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1. Title of the project

Transperineal biopsy in people with suspected prostate cancer

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3. Plain English Summary

Prostate cancer is the most commonly diagnosed cancer in men in the UK. Around one in six males born after 1960 in the UK will be diagnosed with prostate cancer. Various procedures and tests can be used to investigate cases of suspected prostate cancer, such as blood testing to measure levels of prostate specific antigen (PSA) (increased PSA levels can indicate presence of cancer). The prostate itself may have felt abnormal during a digital rectal examination (a procedure in which a doctor inserts their finger into the person's rectum so they can feel the prostate gland). Prostate cancer may be suspected if the prostate gland appears abnormal in shape and size on images taken during a multiparametric magnetic resonance imaging (mpMRI) test. Other risk factors may be taken into account such as whether there is any family history of prostate cancer. Information from the above tests and procedures can help inform the decision to do a prostate biopsy (the taking of small samples of the prostate using a biopsy needle) to diagnose prostate cancer.

During a prostate biopsy an ultrasound probe is placed in the rectum (back passage). The ultrasound probe uses sound waves to make an image of the prostate which is displayed on a small screen. The image helps the doctor move the biopsy needle to the correct location. Local anaesthetic is used to numb the area that the biopsy needle is passing through. The biopsy needle can either be inserted through the wall of the rectum (trans-rectal ultrasound [TRUS] method) or through the perineum (the skin area between the anus and the scrotum) in a transperineal prostate biopsy. Traditionally, most prostate biopsies in the NHS used the TRUS method but recently there has been a trend towards performing transperineal biopsy (particularly due to the COVID-19 pandemic).

The aim of our research is to investigate whether the use of local anaesthetic transperineal (LATP) prostate biopsies gives an accurate diagnosis of prostate cancer, and whether the costs of LATP biopsy, and any cancer treatments then given, produce benefits to patients that are considered to represent an acceptable use of NHS resources (i.e. are they clinically effective and cost-effective?). Additionally, we will also examine if freehand transperineal biopsy devices that have been developed as aids to conducting LATP are a clinically and cost-effective use of NHS resources.

We will review all the relevant available research studies, using detailed systematic methods. We will examine how accurate LATP biopsies are to correctly detect prostate cancer and if there are any harmful effects from the biopsy. We will also look at how much LATP biopsy costs, per patient. To do this we will create a computer-software based economic model to estimate the costs and benefits to patients and the NHS of LATP biopsies.

4. Decision problem

4.1. Purpose of the decision to be made

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

- Lower back, or bone pain
- Lethargy
- Erectile dysfunction
- Haematuria
- Weight loss
- Lower urinary tract symptoms, such as frequency, urgency, hesitancy, terminal dribbling and/or overactive bladder.

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[5]) 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 2 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[6]) 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.[7]

- 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[8] and updated in 2015[9] and 2019.[10] 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[11] 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 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 (e.g. the person has a pacemaker fitted or experiences claustrophobia) factors such as PSA density and family history of prostate cancer would influence a decision about whether a systematic biopsy would be appropriate.

In a **transrectal ultrasound (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.[12]) Sepsis is a serious infection which requires a hospital admission and antibiotics.

Traditionally, most prostate biopsies in the NHS used the TRUS method. However, recently 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[13] recommended that TRUS biopsies should be avoided if possible.

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.

Traditionally, transperineal biopsies were performed using a **grid-stepper unit**. This meant the biopsy needle was 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.

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. Alternatively, 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. In 2020, more than 65% of all prostate biopsies in the NHS were transperineal biopsies.

One of the potential benefits of more widespread use of local anaesthetic transperineal prostate (LATP) biopsies in comparison to TRUS biopsies would be fewer serious infections caused by puncture of the rectum by the biopsy needle. This can reduce the risks of patient infection and reduce antibiotic use (including preventive antibiotics) and infection-related hospital admissions. A potential benefit of LATP compared to a grid-stepper transperineal biopsy approach conducted under general anaesthetic 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.

Based on the above considerations, two decision questions have been identified as relevant to this NICE diagnostic technology appraisal:

1. Do local anaesthetic transperineal (LATP) prostate biopsies in patients 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 patients with suspected prostate cancer represent a clinically and cost-effective use of NHS resources?

4.2. Aims and objectives

The aim of this diagnostic assessment is to assess the clinical effectiveness and cost-effectiveness of LATP prostate biopsies performed using: a grid and stepping device, a double freehand approach or a freehand transperineal biopsy device, in people with suspected prostate cancer. The results will inform a NICE appraisal of the technology for use in the NHS.

The objectives of this diagnostic assessment are:

1. To conduct a systematic review of diagnostic test accuracy and clinical effectiveness of LATP prostate biopsies, performed using a grid and stepping device, a double freehand approach or a freehand transperineal biopsy device in people with suspected prostate cancer.
2. To conduct systematic reviews to inform an economic evaluation of LATP prostate biopsies. This will include a systematic review of cost-effectiveness studies of LATP prostate biopsies in people with suspected prostate cancer; and systematic reviews of health-related quality of life (utility), resource use and costs for people with suspected or diagnosed prostate cancer.
3. To conduct an economic evaluation using decision-analytic modelling to assess the cost-effectiveness of LATP prostate biopsies and freehand devices in people with suspected prostate cancer.

4.3. Clear definition of 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 (using one of the devices listed in the NICE scope for this appraisal).

Each intervention is briefly described in the following subsections.

4.3.1. LATP prostate biopsy using a grid and stepping device

Stepper devices are used to cradle the ultrasound probe and the grid provides a guide for needle insertion. Grid and stepper units are also used to perform brachytherapy for prostate cancer so the equipment may already be available. 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.

4.3.2. LATP prostate biopsy using a coaxial needle (double freehand)

A coaxial needle enables one skin puncture to be used to take several biopsy samples. The introducing needle is advanced under local anaesthetic to the prostate and biopsy is performed under ultrasound guidance. The angle of the introducing needle is adjusted by the clinician to target different areas of the prostate. There is no needle positioning guide and nothing to attach the needle to the ultrasound probe. The user has to keep the needle (held in one hand) and the ultrasound probe (held in the other hand) in phase manually.

4.3.3. LATP prostate biopsy using a freehand device

4.3.3.1. PrecisionPoint (BXTAccelyon)

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. 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, and it is compatible with any biplane TRUS or transperineal probe from any ultrasound manufacturer.

4.3.3.2. UA1232 puncture attachment (BK medical)

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.

