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

Produced by Southampton Health Technology Assessments Centre (SHTAC)

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Declared competing interests of the authors

The authors declare none.

1. Page 2 – an amendment was made to Alistair Grey's academic designation from:
"Division of Surgical and Interventional Sciences, University College London, London, UK."
To
"University College London Hospital, London, UK."
2. Page 6 – the manufacturer and location of the EZ EZU-PA3U freehand device was added for consistency with the other devices listed. "EZU-PA3U (Hitachi Ltd, Tokyo, Japan)"
3. Page 48 We revised the sentence to correct a typo and improve readability, from:
"Likewise, we examined the evidence submissions to NICE from companies associated with manufacture and/or distribution of the freehand transperineal biopsy devices"
To:
"Likewise, we examined the evidence submissions to NICE from manufacturers and/or distributors of the freehand transperineal biopsy devices"
4. Page 50 we corrected a typo for the word "title" from:
"At the second stage of screening one reviewer screened the full texts of references judged potentially relevant on tile and abstract screening"
To:
"At the second stage of screening one reviewer screened the full texts of references judged potentially relevant on title and abstract screening
5. Page 63
We added the author name and year for reference 28 for consistency with other reference citations. The relevant sentence was revised from:
"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])"
To:
"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 Bojin 2019[28], Chen et al 2021 [29], Kum et al 2018 [32])"
6. Page 73
We corrected an error in the first sentence, in which the word 'gave' had been omitted. From:
"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 2)".*

To:

“Available information on the characteristics of study participants (e.g. age, PSA level, prostate volume) is extremely limited, and only one study[38] gave adequate detail (*Table 2).”*

7. Page 73

We corrected an incorrect table reference in the final sentence, from:

“All freehand devices are the PrecisionPoint™ device. See Table 9”

To:

“All freehand devices are the PrecisionPoint™ device. See Table 10”

8. Page 74

We corrected an incorrect table reference in the first sentence, from:

“In contrast, only one study compares LATP biopsy using a specific freehand device with GATP (n=1, PrecisionPoint™ device), see Table 10 below”

To:

“In contrast, only one study compares LATP biopsy using a specific freehand device with GATP (n=1, PrecisionPoint™ device), see Table 12 below”

9. **Page 74**

We corrected an incorrect table reference at the end of the second paragraph, from:

“See Table 11 below”

To:

“See Table 13 below”

10. Page 85

We removed rows from the table for two studies which had been included in the table by error – Takuma et al 2012 and Walters et al 2021.

11. Page 88

An error in the penultimate sentence was corrected to t the order of GATP and LATP-any. From:

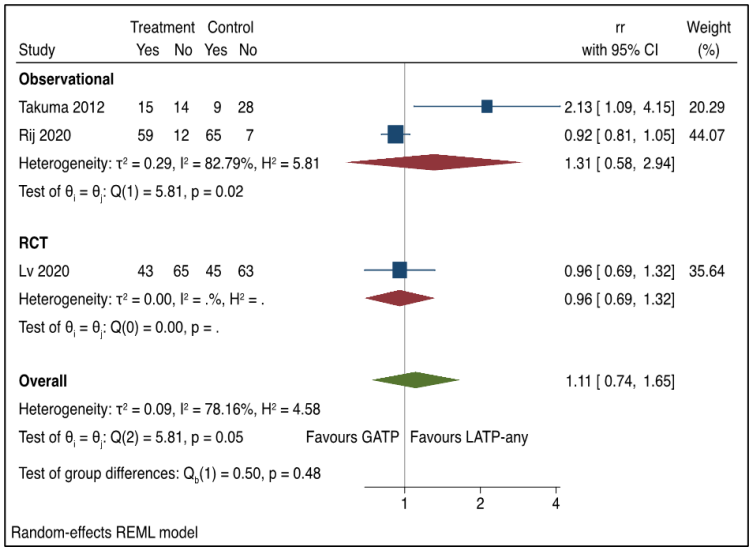
“There was some inconsistency between the studies in the direction of effects, with two studies marginally favouring GATP (Lv et al 2020 [38]; Rij et al 2020 [41]) and another (smaller) study showing a large effect in favour of LATP-any (Takuma et al 2012 [39]).”

