abstract	Unclear Population	No author response
Ng 2019 [185]	Conference abstract	Unclear Population, Intervention and Comparator	No author response
Sharma 2019 [186]	Conference abstract	Unclear Population	No author contact details
Stroman 2019 [187]	Conference abstract	Unclear Intervention	No author response
Stroman 2020 [188]	Conference abstract	Unclear Population	No author response
Stroman 2020 [189]	Conference abstract	Unclear Population	No author response
Ting 2016 [190]	Journal article	Unclear Intervention	No author response
Urkmez 2020 [191]	Conference abstract	Unclear Population, Intervention and Comparator	No author response
Urkmez 2021 [192]	Conference abstract	Unclear Population	No author response
Zattoni 2021 [193]	Conference abstract	Unclear Intervention	No author response

[a] author clarification indicated that data stratified by anaesthetic type might be available for the transperineal biopsy 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 4 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 sub-group 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: **Publication year:** **Linked papers:** **Study name/trial identifier:** **Study design:** **Country:** **Number of centres:** **Recruitment dates:** **Funding:** **Competing interests:**	**Condition being diagnosed / detected:** Prostate cancer *Emphasis here on describing the elements of the biopsy that define this DAR's intervention and comparators: transperineal or transrectal approach, anaesthetic type.* *Further details are in the 'Biopsy characteristics' table below.* **Index test:** **Reference standard:** **Intervention:** **Comparator:**	**Number of participants:** **Sample attrition/dropout:** **Selection of participants:** **Inclusion criteria for study entry:** **Exclusion criteria for study entry:** **Sample size calculation:**	**Primary outcome of study:** *Include definition where available.* **Other relevant outcomes:** *List other (secondary) outcomes briefly. If there are many list a couple of key outcomes and then cross refer to the results tables below (table 5 onwards)* **Definition of clinically significant disease:** *State any definition or threshold(s) used.* **Relevant subgroup analyses:** *If relevant to NICE scope.* *None / See table 3 below.*

Label footnotes within the table alphabetically in superscript (e.g. [a, b, c]) and define them at the foot of the table, size 9pt font. Repeat alphabetical sequence in each subsequent table as applicable.

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 & 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)	*For example, 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%) 10ml injected at 5 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 sub-group 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, positive predictive value (PPV), negative predictive value (NPV) if possible and note whether these agree with any values that may be reported in the paper. Use https://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 x d)/(b x c)		
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 (%)*			
Clinically significant 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				
Inter-observer agreement				
Intra-observer agreement				

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

Individual Risk of Bias assessments of included RCTs using the Cochrane Risk of Bias tool (vers. 1)

Cerruto et al 2014 [23]

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 [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	**LOW** "The randomization procedure was carried out before biopsy using a computer-generated random-number sequence to assign patients to two groups." (p2)

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." (p2)
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" (p2). 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 transperineal biopsy 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 [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	**UNCLEAR** "a prospective randomized study of transperineal versus 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 versus 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.
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 [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 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 [38]

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"
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** Fig. 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 [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** "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, *Table 104*, and included case series, *Table 105*. The reasons for the responses are documented in a spreadsheet available from the review authors on request.

Table 104 Summary of Risk of Bias assessments for included observational cohort studies

JBI Checklist for cohort studies [46]	Study										
	Abdollah et al 2011 [35]	Bojin 2019 [28]	Chen et al 2021 [29]	Emiliozzi et al 2003 [30]	Hung et al 2020 [31]	Jiang et al 2019 [36]	Kum et al 2018 [32]	Rij et al 2020 [41]	Starmer et al 2021 [33]	Takuma et al 2012 [39]	Watanabe et al 2005 [34]
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?	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.	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	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes

JBI Checklist for cohort studies [46]	Study										
	Abdollah et al 2011 [35]	Bojin 2019 [28]	Chen et al 2021 [29]	Emiliozzi et al 2003 [30]	Hung et al 2020 [31]	Jiang et al 2019 [36]	Kum et al 2018 [32]	Rij et al 2020 [41]	Starmer et al 2021 [33]	Takuma et al 2012 [39]	Watanabe et al 2005 [34]
free of the outcome at the start of the study (or at the moment of exposure)?											
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 complications	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
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 utilized?	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
[a] Question edited by EAG to accommodate biopsy methods as an exposure; CDR cancer detection rate; NA not applicable;											

Table 105 Summary of risk of bias assessments for included observational case series studies

JBI Checklist for case series [47]	Study	
	Szabo et al 2021 [37]	Walters et al 2021 [40]
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 Relevance and credibility checklist for full economic evaluations

Table 106 Wilson et al. 2021: study characteristics

Item		Wilson et al. 2021	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	
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*.			