4.3.3.3. CamPROBE (Cambridge Prostate Cancer)

The CAMbridge PROstate Biopsy DevicE (CamPROBE) is a single use transperineal access system designed to enable integrated local anaesthetic delivery. The device comprises an access needle 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. 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.

4.3.3.4. Trinity Perine (Koelis)

The reusable guides Perine grids come in two sizes, to accommodate either an 18-gauge or 14-gauge needle and they are designed to adapt on to a K3DEL00 ultrasound probe. Each Perine grid has 20 marked needle positions spaced 3 mm apart.

4.3.3.5. SureFire Guide (LeapMed)

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 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.

4.3.3.6. Puncture guide fixture EZU-PA3U (Hitachi Medical Systems)

The reusable EZU-PA3U puncture guide fixture is available for attachment to either the Hitachi CC41R or C41L47RP bi-plane tranducers. 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. The puncture guide fixture is compatible with 14-gauge and 18-gauge needles.

4.4. Populations and relevant subgroups

The population of relevance to 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 (those receiving treatment for prostate cancer and those whose cancer is being monitored by either active surveillance or watchful waiting fall into this group). People who are already known to have metastatic prostate cancer are also not included.

4.5. Place of the intervention in the treatment pathway(s)

LATP biopsy for people with suspected prostate cancer takes place at the same point in the treatment pathway as current clinical practice using local anaesthetic TRUS biopsy and in the same setting (secondary care, outpatients).

4.6. Relevant comparators

There are three comparators for this assessment (although only two apply to the first of the two decision questions, see section 5.3 and Table 1). The three comparators are:

- local anaesthetic transrectal ultrasound biopsy (LA-TRUS)

- 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

For each comparator the biopsy approach taken could be either targeted (i.e. informed by a prior mpMRI) or systematic.

4.6.1. Local anaesthetic TRUS biopsy

Local anaesthetic TRUS biopsy is done in an outpatient setting. For a TRUS prostate biopsy a transrectal ultrasound probe is inserted into the anus to image the prostate. The biopsy needle is usually inserted through a needle guide that is attached to the ultrasound probe enabling the needle to be correctly placed as it passes through the rectal wall and into the prostate.

4.6.2. LATP biopsy using a grid or template and stepping device

In this version of an LATP biopsy, a grid or template is mounted on a stepping device as described previously in section 4.3.1. The biopsy needle is inserted multiple times, using the grid to help target different areas of the prostate.

4.6.3. General anaesthetic transperineal biopsy using a grid or template and stepping device

Transperineal biopsy using a grid or template and stepping device can also be conducted under general anaesthetic instead of local anaesthetic as in section 4.6.2 above.

4.7. Key factors to be addressed (e.g. clinical and cost outcomes, further considerations, problematic factors)

No additional key factors have been identified.

4.8. Areas of agreement at the scoping workshop that are outside the scope of the appraisal and therefore do not require any detailed assessment (e.g. key factors for which evidence is already accepted).

The use of software to overlay the MRI scan image onto a live ultrasound image of the prostate (e.g. by a fusion biopsy system) during the biopsy procedure is outside the scope of this assessment.

5. Report methods for assessing the outcomes arising from the use of the interventions

The following sub-sections specify the scope (inclusion criteria) and methods for the systematic review of LATP prostate biopsy test accuracy and clinical effectiveness.

5.1. Population

People with suspected prostate cancer where prostate biopsy is indicated.

Where data permits, the following subgroups may be considered:

- 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 of 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

5.2. Interventions

Two groups of interventions, aligned with the decision questions, are included in this assessment:

- Local anaesthetic transperineal prostate biopsy (LATP) (for example, using a grid and stepping device, a coaxial needle, or a freehand transperineal biopsy device). (Decision question 1).
- Local anaesthetic transperineal prostate biopsy (LATP) done using one of the following freehand transperineal biopsy devices: (Decision question 2):
    - PrecisionPoint transperineal access device (BXTAccelyon)
    - UA1232 puncture attachment (BK Medical)
    - Trinity Perine Grid (Koelis)
    - CamPROBE
    - SureFire (LeapMedical)
    - Puncture guide fixture EZU-PA3U (Hitachi Medical Systems)

5.3. Comparators

The three comparators for this assessment (described in more detail in section 4.6) apply to each of the decision questions as follows: (see also Table 1):

For LATP prostate biopsies grouped (i.e. using a grid and stepping device, a coaxial needle, or a freehand transperineal biopsy device) the comparators are:

- local anaesthetic TRUS biopsy (LA-TRUS)
- general anaesthetic transperineal biopsy (GATP) using a grid or template and stepping device

For LATP prostate biopsies using a freehand transperineal biopsy device, the comparators are:

- local anaesthetic TRUS prostate biopsy (LA-TRUS)
- LATP prostate biopsy using a grid or template and stepping device
- general anaesthetic transperineal biopsy (GATP) using a grid or template and stepping device

In all cases biopsies can be either targeted or systematic.

Table 1 Relevant comparators for each decision question

Decision question (intervention)	1. Do local anaesthetic transperineal prostate LATP biopsies in patients 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 patients with suspected prostate cancer represent a clinically and cost-effective use of NHS resources?
Comparators	Local anaesthetic transrectal ultrasound prostate biopsy (LA-TRUS)	Local anaesthetic transrectal ultrasound prostate biopsy (LA-TRUS)
		Local anaesthetic transperineal prostate (LATP) biopsy using a grid and stepping device
	General anaesthetic transperineal prostate (GATP) biopsy using a grid and	General anaesthetic transperineal prostate (GATP) biopsy using a grid and stepping

	stepping device	device

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

5.4. Outcomes

The following outcome measures will be included if reported by included studies:

Intermediate outcomes

- Measures of diagnostic accuracy
- 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 6 months

Clinical outcomes

- Hospitalisation events after biopsy
- Rates of biopsy related complications, including infection, sepsis and haematuria.
- Rates of urinary retention
- Rates of erectile dysfunction
- Survival
- Progression free survival
- Adverse events from treatment

Patient reported outcomes

- Health related quality of life
- Patient reported tolerability

5.5. Study design

The systematic review of test accuracy and clinical effectiveness will not limit inclusion by type of study, because a range of study designs could potentially be used to assess the accuracy and clinical effectiveness of LATP biopsy in suspected prostate cancer. Our scoping work indicates that much of the published evidence comes from observational studies, though some RCTs are known to be in progress.

If both trial-based and observational evidence is available for any of the comparisons relevant to this review, priority will be given to the trial-based evidence.