To:

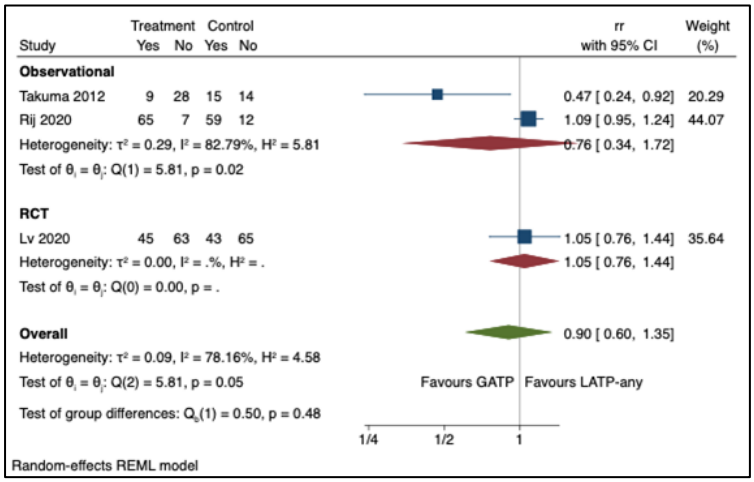
“There was some inconsistency between the studies in the direction of effects, with two studies marginally favouring LATP-any (Lv et al 2020 [38]; Rij et al 2020 [41]) and another (smaller) study showing a large effect in favour of GATP (Takuma et al 2012 [39]).”

12. Page 89

Figure 6 was corrected due to the numbers in the ‘Treatment’ and ‘Control’ columns mistakenly entered the wrong way round. The figure was updated from:



To:



13. Page 91

The first paragraph was corrected due to a formatting error which left the sentences making no sense. From:

“The remaining study4.8.1)ehand 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”

To:

“Cancer detection rates, including clinically significant cancer rates (where available), for six of the seven studies comparing LATP-freehand versus LATRUS are reported in Table 5 (NB. The remaining study (Starmer et al), did not report cancer detection as an outcome. The PrecisionPoint™ freehand device was evaluated in all six studies, and collectively the studies comprise a sub-set of LATP-any studies for decision question 1 presented earlier (section 4.8.1)”

14. Page 92

A typo in the word ‘biopsy’ in the final paragraph was corrected, from:

“As decision question 2 focuses on LATP-freehand device biopsy, to permit incremental assessment of biosy effects in our economic model we considered splitting the ‘LAPT-any’ study category into respective biopsy subtypes”

To:

“As decision question 2 focuses on LATP-freehand device biopsy, to permit incremental assessment of biopsy effects in our economic model we considered splitting the ‘LAPT-any’ study category into respective biopsy subtypes”.

15. Page 103

The word ‘feint’ in the second sentence was replaced with ‘faint’ to convey the intended meaning of the term in this context. From:

“Observation of the data gives a feint suggestion that bleeding is potentially worse for GATP biopsy grid & stepping device than LATP-any biopsy”

To:

“Observation of the data gives a faint suggestion that bleeding is potentially worse for GATP biopsy grid & stepping device than LATP-any biopsy”

16. Page 106

The second column in Table 34 for the study by Cerruto et al 2014 23 erroneously included the footnote ‘a’ with no explanation of what this referred to. The footnote has been deleted.

17. Page 200

An error in the second paragraph, second sentence was corrected to state that ICERs were increasing rather than reducing. From:

“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.

To:

“These are less favourable for LATP-freehand than the base case, increasing the ICERs compared with LATRUS, although they remain below £30,000 per QALY for subgroups A and B.”