Appendix 7 Cost-effectiveness review: excluded references and reason for exclusion

Table 107 Cost-effectiveness review: excluded references and reason for exclusion

Study	Reasons for exclusion
Actrn 2020 [54]	Only protocol/No results posted
Nct 2020 [194]	Only protocol/No results posted
Altok 2018 [195]	Does not include the interventions of interest
Brown 2018 [59]	Does not include the interventions of interest
Faria 2018 [60]	Does not include the interventions of interest

Appendix 8 Study characteristics for included economic evaluations

Table 108 Wilson et al. 2021: study characteristics

Study	Wilson and colleagues	
Year	2021	
Country	UK	
Research question	What is the cost effectiveness of transperineal versus transrectal ultrasound-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) versus TRUS biopsy	
Type of model	Decision tree (diagnostic and short-term treatment pathway) Markov model (long-term consequences; composed by 3 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 Faria et al. 2018 decision model, men referred to secondary care are offered an mpMRI:
	• Men with a positive mpMRI (CS) are recommended an 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: 27.94% Non-clinically significant cancer: 15.99% Intermediate risk cancer: 52.90% High risk cancer: 3.16%	Source: PROMIS

Diagnostic accuracy	<u>mpMRI</u> mpMRI (NC)|NC: 0.33 (0.26-0.4) mpMRI (CNS)|NC: 0.17 (0.11-0.23) mpMRI (CS)|NC: 0.5 (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 mpMRI (CNS)|HR: 0 mpMRI (CS)|HR: 1 <u>First mpMRI-targeted TRUS/TPUS biopsy (if mpMRI = CS)</u> Biopsy1 (NC)|NC: 1 Biopsy1 (CNS)|NC: 0 Biopsy1 (CS)|NC: 0 Biopsy1 (NC)|CNS: 0.79 (0.66-0.89) Biopsy1 (CNS)|CNS: 0.21 (0.11-0.34) Biopsy1 (CS)|CNS: 0 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 Biopsy1 (CNS)|HR: 0 Biopsy1 (CS)|HR: 1 <u>Second mpMRI-targeted TRUS/TPUS biopsy</u> **If first biopsy = NC and mpMRI = CS** Biopsy2 (NC)|NC: 1 Biopsy2 (CNS)|NC: 0 Biopsy2 (CS)|NC: 0 Biopsy2 (NC)|CNS: 0.68 (0.02-1) Biopsy2 (CNS)|CNS: 0.32 (0.02-0.91) Biopsy2 (CS)|CNS: 0 Biopsy2 (NC)|IR: 0.05 (0.02-0.11)	Source: PROMIS, as reported in Faria et al. [60], definition 2, cutoff 3. Assumption, as per Faria et al. PROMIS, Schoots et al., as reported in Faria et al. [60], test 4, definition 2. Assumption, as per Faria et al. [60] PROMIS, Schoots et al., as reported in Faria et al. [60], test 5, definition 2.

	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 Biopsy2 (CNS)|NC: 0 Biopsy2 (CS)|NC: 0 Biopsy2 (NC)|CNS: 0.68 (0.02-1) Biopsy2 (CNS)|CNS: 0.32 (0.02-0.91) Biopsy2 (CS)|CNS: 0 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)	Assumption, as per Faria et al. [60] Assumption, as per NC findings above (see Faria et al. [60])
Biopsy complications	<u>TRUS biopsy</u> No infection: 0.921 Mild infection: 0.042 (0.025-0.069) UTI: 0.033 (0.020-0.056) Sepsis: 0.004 (0.001-0.018) <u>TP biopsy</u> No infection: 1 Mild infection: 0 UTI: 0 Sepsis: 0 Mortality from sepsis: 0.036 (0.027-0.052)	Source: Zani et al. [61] Assumption Lee et al. [104]
Long-term transition probabilities	<u>CNS cancer</u> PF to metastatic: 0.008 (0.004-0.013) PF to dead: 0.05 (0.043-0.058) Metastatic to dead: 0.139 (0.058-0.226) <u>Intermediate risk cancer</u> **Active surveillance** PF to metastatic: 0.018 (0.01-0.026)	 Source: Fit from figures reported in Faria et al. [60]