5.6. Search strategy

A bespoke search strategy will be developed, tested and refined by an experienced information specialist. The strategy will be comprehensive in order to identify all available relevant studies. A draft Medline search strategy is provided in Appendix 1 for illustration.

The main sources of evidence to be searched will be:

- Electronic research databases and resources
- Bibliographies of included studies

The electronic resources that will be searched are:

- General health and biomedical databases
    - MEDLINE (Ovid), including Epub Ahead of Print, In-Process & Other Non-Indexed Citations
    - Embase (Ovid)
    - The Cochrane Library, for the Cochrane Database of Systematic Reviews and the CENTRAL register of controlled trials
    - Web of Science, for the Science Citation Index Expanded (SCI-EXPANDED) and the Conference Proceedings Citation Index – Science (CPCI-S)
    - International HTA Database (INAHTA)
    - Database of Abstracts of Reviews of Effects (DARE)
    - NHS Economic Evaluations Database (NHS EED)
    - EconLit (Ebsco)
    - Epistemonikos (epistemonikos.org)
- Grey literature and research in progress
    - OpenGrey
    - PROSPERO register of systematic reviews
    - ClinicalTrials.gov
    - Cochrane CENTRAL, as above
    - BePartOfResearch (formerly the UK Clinical Trials Gateway)
    - NIHR Clinical Research Network Portfolio

All databases will be searched from database inception to the present date. Searches will be limited to publications reported in the English language. Any relevant systematic reviews identified will be used as a source of potentially relevant primary studies.

Any relevant studies published as abstracts or conference proceedings will be included only if published in the last 4 years (i.e. 2018, 2019, 2020 or 2021) and only if sufficient details are presented to allow appraisal of the methodology and the assessment of results to be undertaken.

5.7. Study selection and data extraction strategies

Studies will be selected for inclusion using a two-stage screening process. Firstly, the titles and abstracts of bibliographic records retrieved using the above search strategy will be assessed independently by two reviewers against the predefined and explicit inclusion criteria described above. Secondly, the full texts of any potentially relevant records will be obtained and then screened against the inclusion criteria by one reviewer and checked by a second reviewer, before a final decision regarding inclusion is agreed.

Relevant data will be extracted from each included study on its methodology, the characteristics of the population, intervention, comparator(s) and outcome measures. Data extraction and critical appraisal will be undertaken by one reviewer using a pre-designed and piloted data extraction form (see Appendix 2 Draft data extraction form for systematic review of test accuracy and clinical effectiveness for a draft data extraction form). The extracted data will be checked by a second reviewer. Separate references that refer to the same primary study will be assessed together to avoid double counting of data.

Any disagreements between reviewers during study selection or data extraction will be resolved by discussion, with the involvement of a third reviewer where necessary.

5.8. Quality assessment strategy

The methodological quality, relevance and risk of bias of the included diagnostic test accuracy studies will be assessed using the QUADAS-2 tool.[14] Other types of study (e.g. those reporting intermediate and/or clinical outcomes) will be assessed using standard criteria appropriate to specific study designs e.g. the Cochrane Risk of Bias

tool for RCTs (version 1),[15] and the Cochrane Effective Practice and Organisation of Care (EPOC) suggested risk of bias criteria for non-randomised studies.[16] Each included study will be critically appraised by one reviewer, and checked by a second reviewer. Any disagreements between reviewers will be resolved through discussion and, if necessary, involvement of a third reviewer.

5.9. Methods of analysis/synthesis

Details of the included studies will be summarised through a structured narrative synthesis, with numerical and statistical data presented in tables and figures/graphs as appropriate. The appropriateness and feasibility of meta-analysis will assessed based on factors including the availability of necessary study data and the degree of clinical and statistical heterogeneity across the included studies. If meta-analysis is considered feasible we will use standard statistical methods as recommended by methodological guidelines in evidence synthesis, including the Cochrane Handbook.[17] For test accuracy, we will use methods such as hierarchical bivariate meta-analysis to generate pooled estimates of diagnostic sensitivity and specificity. Statistical software will be used to run the analyses, such as Stata and its specialist plug-in packages for diagnostic meta-analyses. For clinical outcomes we will meta-analyse intervention effects using statistical tests and effect measures appropriate to the type of outcome data (e.g. binary or continuous data). Cochrane Review Manager (RevMan) software will be used to meta-analyse clinical outcomes. Sensitivity analyses will be performed to test the robustness of results to changes in assumptions such as random effects and fixed effect models. Randomised and non-randomised studies, where available, will be meta-analysed separately, as recommended by methodological guidance.[17]

As noted earlier (section 5.5) although priority will be given to trial-based evidence, we anticipate that much of the available evidence will be from observational studies. Should we find a large volume and wide variety of observational study types, priority will be given to the studies that most closely match the recommendations in the NICE guideline on prostate cancer: diagnosis and management (NG131[6]) and for the population who would receive prostate biopsy.

6. Report methods for synthesising evidence of cost effectiveness

6.1. Systematic review of cost-effectiveness studies

A systematic review will be conducted to identify, critically appraise, and summarise the results of cost-effectiveness studies relevant to the decision problem. The main purpose of this review will be to inform development of our economic model through consideration of alternative model structures, assumptions, and data sources. We will also summarise cost-effectiveness findings that may be applicable to the scope and UK context and which may provide a basis for cross-validation of our model results.

The search for published economic evaluations will be based on the search strategy used for the systematic review of diagnostic test accuracy and clinical effectiveness (section 5.6 above), with the addition of published filters to identify economic evaluations, estimates of resource use and costs, and health-related quality of life (utility). Targeted searches will also be conducted to identify relevant cost-effectiveness studies reported by health technology assessment bodies (including NICE). Studies that meet the population and intervention/comparator inclusion criteria and report outcomes relevant to the economic evaluation (including resource use and costs, health-related quality of life, life-years and QALYs) will be identified for screening by two health economists.

The cost-effectiveness review will only include ‘full economic evaluations’ that assess both the costs and consequences of alternative biopsy strategies using a suitable intermediate or final outcome measure (e.g. cases detected, life years and/or QALYs). Studies that only report resource use or costs (including comparative cost studies as well as non-comparative budget impact analyses) will be excluded but considered separately as possible sources of evidence for resource use and cost parameters in our model. Similarly, reports of health-related quality of life assessments with suitable instruments (such as the EQ-5D), will be considered as a source of evidence for utility inputs to our model.