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Professor Mark Emberton, Professor of interventional oncology, Division of Surgery and Interventional Science, University College London, London, UK

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We thank Joshua Pink and the NICE Guideline Update Team who developed the NG131 economic model which informed development of the model for this assessment, and also to the NICE Centre for Guidelines for sharing the model.

We thank the NICE Diagnostic Assessment Programme team for their assistance during the assessment.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

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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 (Hitachi Ltd, Tokyo, Japan); PrecisionPoint™ Transperineal Access System (BXTAccelyon Ltd, Burnham, UK); SureFire Guide (LeapMed, Jiangsu, China); Trinity®

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 manufacturers and/or distributors 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 ***Error! Reference source not found.***

3.2 Inclusion and exclusion criteria

The predefined inclusion and exclusion criteria are based on the decision problem as outlined earlier in chapter **Error! Reference source not found.**, and are described below. An extended PICO tabulation of these criteria is included in **Error! Reference source not found.**. 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’)

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 **Error! Reference source not found.**).

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 ***Error! Reference source not found.***). Any disagreements between reviewers in judgements about study eligibility were resolved through discussion or with the opinion of a third reviewer where necessary.

At the second stage of screening one reviewer screened the full texts of references judged potentially relevant on title and abstract screening. A second reviewer checked the first reviewer's judgement on eligibility based on the full text. The reviewers discussed any discrepancies in judgement and before agreeing a final decision to include or exclude the

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 Bojin 2019[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

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

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]gave adequate detail (*Table 2).*

Table 2 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 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 10

below. In contrast, only one study compares LATP biopsy using a specific freehand device with GATP (n=1, PrecisionPoint™ device), see Table 12 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 13 below.

Table 3 gives an overview of the LATP-PrecisionPoint™ vs LATRUS biopsy studies.