	PF to dead: 0.064 (0.049-0.078) Metastatic to dead: 0.145 (0.071-0.223) **Radical prostatectomy** PF to metastatic: 0.007 (0.003-0.011) PF to dead: 0.054 (0.045-0.063) Metastatic to dead: 0.142 (0.062-0.226) <u>High risk cancer</u> **Active surveillance** PF to metastatic: 0.022 (0.011-0.034) PF to dead: 0.08 (0.058-0.101) Metastatic to dead: 0.157 (0.087-0.226) **Radical prostatectomy** PF to metastatic: 0.008 (0.002-0.014) PF to dead: 0.07 (0.053-0.085) Metastatic to dead: 0.148 (0.071-0.225)	
Treatment complications	<u>Following radical prostatectomy</u> Sexual dysfunction: 34.56% Urinary incontinence: 8.20% Bowel dysfunction: 5.94% <u>Following active surveillance</u> Sexual dysfunction: 20.05% Urinary incontinence: 3.12% Bowel dysfunction: 5.52%	Source: Will et al., converted to 1-year probabilities as per Faria et al. [60]
Unit costs	<u>Diagnosis</u> mpMRI: £217 TRUS biopsy: £16.71 TP biopsy: £0 <u>Complications</u> Fever: £39.63 UTI: £46.16 Sepsis: £2,206 <u>Treatments</u>	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

	Watchful waiting (per year): £123	1x follow-up visit + 3xPSA test
	Radical prostatectomy: £6,667	Surgery + 1x first visit + 2x follow-up visits
	Radical prostatectomy AEs (per year): £207	Weighted average of 1-year probabilities
	Metastatic disease (per year): £1,990	As calculated by Faria et al. [60]
	<u>Components for compound costs</u>	
	Radical prostatectomy surgery: £6,330	NHS Ref Costs 2018/19, EL, weighted average LB21A, LB21B, LB22Z
	Surgical consultation pre surgery: £127	NHS Ref Costs 2018/19, CL, WF01B, 101, urology.
	Surgical consultation follow-up: £105	NHS Ref Costs 2018/19, CL, WF01A, 101, urology.
	Primary care PSA test: £6	NHS Ref Costs 2018/19, DAPS, DAPS09.
	Sexual dysfunction management: £217	NHS Ref Costs 2018/19, Total HRGs, LB43Z.
	Urinary incontinence management: £296	Inflated to 2018/19 from Faria et al. [60]
	Bowel dysfunction management: £1,810	Inflated to 2018/19 from Faria et al. [60]
	GP visit: £39.23	PSSRU 2019, p.120
	Trimethoprim, 3 days: £0.40	Drug Tariff, March 2019, trimethoprim 200mg x6
	Trimethoprim, 7 days: £0.93	Drug Tariff, March 2019, trimethoprim 200mg x14
	Urinalysis: £6	Assumption (same as PSA test)
Utilities	QALY loss	Source:
	Fever: 0.0008	Assumption
	UTI: 0.0058	Barry et al. [105]
	Sepsis: 0.0403	
	Utility of progression free: age-dependent	Faria et al. [60]
	Disutility of metastatic disease: 0.137	Faria et al. [60]
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: £5051.52, QALYs: 10.291 TP biopsy Cost: £5021.91, QALYs: 10.292 Increment Cost: -£29.61, QALYs: 0.0015, 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: £29.27, QALYs: 0.0015, ICER: £19,999 2. One-way sensitivity analysis on risk of infection with TPUS biopsy, varying the risk between 0 and 100% 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 £14.50.
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; CNS, clinically non-significant cancer; CS, clinically significant cancer; HR, high risk; ICER, incremental cost-effectiveness ratio; IR, intermediate risk; mpMRI, multiparametric magnetic resonance imaging; NC, no cancer; PC, prostate cancer; PF, progression free; QALY, quality-adjusted life years; TP, transperineal biopsy; TRUS, transrectal ultrasound; UK, United Kingdom; UTI,	

Appendix 9 Results of the systematic searches 'HRQoL 1'

The systematic searches 'HRQoL 1' identified 244 potentially relevant studies (see *Figure 27*). Of the 244 references, 34 were retrieved for full-text screening and nine studies [107 196-203] were included after full text screening. Of the excluded studies, 18 exclusions were based on HRQoL measure and one on study design, three studies were protocols, and we couldn't find the full texts for other three. The excluded references and reasons for exclusion are shown in Appendix 10.