The methods and parameter sources of the included cost-effectiveness studies will be summarised in tables. The relevance and credibility of the included cost-effectiveness studies and their relevance to current UK practice will be assessed using a pre-defined checklist, similar to that in Appendix Appendix 3 Relevance and credibility checklist for full economic evaluations Cost-effectiveness results will be

summarised in a table and discussed in a narrative review. Any results that provide a suitable basis for cross-validation will be identified.

Our preliminary scoping searches for this protocol identified seven economic evaluations of biopsy strategies for the diagnosis of prostate cancer. [18] [19] [20] [21] [22] [23] [24] All seven studies are cost-effectiveness analyses. The main objective of six of these studies was to compare the costs and benefits of the TRUS biopsy versus an MRI guided biopsy. [19] [20] [21] [22] [23] [24] Only one study assessed the cost-effectiveness of other modalities, such as general anaesthetic transperineal biopsy. [18] Two studies used decision trees to model the costs and benefits of the biopsy strategies in comparison, [21] [22] two used a combination of decision trees and Markov models, [20] [24] one used a Markov model only [19] and two studies did not use a model at all. [18] [23] Four studies presented the effectiveness outcomes as QALYs, [19] [20] [22] [24] two as the number of cancers detected [18] [21] and one as test accuracy and time to diagnosis. [23]

None of the studies assessed the biopsy strategies relevant for the current decision problem (i.e. local anaesthetic transperineal biopsy strategies). Nevertheless, we will review the models used in these studies, as well as any further models that will be included in the systematic review of cost-effectiveness, to inform the structure, assumptions and parameter sources of our model.

6.2. Development of a health economic model

6.2.1. Approach to economic analysis

A decision analytic model will be developed to assess the relative cost-effectiveness of alternative biopsy methods for people with suspected prostate cancer.

The model will be designed to address the decision questions specified in the NICE scope and discussed earlier in this protocol (section 4.1). We anticipate that a single model will be developed to compare the included interventions and comparators (as far as data will allow). This will enable full incremental analysis of all included biopsy strategies, as well as separate analyses to address the two decision questions or to provide pairwise comparisons if required. The model will also be designed to produce stratified cost-effectiveness results for the patient subgroups as specified in the NICE scope, if data allows.

Analysis will follow the NICE reference case, as specified in section 15 of the Diagnostics Assessment Programme (DAP) manual.[25]

- The model will use a lifetime horizon to reflect the potential long-term impacts of any differences between the strategies in terms of diagnostic or prognostic accuracy or rates of serious adverse events.
- Health outcomes will be quantified as quality-adjusted life years (QALYs), with health-related quality of life (utilities) estimated from EQ-5D data with NICE-recommended UK general population values, if available.[26 27]
- Costs will be estimated from an NHS and personal social services (PSS) perspective. The base case will use long-term average cost estimates for the interventions and comparators, with annuitized costs for all capital equipment. Scenario analysis will be used for alternative cost assumptions, including marginal costing without costs for existing NHS equipment (e.g. ultrasound machines).
- Standard time discount rates will be used for costs and QALYs, as recommended by NICE (currently 3.5% per year).

We will also follow methods for model development and standards of reporting as recommended in the DAP manual and good practice guidelines.[25 28-34]

6.2.2. Model population and subgroups

The model will estimate costs and health outcomes for the population specified in the NICE scope: *people with suspected prostate cancer where prostate biopsy is indicated.* We will aim to reflect characteristics of this population in routine NHS practice, including age and probability of prostate cancer (stratified by risk) prior to biopsy.

If data permits, we will tailor the model for the subgroups listed in the NICE scope. These subgroups are defined by:

- Location of lesions (anterior, posterior, apical, basal)
- Likert or PI-RADS score (≤2 or >2)
- Enlarged prostate
- History of prostate biopsy (none, previous negative)

The subgroups will be characterised in the model by tailored sets of input parameters. In particular, the prior probabilities of prostate cancer are likely to differ

for patients with a low Likert or PI-RADS score and for those who have/have not had a previous biopsy. The biopsy strategies may differ in their ability to obtain accurate samples from different locations in the prostate.

6.2.3. Modelled biopsy strategies

The model will be designed to evaluate the biopsy strategies and decision questions defined in the NICE scope:

Interventions

- Local anaesthetic transperineal biopsy including use of grid and stepping device, coaxial needle or freehand device (LATP grouped)
- LATP with freehand device (PrecisionPoint, UA1232, Trinity Perine Grid, CamPROBE, SureFire or EZU-PA3U)

Comparators

- Local anaesthetic transrectal ultrasound biopsy (LA-TRUS)
- General anaesthetic transperineal biopsy using a grid and stepping device (GATP)
- LATP without freehand device

Decision question 1: LATP (grouped) versus LA-TRUS and GATP
Decision question 2: LATP (freehand) versus LA-TRUS, GATP and LATP (no freehand)

6.2.4. Modelled outcomes

The model will need to reflect evidence on key outcomes associated with the different biopsy strategies, as listed in the NICE scope:

- Measures of diagnostic or prognostic accuracy
- Biopsy completion and the need for repeat procedures that may be associated with the quality of the procedure or tolerability for patients
- Adverse events associated with the biopsy procedure
- Health-related quality of life for health states and adverse events
- Clinical outcomes related to cancer (progression and survival)
- Costs of biopsy, treatment of adverse events, follow-up, active surveillance, watchful waiting, cancer treatment and end of life care

There are two main types of 'biopsy error' related to the number and accurate targeting of samples taken:

- Although we assume that there can be no false positives (pathology is 100% accurate), there is the risk of over-diagnosis in the sense of identification of clinically insignificant cancer. This can lead to unnecessary follow-up, costs for the NHS, anxiety and potential harm to patients.
- False negative results or misclassification of risk resulting from the failure to sample lesions, which can cause delayed or inappropriate treatment with effects on quality of life and survival, as well as overall NHS costs.

Increasing the number of samples per procedure would be expected to reduce the risk of false negatives, but this could potentially come at the cost of increased risk of over-diagnosis and adverse effects. Better targeted sampling should reduce both types of error and the risk of adverse events.

The number of samples taken and use of targeted versus systematic sampling strategies is expected to differ between the biopsy methods in the scope. This may be a natural consequence of tolerability for patients and/or ease of use for operators – in which case, any such differences should be integrated within the cost-effectiveness evaluation of the biopsy strategies. We would therefore favour the use of diagnostic accuracy evidence from studies that have not attempted to control for these effects by mandating the number of samples or sampling strategy in the study protocol.