Table 3 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

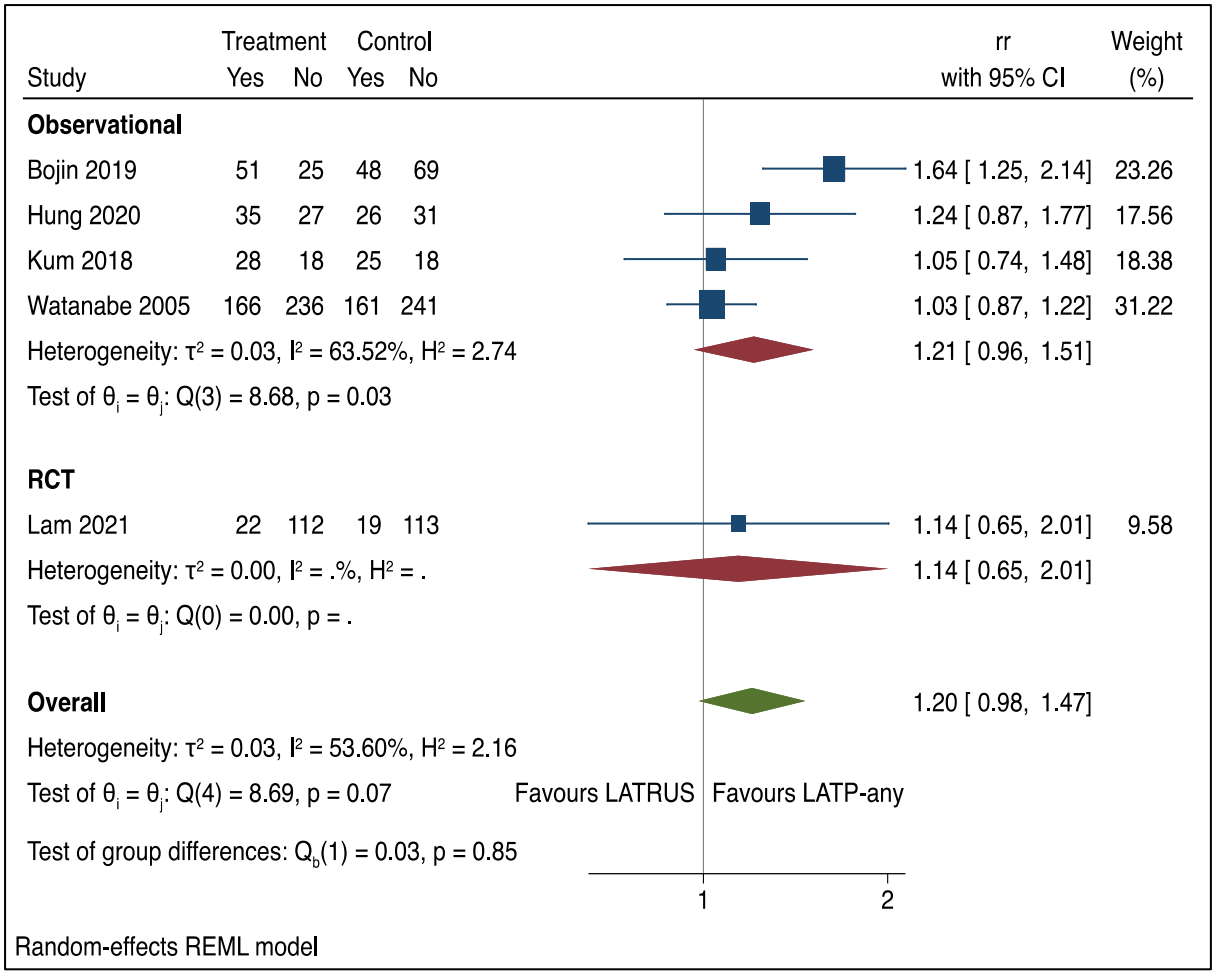
	Clinically significant cancer detection rate[a]	22/134 (16.4)	19/132(14.4)	p=0.74
Takenaka et al 2008 [27]	Cancer detection rates overall, n/N (%)	47/100 (47)	53/100 (53)	0.333
Other prospective studies				
Bojin (2019) [28]	Cancer detection rates malignant, n/N (%)	76/103 (73.7)	117/189 (61.9)	Not reported
	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
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



REML = Random effects maximum likelihood

Figure 1 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 4 reports study cancer detection rates from the four studies which compared LATP-any biopsy versus GATP biopsy using grid and stepping device, and