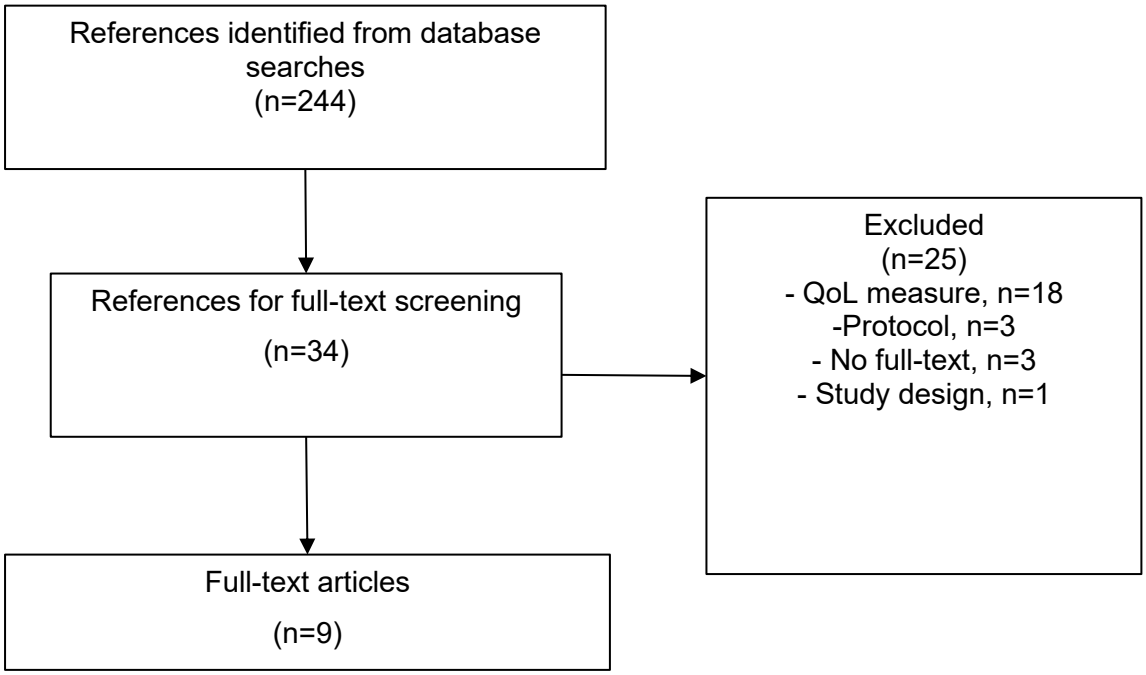

Figure 27 Flow chart for the identification of HRQoL studies (searches 'HRQoL 1')

The main characteristics of the nine studies included in searches 'HRQoL 1' are presented below (see *Table 109*). *Table 110* summarise the utility values reported by the HRQoL studies. We mapped the SF-12 and SF-36 scores into EQ-5D, using the equations from Sullivan and colleagues [204] and Ara and Brazier [205], respectively.

Table 109 Characteristics of included HRQoL studies (searches 'HRQoL 1')

First Author, Year	N [a]	Country	Instrument	Health state(s) described
Blazevski et al. 2020	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 et al. 1998	1126	The 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 et al. 2020	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.
Hamid et al. 2019	110	UK	EQ-5D-5L	Before repeat biopsy, at 1- and 6-weeks after repeat biopsy
Kasivisvanathan et al. 2018	483	Several [b]	EQ-5D-5L	At baseline, 24 hours and 30 days after the interventions (MRI-targeted biopsy or TRUS biopsy).
Peters et al. 2014	14	The Netherlands	SF-36	At baseline, 1- and 6-months and then annually after focal salvage treatment for prostate cancer
Sefik et al. 2020	114	Turkey	SF-36	Before and 1 month after TRUS biopsy.
Shankar et al. 2019	110	USA	SF-12	1- to 3-days after the diagnostic test (mpMRI or TRUS biopsy) as part of active surveillance.
Vasarainen et al. 2013	386	Finland	SF-36	At invitation to participate in the trial, after PSA blood sample collection, after digital rectal

First Author, Year	N [a]	Country	Instrument	Health state(s) described
				examination (unaware of its result but aware of PSA result), after TRUS biopsy (unaware of its results but aware of PSA result).

[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.
HRQoL, health-related quality of life; PSA, prostate specific antigen; TRUS, transrectal ultrasound; UK, United Kingdom.

Table 110 Included HRQoL studies: summary of utility values reported (searches 'HRQoL 1')

Health states	Utility	Source
Pre-screening		
3 weeks before	0.86785	Essink-Bot et al. 1998
Before screening	0.9387	Vasarainen et al. 2013
Screening		
Right after collecting blood for PSA analysis	0.936	Vasarainen et al. 2013
PSA result known (positive or negative)	0.920	Vasarainen et al. 2013
Right after DRE (result unknown)	0.906	Vasarainen et al. 2013
Screening negative result	0.88215	Essink-Bot et al. 1998
Screening positive result	0.908	Kasivisvanathan et al. 2018
	0.692	Sefik et al. 2020
Diagnostic		
24h after MRI-targeted biopsy	0.907	Kasivisvanathan et al. 2018
30 days after MRI-targeted biopsy	0.917	Kasivisvanathan et al. 2018
After TRUS biopsy (result unknown)	0.936	Vasarainen et al. 2013
24h after TRUS biopsy	0.894	Kasivisvanathan et al. 2018
30 days after TRUS biopsy	0.921	Kasivisvanathan et al. 2018
	0.790	Sefik et al. 2020
30 days after TRUS biopsy (with tamsulosine)	0.791	Sefik et al. 2020
Repeat biopsy	0.879	Hamid et al. 2019
Biopsy negative result	1.14889	Essink-Bot et al. 1998
Biopsy positive result	0.883	Hamdy et al. 2020
Treatment		
Active surveillance		
Before procedure (mpMRI or TRUS biopsy)	0.961	Shankar et al. 2019
Before mpMRI	0.965	Shankar et al. 2019