6.2.5. Model structure and assumptions

The model will comprise a decision tree to map out the diagnostic pathway and a Markov model to estimate long-term treatment costs and health outcomes.

6.2.5.1. Decision tree

Figure 1 below illustrates the type of structure that will be developed to reflect the short-term costs, adverse effects and diagnostic accuracy of alternative biopsy strategies. It starts with a cohort of people referred for biopsy with suspected prostate cancer. An initial decision node indicates the biopsy strategies to be compared: here we show a simplified version to address decision question 2 (LATP with freehand devices compared with LATP without a freehand device, GATP and TRUS). The tree then shows adverse events related to the biopsy and potential diagnostic results:

including correct diagnosis of significant disease, ‘over diagnosis’ of insignificant disease, missed cases of significant disease, and ‘true negatives’ (including no cancer and insignificant disease). The modelled cohort will then enter a Markov model, which will predict long-term costs and health outcomes.

6.2.5.2. Markov model

We anticipate that the Markov model will be based on the health economic model developed for the 2019 update of the NICE guideline on diagnosis and management of prostate cancer (NG131).[6 35] 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 MRI and/or biopsy result. Although this is a different question, we think that the NG131 model will provide a suitable platform that can be adapted for the current decision problem. The structure of the model, the underlying assumptions and input parameters are well-described in an evidence report on the NICE website.[35]

The NG131 model is a discrete time, Markov cohort model with a 3-month cycle. The structure is illustrated in Figure 2 below, reproduced from the NG131 model report. We also reproduce definitions of the 11 health states and key assumptions in the NG131 model in Table 2 and Table 3 below. A total of 11 health states are grouped in four categories: ‘true negatives’ (no prostate cancer or undiagnosed low-risk insignificant disease); ‘false negatives’ (undiagnosed significant stages of disease, from intermediate-risk to metastatic); ‘true positives’ (diagnosed disease from low-risk to metastatic); and death related to prostate cancer or from other causes.
The cohort is distributed between these health states after the initial diagnostic process, which is modelled with a decision tree similar to that below. Incidence and progression of cancer, diagnosis of prevalent and incident cases and mortality is then estimated using a Markov health-state transition model.

The decision tree and Markov model structures in Figure 1 and Figure 2 below are intended to be illustrative. The final model structure will be developed after further consideration of published models, available evidence and expert advice.

6.2.6. Input parameters

The NG131 health economic model report describes the input parameters that govern the initial distribution of the cohort between health states, transitions between

health states, adverse events costs and utilities (Tables HE05 to HE14). Calibration methods were used to infer unknown (or unknowable) parameters, such as prevalence and rates of progression of undiagnosed disease. Appendix 4 Input parameters used in the NG131 economic model presents the input parameters used in the NG131 model and the corresponding sources of evidence. We intend to start by replicating the NG131 model, using the parameter values as previously reported. We will then adapt the model structure for the current decision problem and update the input parameters.

6.2.6.1. Decision tree

- Baseline prevalence of significant/ insignificant prostate cancer – by subgroup
- Sensitivity of biopsy strategies for intermediate-risk, high-risk and metastatic prostate cancer
- Incidence of adverse events related to biopsy - infection, sepsis, urinary retention
- Utilities for biopsy-related adverse events
- Costs for biopsy diagnosis and treatment of biopsy-related side effects

6.2.6.2. Markov

- Progression rates with/without diagnosis (from calibration)
- Mortality from prostate cancer and other courses
- Health state utilities and disutilities related to adverse events
- Resource use and costs for treatment, active surveillance. follow-up and care