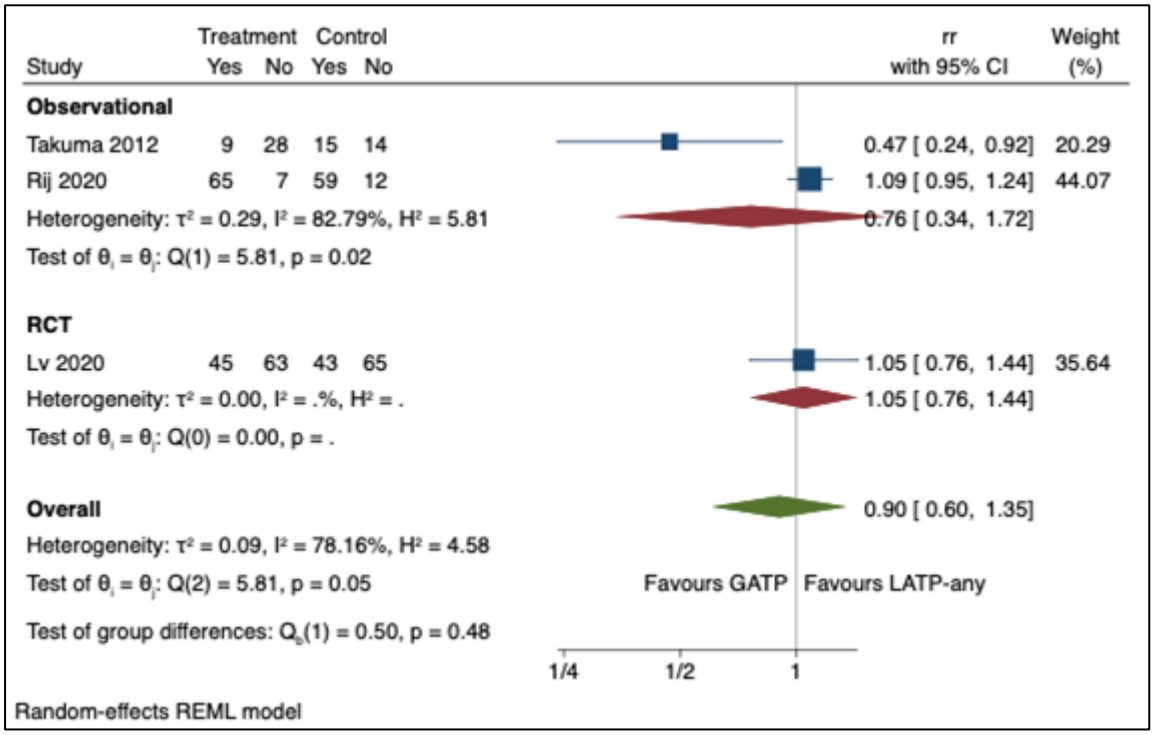


Figure 2 shows a meta-analysis forest plot containing three of the four studies (NB. The study publication by Walters et al 2021 did not provide numerical cancer detection rates and was therefore not included in the meta-analysis [40]). There was some inconsistency between the studies in the direction of effects, with two studies marginally favouring LATP-any (Lv et al 2020 [38]; Rij et al 2020 [41]) and another (smaller) study showing a large effect in favour of GATP (Takuma et al 2012 [39]). Overall, there is no statistically significant difference between the two biopsy modalities in detection of prostate cancer.

Table 4 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 [40]	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