Health states	Utility	Source
Before TRUS biopsy	0.956	Shankar et al. 2019
Irreversible electroporation		
Before treatment	0.979	Blazevski et al. 2020
Between 6 weeks and 24 months after	0.979	Blazevski et al. 2020
Focal salvage treatment		
Before treatment	1.015	Peters et al. 2014
1 month	0.967	Peters et al. 2014
6 months	0.937	Peters et al. 2014
3 years	0.977	Peters et al. 2014
DRE, digital rectal examination; HRQoL, health-related quality of life; mpMRI, multiparametric magnetic resonance imaging; PSA, prostate specific antigen; TRUS, transrectal ultrasound.		

Appendix 10 HRQoL review: excluded references and reason for exclusion

Table 111 HRQoL review: excluded references and reason for exclusion (searches 'HRQoL 2'

Study	Reasons for exclusion
Donnelly et al. 2018 [206]	No prostate cancer
Downing et al. 2019 [207]	No relevant results
Glaser et al. 2013 [208]	No relevant results
Kuppen et al. 2020 [209]	Non-UK value set
Lemanska et al. 2021 [210]	Different population
Lloyd et al. 2015 [211]	Assess specific interventions
Loeb et al. 2018 [212]	Non-UK value set
Lopez-Calderero et al. 2017 [213]	Unclear value set
Maguire et al. 2019 [214]	No relevant results
Murasawa et al. 2019 [215]	Non-UK value set
Smith et al. 2020 [216]	No relevant results
Uemura et al. 2020 [217]	Unclear value set
Venderbos et al. 2020 [218]	No relevant results
Wilding et al. 2020 [219]	No relevant results
Yao et al. 2020 [220]	No relevant results

Table 112 HRQoL review: excluded references and reason for exclusion (searches 'HRQoL 1'

Study	Reasons for exclusion
Ahmed et al. 2011 [221]	Different HRQoL outcome
Aktas et al. 2014 [222]	Different HRQoL outcome
Awsare et al. 2008 [223]	Different HRQoL outcome
Azzouzi et al. 2013 [224]	Different HRQoL outcome
Burns et al. 2019 [225]	Can't find full text
Cantor et al. 1995 [226]	Can't find full text
Chaussy & Thüroff 2001 [227]	HRQoL outcome not specified
Dickinson et al. 2013 [228]	Protocol
Donovan et al. 2003 [91]	Can't find full text
Egan et al. 2021 [229]	Different HRQoL outcome
Ganzer et al. 2018 [230]	Different HRQoL outcome
Ghai et al. 2015 [231]	Can't find SF-12 results
Gu et al. 2015 [232]	HRQoL outcome not specified
Koch et al. 2007 [233]	Can't find results
Kok et al. 2006 [234]	Different HRQoL outcome
Mettlin et al. 1997 [235]	No HRQoL outcomes
Miki et al. 2010 [236]	Different HRQoL outcome
Natarajan et al. 2016 [237]	Different HRQoL outcome

Study	Reasons for exclusion
Naughton et al. 2001 [238]	Different HRQoL outcome
Pane-Alemany et al. 2021 [239]	Protocol
Pisters et al. 1997 [240]	Different HRQoL outcome
Soloway et al. 2010 [241]	Different HRQoL outcome
Uchida et al. 2005 [242]	Different HRQoL outcome
Valerio et al. 2014 [243]	Protocol
Van de Ven et al. 2013 [244]	Different study design