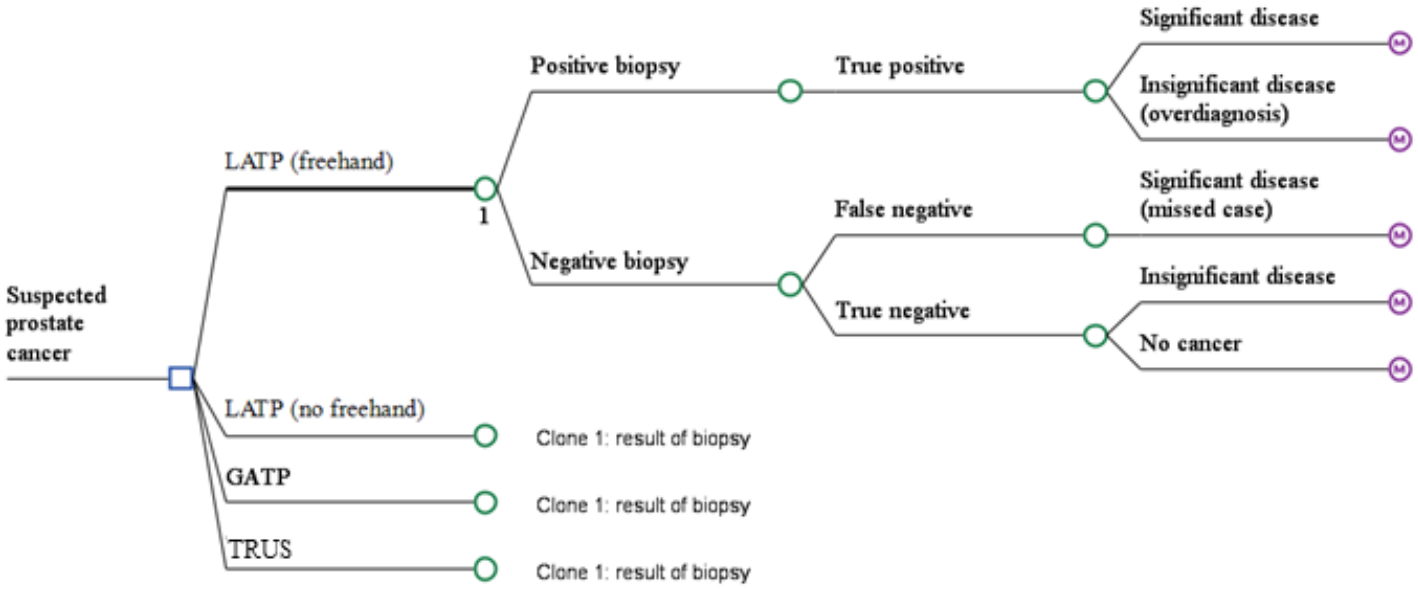

Figure 1 Simplified illustration of decision tree for diagnostic pathway

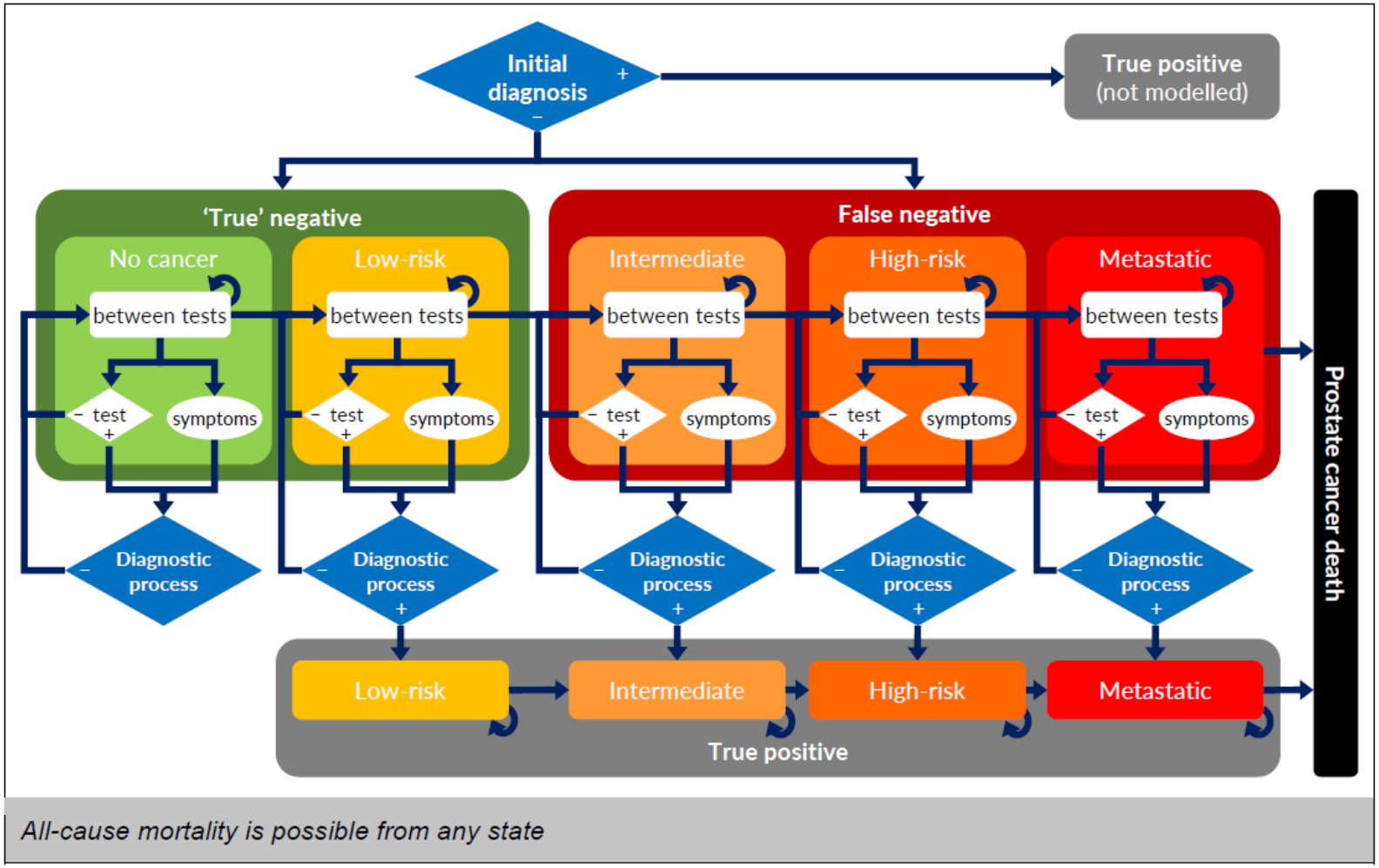

Figure 2 Schematic depiction of NG131 health economic model

Reproduced from Figure HE01, Health economic report, NICE NG131, 2019[35]

Table 2 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
TP – low-risk	People with low-risk cancer and were truly captured
TP – intermediate-risk	People with intermediate-risk cancer and were truly captured, receiving relevant treatments
TP – high-risk	People with high-risk cancer and were truly captured, receiving relevant treatments
TP – metastatic	People with metastases truly captured and receiving relevant treatments
Death from PCa	Allowed only from diagnosed metastatic prostate cancer
Death from other causes	Allowed from any other alive states and sourced from life table data

Adapted from Table HE03, Health economic report, NICE NG131, 2019[35]

Table 3 Key assumptions in NG131 health economic model

Baseline population with negative prostate findings comprises true negative and false negative based on previous diagnostics;
People in true negative developing the disease move to low-risk prostate cancer
People diagnosed with prostate cancer, moving to true positive states, must pass through false negative, having the disease not identified;
People with prostate cancer (diagnosed and undiagnosed) are at continuous risk of progression;
Progression occurs subsequently i.e. from low to intermediate to high and then to metastases;
Two types of prostate biopsies are included (TRUS and Template Prostate Mapping (TPM)) and assumed perfectly specific, and TPM biopsy is perfectly sensitive too;
Cases with localised prostate cancer are not at risk of prostate cancer death;
Prostate cancer specific death occurs only among metastatic patients.
Apart from subsequent TRUS, we assumed screening tests still have the same accuracy data when applied subsequently.

Reproduced from Table HE04, Health economic report NICE NG131, 2019[35]

6.2.7. Process of model adaptation and validation

The key steps in the process of adapting and validating the model for use in this assessment include:

- Replicating the NG131 2019 model
- Adapt model for evaluation of biopsy strategies
- Review and update model parameters:
    - Epidemiology (baseline prevalence, progression, mortality)
    - Biopsy cancer detection rates
    - Adverse event rates
    - Utilities for health states and adverse events
    - Resource use and costs
- Calibration if required to infer unknown parameter values
- Produce draft results
- Model validation:
    - Quality assurance checks by member of SHTAC team not involved in model development – checklist of 'white box' and 'black box' tests
    - Expert opinion on face validity of modelled outcomes
    - Cross-validation against results from cost-effectiveness models from published literature or company submissions
    - Validation against internal/external data sources
- Produce final model results

6.2.8. Addressing uncertainty

The following methods will be used to assess uncertainty in model results:

- Deterministic one-way sensitivity analysis for uncertain parameters
- Probabilistic sensitivity analysis for uncertain parameters
- Scenario analysis to explore alternative assumptions and data sources.