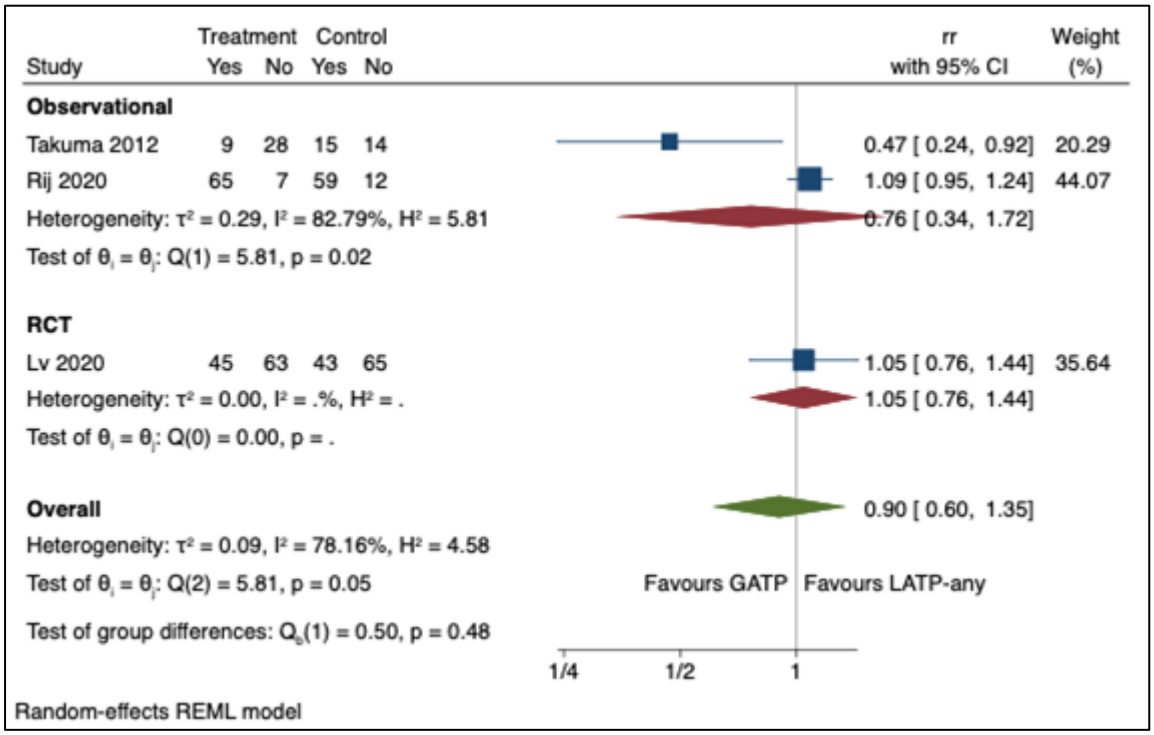
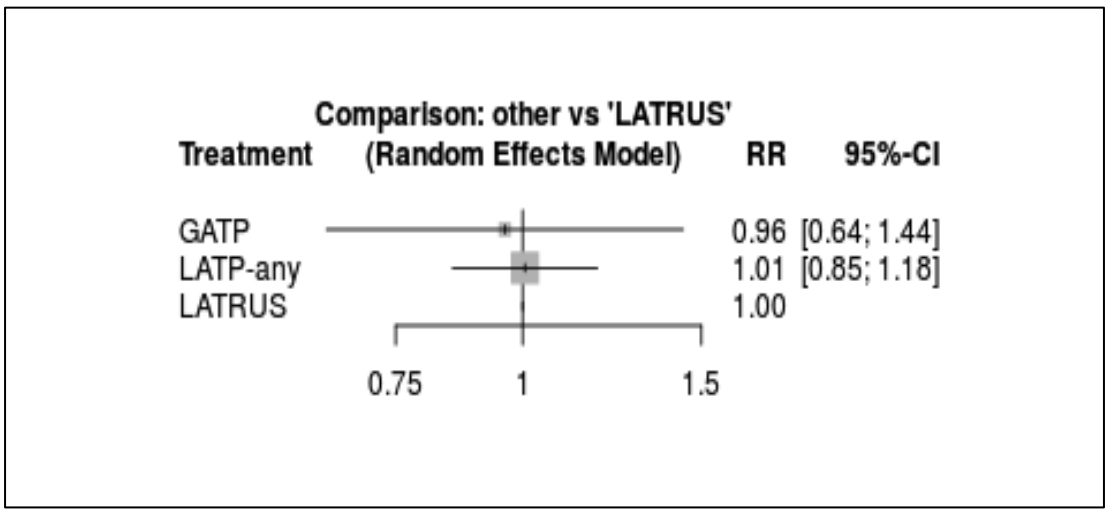


Figure 2 Meta-analysis forest plot of cancer detection rates for LATP-any vs GATP grid and stepping device (decision question 1)

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 (**Error! Reference source not found.Error! Reference source not found.**). The NMA provides an indirect comparison between LATP-



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

Figure 3 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 in Table 5 (NB. The remaining study (Starmer et al), did not report cancer detection as an outcome. The PrecisionPoint™ freehand device was evaluated in all six studies, and collectively the studies comprise a sub-set of LATP-any studies for decision question 1 presented earlier (section 4.8.1)

Table 5 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
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
	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 (*Error! Reference source not found.*). 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 biopsy effects in our economic model we considered splitting the 'LAPT-any' study category into respective biopsy subtypes, i.e. LATP-freehand, LATP grid and stepping device and LATP coaxial needle (double freehand). 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

	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 6). Observation of the data gives a fant 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 6 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				

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 7**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 7 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, 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 8 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

, **Error! Reference source not found.**, and **Error! Reference source not found.**) 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 8 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

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 9 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	£15,314	9.4783					
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

Error! Reference source not found. shows the scenario results for decision question 2. These are less favourable for LATP-freehand than the base case, increasing 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.