Appendix 11 Searches 'HRQoL 2': study characteristics

<table>
<tr><td>Study</td><td>Booth and colleagues</td></tr>
<tr><td>Year</td><td>2014</td></tr>
<tr><td>Country</td><td>Finland</td></tr>
<tr><td>Type of study</td><td>Surveys conducted among men in the Finnish trial of screening for prostate cancer</td></tr>
<tr><td>Study objective</td><td>To quantify the long-term HRQoL impact associated with screening for prostate cancer</td></tr>
<tr><td>Population</td><td>Men born in from 1929 to 1944 who resided in the Helsinki or Tampere region during recruitment period (1996-1999) 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, both in the screening and control arm, were subsequently diagnosed with the disease.</td></tr>
<tr><td>Sample size</td><td>5,516</td></tr>
<tr><td>HRQoL instrument</td><td>15D, EQ-5D (UK value set) and SF-6D.</td></tr>
<tr><td>Health states</td><td>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)</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td rowspan="2">Utilities</td><td colspan="2">EQ-5D results from 2011</td></tr>
<tr><td>Screening arm</td><td>Control arm</td></tr>
<tr><td>Men free of PC from trial subsample</td><td>0.830</td><td>0.857</td></tr>
<tr><td>Men with PC (vs. no PC)</td><td>+0.005</td><td>-0.031</td></tr>
<tr><td>Men with organ-confined PC (vs. no PC)</td><td>+0.01</td><td>-0.031</td></tr>
<tr><td>Men with advanced PC (vs. no PC)</td><td>-0.039</td><td>-0.051</td></tr>
</table>
</td></tr>
<tr><td>Conclusions/Limitations</td><td>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.</td></tr>
</table>

HRQoL, health-related quality of life; PC; prostate cancer; UK, United Kingdom

Study	Drummond and colleagues
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	3,348 responders (1,010 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
HRQoL, health-related quality of life; PROMs, patient reported outcome measures; UK, United Kingdom.	

Study	Farkkila and colleagues
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.
HRQoL, health-related quality of life; UK, United Kingdom	

Study	Gavin and colleagues
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	N= 282

		0.8	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.		
UK, United Kingdom.			

Study	Torvinen and colleagues
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. Less than six months after diagnosis (Loc1) 2. Following 12 months (Loc2) 3. Subsequent years of remission (Loc3) 4. Metastatic disease (Metastatic) 5. Palliative care (Palliative)
Results	

EQ-5D	**N**	**Mean**	**SD**	**95% CI**	**∆ vs. general population**
Loc1	46	0.90	0.19	0.84-0.96	+0.103
Loc2	91	0.89	0.14	0.86-0.92	+0.089

	Loc3	309	0.87	0.19	0.85-0.89	+0.043
	Metastatic	85	0.74	0.27	0.69-0.80	-0.054
	Palliative	17	0.59	0.22	0.48-0.70	-0.157
	All patients	621	0.85	0.03	0.83-0.86	-
Conclusions/Limitations	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 standardized for gender and age. A significant proportion of patients entering prostate cancer treatment because of elevated prostate-specific antigen (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)					
CI, confidence interval; HRQoL, health-related quality of life; TTO, time trade off; UK, United Kingdom						

<table>
<tr><td>Study</td><td>Watson and colleagues</td></tr>
<tr><td>Year</td><td>2016</td></tr>
<tr><td>Country</td><td>UK</td></tr>
<tr><td>Type of study</td><td>Cross-sectional study</td></tr>
<tr><td>Study objective</td><td>To explore ongoing symptoms, unmet needs, psychological wellbeing, self-efficacy, and overall health status in prostate cancer survivors.</td></tr>
<tr><td>Population</td><td>Men diagnosed 9-24 months previously, regardless of treatment modality, whose condition was considered stable as judged by the most recent PSA test result</td></tr>
<tr><td>Sample size</td><td>316</td></tr>
<tr><td>HRQoL instrument</td><td>EPIC-26, EQ-5D-5L</td></tr>
<tr><td>Mapping</td><td>Conversion to EQ-5D-3L using a crosswalk algorithm (van Hout et al. Value Health 2012; 15:708-715)</td></tr>
<tr><td>Health states</td><td>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)</td></tr>
<tr><td>Results</td><td>
<table>
<tr><th>Utilities</th><th>No/mild problems</th><th>Moderate/big problems</th><th>p-value</th></tr>
<tr><td>Urine Function</td><td>0.868 (0.160)</td><td>0.773 (0.222)</td><td>0.001</td></tr>
<tr><td>Bowel Function</td><td>0.862 (0.166)</td><td>0.653 (0.195)</td><td>0.000</td></tr>
<tr><td>Sexual Function</td><td>0.861 (0.176)</td><td>0.838 (0.170)</td><td>0.261</td></tr>
</table>
</td></tr>
<tr><td>Conclusions/Limitations</td><td>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.</td></tr>
<tr><td colspan="2">PSA, prostate specific antigen; UK, United Kingdom</td></tr>
</table>