7. Handling information from the companies

All data submitted by the manufacturers/sponsors will be considered for inclusion if received by the EAG no later than 27th September 2021. Data arriving after this deadline will not be considered. If the data meet the inclusion criteria for the systematic reviews in this protocol they will be extracted and critically appraised in accordance with the procedures described earlier in this protocol.

Any 'commercial in confidence' data provided by a manufacturer and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any academic-in-confidence data provided will be highlighted in yellow and underlined.

8. Competing interests of authors

None

9. Timetable/milestones

Milestone	Date to be completed
Final protocol	01 June 2021
Progress report to NETSCC, HTA	27 August 2021
Draft report submitted to NICE	25 October 2021
Submission of final report to NETSCC, HTA; NICE	22 November 2021

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11. Appendices

11.1. Appendix 1 Draft Medline search strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to May 18, 2021

#	Searches	Results
1	exp Prostatic Neoplasms/	133413
2	(prostat* adj3 (cancer* or carcinoma* or malignan* or neoplasm* or tumour* or tumor*)).tw.	149630
3	1 or 2	174814
4	(suspected or suspicion or suspicious).tw.	279243
5	3 and 4	4183
6	(prostat* adj3 biops*).tw.	12094
7	Biopsy/	178741
8	exp Biopsy, Needle/	67361
9	((needle or puncture or aspiration) adj3 biops*).tw.	32516
10	or/6-9	261939
11	(transperineal or perineal or transrectal).tw.	28133
12	10 and 11	5480
13	PrecisionPoint.tw.	7
14	BXTAccelyon.tw.	1
15	UA1232.tw.	0
16	"BK Medical".tw.	34
17	((Trinity or Perine) and prostat*).tw.	6
18	Koelis.tw.	22
19	CamPROBE.tw.	2
20	"cambridge prostate biopsy device".tw.	1
21	SureFire.tw.	51
22	LeapMed*.tw.	0
23	EZU-PA3U.tw.	0
24	(Hitachi and prostat*).tw.	21
25	(needle adj (device or grid or guide or template)).tw.	323
26	(stepping adj (device or grid or guide or template)).tw.	15
27	(device adj2 (grid or guide or stepping or template)).tw.	272
28	((freehand or free?hand) adj2 (device* or needle* or biops*)).tw.	79
29	"local an?esthetic transperineal".tw.	3
30	"local an?esthesia transperineal".tw.	2
31	"general an?esthetic transperineal".tw.	1
32	"general an?esthesia transperineal".tw.	1
33	(LATP adj5 (biops* or prostat*)).tw.	2
34	(transperineal adj2 biops* adj12 ("local an?esthesia" or "local an?esthetic")).tw.	22
35	(transperineal adj2 biops* adj12 ("general an?esthesia" or "general	5

	an?esthetic")).tw.	
36	(perineal adj2 biops* adj12 ("local an?esthesia" or "local an?esthetic")).tw.	1
37	(perineal adj2 biops* adj12 ("general an?esthesia" or "general an?esthetic")).tw.	1
38	(("transrectal ultraso*" or TRUS) adj2 biops* adj12 ("local an?esthesia" or "local an?esthetic")).tw.	29
39	"cognitive MRI-targeted biops*".tw.	7
40	"cognitive fusion biops*".tw.	19
41	or/13-40	873
42	12 or 41	6225
43	5 and 42	1058
44	limit 43 to english language	903

11.2. Appendix 2 Draft data extraction form for systematic review of test accuracy and clinical effectiveness

NB. this draft template may undergo changes to its structure and format, where appropriate, to suit the specific type(s) of data to be extracted from included studies

Reference and design	**Diagnostic tests**	**Participants**	**Outcome measures**
First author: **Publication year:** **Country:** **Study design:** **Number of centres:** **Funding:** **Competing interests:**	**Condition being diagnosed / detected:** **Index test/intervention:** **Reference standard/comparator:** **Intervention:** **Comparator:**	**Number of participants:** **Sample attrition/dropout:** **Selection of participants:** **Inclusion criteria for study entry:** **Exclusion criteria for study entry:**	**Primary outcome of study:** **Other relevant outcomes:** **Diagnostic threshold:** **Recruitment dates:**
Participant characteristics			
Age, years, mean (SD)			
PSA level			
Previous biopsy experience			
Lesion location (posterior, anterior, basal, apical)			
MRI performed and Likert or PI-RADs score			
Other key patient characteristics (list, e.g. prostate volume)			
Clinician's experience and training in prostate biopsy			
Sample size calculation			
Results *(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

Cancer detection rates	
Clinically significant cancer detection rates	
Clinically insignificant cancer detection rates	
Low, medium, high risk cancer detection rates	
Interpretability of test	
Inter-observer agreement	
Intra-observer agreement	
OTHER INTERMEDIATE OUTCOMES	
Biopsy sample suitability/quality	
Number of biopsy samples taken	
Procedure completion rates	
Re-biopsy events within 6 months	
Length of time to perform the biopsy	
CLINICAL OUTCOMES	
Hospitalisation events after biopsy	
Rates of biopsy related complications, including infection, sepsis and haematuria.	
Rates of urinary retention	
Rates of erectile dysfunction	
Survival	
Progression free survival	
Adverse events from treatment	
PATIENT REPORTED OUTCOMES	
Health related quality of life	
Patient reported tolerability	

11.3. Appendix 3 Relevance and credibility checklist for full economic evaluations

Questions in this checklist are based on the ISPOR checklist[36] and Philips and colleagues[37] checklist

	Item	Study ID	Comments
RELEVANCE			
1	Is the population relevant? *E.g., demographics, risk factors, medical condition…*		
2	Are any critical interventions missing?		
3	Are any relevant outcomes missing?		
4	Is the context (settings and circumstances) applicable? *E.g., geographic location, health care system, time horizon, perspective of analysis, discount rate…*		
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?		
Data inputs			
2	Are the data inputs for the model described and justified?		
Uncertainty			
3	Has uncertainty been assessed?		
Validation			
4	Has the model been validated?		
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*.			

11.4. Appendix 4 Input parameters used in the NG131 economic model

Parameters		Source
Diagnostic accuracy		
Sensitivity of TRUS		Ahmed (2017) [38]
Diagnostic accuracy for follow-up screening procedures		From clinical evidence review
Natural history		
Probability of developing low-risk prostate cancer		Andriole (2010) [39] Schoots (2015) [40] Roehl (2002) [41] Brown (2018) [42]
Parameters used in model calibration for undiagnosed cases		
Mean age		Bill-Axelson (2014) [43]
Metastases cumulative incidence at 18 years		
Parameters used in model calibration for diagnosed cases		
Low, intermediate and high risk	Mean age	Gnanapragasam (2016) [44]
	Prostate cancer death cumulative incidence at 10 years	
Metastases	Median age (IQR)	James (2016) [45]
	Overall mortality at 43 months (ADT arm)	
	Overall mortality at 43 months (ADT + docetaxel arm)	
Probability of developing symptoms for people undiagnosed		
People without prostate cancer or low-risk prostate cancer at 1 year		Kirby (2003) [46]
Intermediate or high-risk prostate cancer at 5 years		Studer (2006) [47]
Metastatic at 22 months		James (2016) [45]
Complications from prostate biopsy and treatments		
Adverse events associated with TRUS biopsy		
Hospital admission		Rosario (2012) [48]
Reasons for hospital admission		
Urinary infection		Nam (2010) [49]
Urinary bleeding		Nam (2010) [49]
Urinary obstruction		Nam (2010) [49]
Sepsis		Hoeks (2012) [50]
Adverse events associated with radical prostatectomy		
Erectile dysfunction		Donovan (2016) [51]
Urinary incontinence		Donovan (2016) [51]
Bowel dysfunction		Donovan (2016) [51]
Adverse events associated with radical radiotherapy		
Erectile dysfunction		Donovan (2016) [51]
Urinary incontinence		Donovan (2016) [51]
Bowel dysfunction		Donovan (2016) [51]
Adverse events associated with ADT plus docetaxel		
Erectile dysfunction		James (2016) [45]
Febrile neutropenia		James (2016) [45]
Neutropenia		James (2016) [45]
General disorders		James (2016) [45]
Musculoskeletal disorders		James (2016) [45]

Gastrointestinal disorders		James (2016) [45]
Urinary infection		James (2016) [45]
Respiratory disorders		James (2016) [45]
Cardiac disorders		James (2016) [45]
Nervous system disorders		James (2016) [45]
Resource use and costs		
PSA measure		Mowatt (2013) [52]
Resources used for mpMRI		
Radiographer 1		Mowatt (2013) [52]
Radiographer 2		Mowatt (2013) [52]
Consultant		Mowatt (2013) [52]
Equipment cost per patient		Mowatt (2013) [52]
Administration and consumable cost per patient		Mowatt (2013) [52]
Resources used for TRUS		
TRUS only		NHS reference costs 2016/17 [53]
Histopathology		Nicholson (2015) [54]
General practitioner		Rosario (2012) [48], PSSRU 2017 [55]
Specialist nurse		Rosario (2012) [48], NHS reference costs 2016/17
Other NHS direct		Rosario (2012) [48], Mowatt (2013) [52]
Transperineal template biopsy		NHS reference costs 2016/17 [53]
Treatments or strategies used in the model for localised disease when diagnosed		Gnanapragasam (2016) [44]
Active surveillance	PSA test every 3 months for first year	Ramsay (2015) [56], Mowatt (2013) [52]
	DRE every 6 months	Ramsay (2015) [56], PSSRU 2017 [55]
	Nurse-led outpatient appointments every 3 months for first year	Ramsay (2015) [56], PSSRU 2017 [55]
Brachytherapy		NHS reference costs 2016/17 [53]
External radiotherapy		NHS reference costs 2016/17 [53]
Radical prostatectomy		NHS reference costs 2016/17 [53]
First surgery consultation appointment		NHS reference costs 2016/17 [53]
Follow-up surgery consultation appointment		NHS reference costs 2016/17 [53]
Hormone therapy	Decapeptyl 11.25 injection	Mowatt (2013) [52], BNF [57]
	Delivered by a practice nurse	Mowatt (2013) [52], PSSRU 2017 [55]
	Bicalutamide 50	Mowatt (2013) [52], BNF [57]
Treatments used in the model for metastases when diagnosed (including costs of related adverse events)		James (2016) [45]
Docetaxel for age less than 60		Woods (2018) [58]

Docetaxel for age 60-64	Woods (2018) [58]
Docetaxel for age 65-69	Woods (2018) [58]
Docetaxel for age greater than 69	Woods (2018) [58]
Further life extending treatments used in the model for metastases in hormone resistant stage	De Bono (2011) [59], James (2016) [45]
Abiraterone 250mg	BNF BNF [57]
Docetaxel for age less than 60	Woods (2018) [58]
Docetaxel for age 60-64	Woods (2018) [58]
Docetaxel for age 65-69	Woods (2018) [58]
Docetaxel for age greater than 69	Woods (2018) [58]
Adverse events associated with biopsy and treatments	
Urinary infection	NHS reference costs 2016/17 [53]
Urinary bleeding	NHS reference costs 2016/17 [53]
Urinary obstruction	NHS reference costs 2016/17 [53]
Sepsis	NHS reference costs 2016/17 [53]
Erectile dysfunction	NHS reference costs 2016/17 [53]
Urinary incontinence	NICE CG175 [60]
Bowel dysfunction	NICE CG175 [60]
Neutropenia	NHS reference costs 2016/17 [53]
Musculoskeletal disorders	NHS reference costs 2016/17 [53]
Gastrointestinal disorders	NHS reference costs 2016/17 [53]
Respiratory disorders	NHS reference costs 2016/17 [53]
Cardiac disorders	NHS reference costs 2016/17 [53]
Nervous system disorders	NHS reference costs 2016/17 [53]
Resources used for monitoring high-risk and metastases	
Computerised tomography scan	NHS reference costs 2016/17 [53]
Bone scan	NHS reference costs 2016/17 [53]
Health-related quality of life	
People with no cancer/localised prostate cancer	Kind (1999) [61]
Decrement associated with metastases	Torvinen (2013) [62]
Decrement associated with template prostate mapping biopsy (2 weeks)	Brown (2018) [42]
Decrement associated with TRUS (2 weeks)	Heijnsdijk (2012) [63], Li (2016) [64]
QALY loss due to transition to true positive (low risk)	Donovan (2016) [51], Mowatt (2013) [52]
QALY loss due to transition to true positive (intermediate	Donovan (2016) [51], Mowatt

risk)	(2013) [52]
QALY loss due to transition to true positive (high risk)	Donovan (2016) [51], Mowatt (2013) [52]
ADT, androgen deprivation therapy; DRE, digital rectal exam; mpMRI, multiparametric magnetic resonance imaging; NHS, National Health Service; PSA, prostate specific antigen; QALY, quality-adjusted life years; TRUS, transrectal ultrasound biopsy.	