Appendix 12 Cost breakdown of biopsy methods

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 £1,825.5 for orders with quantity >5 and £2,000 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 £19.13.
    - UA1232: cost of £1,400 (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 £754.4 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 £7.54.
    - SureFire Guide: As the company has not provided a cost for SureFire Guide, we assumed an average cost of the other two disposable LATP devices (CamPROBE and PrecisionPoint™) – resulting in a cost per biopsy of £135.
    - Grid and stepper unit:
        - 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, from which 15 are biopsies) for a lifetime of 10 years (informed by our clinical expert) – resulting in a cost per biopsy of £1.95.
    - Double freehand device: not applicable
- GATP biopsy: we assumed the same cost of the grid and stepper unit as for the LATP biopsy – resulting in a cost per biopsy of £78 for grid and £1.95 for stepper.
- LA-TRUS biopsy: not applicable

Cost of consumables

General consumables

- See *Table 113* below with the cost and quantity of each consumable per type of biopsy.
- LATP biopsies
    - LATP biopsies using freehand devices: we summed up the costs of the consumables that are common to all biopsies (£57.20) with the costs for the consumables that are used for TP biopsies (£8), for biopsies carried out under local anaesthesia (£17.69) and the cost of the co-axial needle (£21.40, assumed to be used for biopsies using freehand devices only) – resulting in a cost per biopsy of £104.29.
    - LATP biopsies using grid and stepper unit: we assumed the same costs as above except for the cost of the co-axial needle – resulting in a cost per biopsy of £82.89.
- GATP biopsy: we summed up the costs of the consumables that are common to all biopsies (£57.20) with the costs for the consumables that are used for TP biopsies (£8) and the cost of general anaesthesia (£100) – resulting in a cost per biopsy of £165.20.
- LA-TRUS biopsy: we summed up the costs of the consumables that are common to all biopsies (£57.20) with the costs for the consumables that are used for TRUS biopsies (£1.85) and for biopsies carried out under local anaesthesia (£17.69) – resulting in a cost per biopsy of £76.74.

Table 113 Cost of consumables used for each biopsy method

CONSUMABLES	Cost per biopsy	Unit cost	Source	Pack	Source	Quantity required	Source	Notes
All biopsies								
Biopsy gun	**£25.96**	£25.96	YHEC study	1	Assumption	1	Assumption	YHEC study reported the cost per biopsy directly
Biopsy needle	**£27**	£135	Wilson 2021	5	Wilson 2021	1	Wilson 2021	
Condoms	**£0.06**	£27.77	Wilson 2021	500	Wilson 2021	1	Wilson 2021	
Ultrasound lubricant gel	**£0.01**	£3.54	Wilson 2021	5000	Wilson 2021	10	Wilson 2021	ml
Sterile gloves	**£3.14**	£78.6	Wilson 2021	50	Wilson 2021	2	Wilson 2021	
Dressing towel	**£0.20**	£0.2	Wilson 2021	1	Wilson 2021	1	Wilson 2021	
Syringe	**£0.07**	£3.72	Wilson 2021	100	Wilson 2021	2	Wilson 2021	
Antiseptic wash	**£0.04**	£2.59	Wilson 2021	600	Wilson 2021	10	Wilson 2021	ml
Sterile saline	**£0.04**	£3.72	Wilson 2021	1000	Wilson 2021	10	Wilson 2021	ml

Sponges/Cassettes	**£0.68**	£0.1	Wilson 2021	1	Wilson 2021	12	Wilson 2021	Average between cost reported by Wilson 2021 and YHEC study; YHEC study reported the cost per biopsy directly.
		£0.16	YHEC study	1	Assumption	1	Assumption	
TP biopsies								
Orange needles	**£0.06**	£2.89	JEB/Wilson 2021	100	JEB/Wilson 2021	2	JEB/Wilson 2021	
Green needles	**£0.04**	£1.78	JEB/Wilson 2021	100	JEB/Wilson 2021	2	JEB/Wilson 2021	
Marker skin pen with ruler	**£0.33**	£1.67	JEB	5	JEB submission	1	JEB	
Cotton gauze	**£0.09**	£0.9	JEB/Wilson 2021	100	JEB/Wilson 2021	10	JEB/Wilson 2021	
Steristrips	**£0.31**	£7.74	JEB/Wilson 2021	50	JEB/Wilson 2021	2	JEB/Wilson 2021	
Sterile drapes/gowns	**£1.90**	£111.46	JEB/Wilson 2021	50	JEB/Wilson 2021	1	JEB/Wilson 2021	Average between cost reported by Wilson 2021 and YHEC study; YHEC study reported the cost per biopsy directly.
		£1.57	YHEC study	1	Assumption	1	Assumption	
Shallow sterile plastic tray	**£0.36**	£18.2	JEB/Wilson 2021	50	JEB/Wilson 2021	1	JEB/Wilson 2021	
Balloon/probe cover	**£4.60**	£4.6	YHEC study	1	Assumption	1	Assumption	YHEC study reported the cost per biopsy directly

Antibiotics prophylaxis	**£0.31**	£3.08	emiT 2020	10	emiT 2020	1	Expert opinion	Assumed as one prophylactic dose of ciprofloxacin (500mg), as advised by EAG expert
TP biopsies using freehand devices								
Co-axial needles	**£21.40**	£107	Hitachi	5	Hitachi	1	Hitachi	
TRUS biopsies								
Antibiotics course	**£1.85**	£3.08	emiT 2020	10	emiT 2020	6	SmPC/ Assumption	Assumed as a course of ciprofloxacin 500mg twice a day for 3 days, according to SmPC and as advised by EAG expert
LA biopsies								
Spinal needles	**£5.74**	£5.74	YHEC study	1	Assumption	1	Assumption	YHEC study reported the cost per biopsy directly
Local anaesthetic	**£11.95**	£11	Wilson 2021	20	Wilson 2021	20	Wilson 202	ml; Average between cost reported by Wilson 2021 and YHEC study; YHEC study reported the cost per biopsy directly.
		£12.9	YHEC study	20	Assumption	20	Assumption	
GA biopsies								
General anaesthetic	**£100**	£100	YHEC study	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; TRUS, transrectal ultrasound; YHEC, York Health Economics Consortium.

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), number of procedures (18 per week) and proportion of biopsies (15/18) as for stepper.
- EZU-PA3U: cost of £38,000 for a FUJIFILM Transperineal transducer and FUJIFILM Ultrasound system – resulting in a cost per biopsy of £3.37.
- UA1232: cost of £40,050 for a BK ultrasound system, urology software with 9048 Transducer - resulting in a cost per biopsy of £3.55.
- 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 £6.08.
- Remaining devices and methods: cost of £48,853 as the average of the abovementioned machines - resulting in a cost per biopsy of £4.33.

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 2020 [96]. 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 £2.38.
    - PrecisionPoint™ : one day (8 hours) spent on training per person – resulting in a cost per biopsy of £4.76.
    - EZU-PA3U: one hour spent on training per person – resulting in a cost per biopsy of £0.60.
    - UA1232: two hours spent on training per person – resulting in a cost per biopsy of £1.19.
    - Trinity® Perine: one 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 stepper unit 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 £4.76.
- 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 £4.76.
- LA-TRUS biopsy: We assumed that this would only require one 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 on 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 2020 [96] 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 2020 [96].
- LATP biopsies
  - CamPROBE: a procedure time of 0.41h was based on the study by Wilson 2021 [58] – resulting in a cost per biopsy of £48.79 for the urologist and £25.42 for the two nurses.
  - PrecisionPoint™ : a procedure time of 0.33h was based on the study by Szabo 2021[37] – resulting in a cost per biopsy of £39.67 for the urologist and £20.67 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™ (0.37h) - resulting in a cost per biopsy of £44.23 for the urologist and £23.04 for the two nurses.
- GATP biopsy: A procedure time of 1 hour was assumed – resulting in a cost per biopsy of £119 for the urologist and anaesthetist and £62 for the two nurses.
- LA-TRUS biopsy: a procedure time of 0.31h was assumed. This was obtained by multiplying the average procedure time of LATP biopsies (0.37h) by the LATRUS/LATP procedure time ratio (0.84) derived from Guo 2015.[24] This study reported a procedure time of 14.73 min for LATRUS and 17.51 min for LATP –

resulting in a cost per biopsy of £37.21 for the urologist and £19.38 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 £193.50. We assumed that the cost of the outpatient room corresponds to a procedure time of 0.33h (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 hour
- LATP biopsies
    - CamPROBE: assuming the use of an outpatient room and a procedure time of 0.41h, results in a cost per biopsy of £52.89.
    - PrecisionPoint™ : assuming the use of an outpatient room and a procedure time of 0.33h, 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 0.37h, results in a cost per biopsy of £47.95.
- GATP biopsy: assuming the use of a theatre session and a procedure time of 1 hour, results in a cost per biopsy of £193.50.
- LA-TRUS biopsy: assuming the use of an outpatient room and a procedure time of 0.31h, results in a cost per biopsy of £40.33.

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 grid and stepper units.
- 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 histopathologic analysis was applied to all biopsy methods. The unit cost of the diagnostic histopathology was based on a published document from the University of Surrey [245]. A cost of £37.50 includes the analysis of one or two samples. For each additional sample, an incremental cost of £7 was applied. For the base case, we assumed that 12 samples were taken from a prostate biopsy – resulting in a cost per biopsy of £107.50.