PharmacoEconomics - Open (2021) 5:737–753
https://doi.org/10.1007/s41669-021-00277-4

ORIGINAL RESEARCH ARTICLE

Economic Evaluation of Transperineal versus Transrectal Devices for Local Anaesthetic Prostate Biopsies

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Accepted: 31 May 2021 / Published online: 9 July 2021

Abstract

Background Biopsy of the prostate for suspected cancer is usually performed transrectally under local anaesthesia in the outpatient clinic setting. As this involves piercing the bowel wall, the procedure is associated with a risk of infection. Recently, devices that facilitate transperineal biopsy approaches have been developed that avoid piercing the bowel and so should reduce the risk of infection.

Objective The aim of this study was to estimate the cost effectiveness of transperineal versus transrectal ultrasound-guided local anaesthesia procedures for prostate biopsy from the perspective of the UK NHS and to estimate the value of further research in the area.

Methods a) Decision tree and Markov model synthesising all relevant evidence estimating the life-time costs and QALYs accrued from each biopsy mode. b) Value of information analysis to predict the return from further research and thus guide future research efforts.

Results Transperineal biopsy yields an ICER below £20,000 per QALY gained at a per-procedure device acquisition cost below £81, or £41 for cost-neutrality. These results are driven by differences in consumables cost, reduced cost of treating infections, and QALY gains associated with reduced infections. There is value in future research on the diagnostic accuracy of transperineal versus transrectal biopsies and the incidence of iatrogenic infection and sepsis; consideration should be given to enriching the patient population with men with intermediate-risk disease.

Conclusions Transperineal biopsy devices may be cost effective compared with transrectal biopsy at per-procedure acquisition costs below £81 and cost-neutral if under £41. Future research is required to confirm or refute these findings, particularly randomised comparisons of the diagnostic accuracy and infection risks between the methods.

1 Introduction

Prostate cancer is the fourth most common cancer globally, with an estimated 1.8 m cases world-wide in 2018 [1] and 48,500 cases in the UK every year [2]. Current practice for the diagnosis of prostate cancer is for referred men to undergo a multiparametric MRI scan, followed by a transrectal ultrasound-guided biopsy (TRUSBx) [3]. However TRUSBx is not without risk, with an incidence of sepsis of

Key Points for Decision Makers

Subject to a number of assumptions and based on current information, we estimate that transperineal biopsies are cost effective compared with transrectal as long as the per-procedure acquisition cost is below £81.

Future research should focus on comparative diagnostic accuracy and infection risk, focusing particularly on men with intermediate-risk disease.

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around 1%, and other less serious complications occurring with greater frequency [3]. The cause of infection is most likely due to piercing of the bowel wall with the biopsy needle, before insertion into the prostate to retrieve the sample. To address this, there has been a move to perform prostate biopsies using the much more sterile transperineal route [4]. These 'template biopsies' (making use of a grid placed over the perineum to guide needle insertion points) usually necessitate general anaesthesia (GA) with significant attendant costs. To overcome this, devices have been developed to permit transperineal biopsies (TPUSBx) to be performed under local anaesthesia (LA) and hence be more suited to the outpatient clinic setting [5–7]. To date however, it is not known how cost effective these devices are, especially given the relatively low cost and wide availability of the transrectal biopsy method.

Here we investigated the cost effectiveness of TPUSBx devices compared with TRUSBx in the diagnosis of prostate cancer in a UK secondary care setting from the perspective of the UK National Health Service (NHS). As a case study, we used the novel Cambridge Prostate Biopsy (CamPROBE) device, which has been recently evaluated for clinical effectiveness and safety [7]. The CamPROBE is based on the concept of a co-axial cannula, but designed specifically for transperineal prostate biopsies under LA. The device and how it is used can be seen at https://www.youtube.com/watch?v=Q3XYLq5po8s&t=196s. Although we have used this device in this analysis, our findings should be broadly transferable to any TPUSBx device.

2 Method

We developed a decision model comprising a decision tree with Markov models at the terminal nodes. Data informing the decision model were taken from a prospective case series representing the first rigorous data on the safety and acceptability of the CamPROBE [7], and other data from the literature to inform the likely cost effectiveness of the device, at various price points. We also conducted a value of information analysis (VoI) to guide the direction of further research to reduce uncertainty as to the cost effectiveness of TPUSBx devices.

The design of the model mirrors the clinical diagnostic pathway (described below) to compare the expected lifetime costs and QALYs accrued with TPUSBx and TRUSBx.

2.1 Clinical Diagnostic Pathway: Current Management

Men presenting in primary care for suspected prostate cancer are typically offered a prostate-specific antigen (PSA) test. If sufficiently raised and concerning [8], patients are referred to secondary care. Current (2019) NICE guidance [3] recommends multiparametric MRI (mpMRI) as first-line investigation of men with suspected localised prostate cancer. Results are reported on a five-point Likert scale (PI-RADS score); those scoring 3 or more are recommended biopsy (TRUSBx) using the results of the MRI to inform placing of the needle. Those scoring 1 or 2 may omit a biopsy, or be offered systemic prostate biopsy (i.e. sampling a wide area of the prostate rather than focusing on anomalies identified in the MRI scan).

For those with MRI Likert of ≥ 3 but a negative biopsy, repeat biopsy might be considered. For those with a raised PSA but MRI Likert of 1 or 2 who have not had a biopsy, or for whom the biopsy was negative, the PSA test may be repeated at 3–6 months and biopsy offered if there is ongoing strong suspicion of cancer. Alternatively, the patient can be discharged to primary care with referral if pre-determined PSA thresholds are reached. Treatment options for localised cancer include active surveillance, radical prostatectomy or radical radiotherapy depending on prognosis.

Much of the current NICE guidance on the appropriate diagnostic pathway is based on a recent decision model comparing many permutations of testing strategies, comprising combinations of one or two TRUSBx or template-guided biopsies (under GA), with and without mpMRI (Faria et al. [9]). This model itself draws on data from a large trial of MRI imaging and biopsy in diagnosing prostate cancer (the diagnostic Prostate MR Imaging Study, PROMIS [10]), *inter alia*. The cost-effective pathway is mpMRI first line, followed by mpMRI-guided TRUSBx where clinically significant cancer is suspected, followed by a second TRUSBx if the first is negative (strategy 'M7' of Faria et al. [9]).

2.2 Modelled Clinical Diagnostic Pathway and Structure

In this analysis, we replicated strategy M7 as modelled by Faria et al. [9], but added TPUSBx as a comparator strategy in place of TRUSBx, and included the cost and consequences of adverse events such as fever and sepsis associated with TRUSBx (Fig. 1). Entry point into the model is referral to secondary care. In the TRUSBx arm (status quo), a man referred has a probability of having either clinically significant cancer (which is defined as either high or intermediate risk), clinically non-significant cancer or no cancer, according to the prevalence in the referred population. Firstline diagnostic is mpMRI, the results of which are either negative (i.e. no cancer), clinically non-significant or clinically significant.

A man with an mpMRI result of no cancer or clinically non-significant cancer is discharged to routine follow-up and exits the model. A man diagnosed with clinically significant

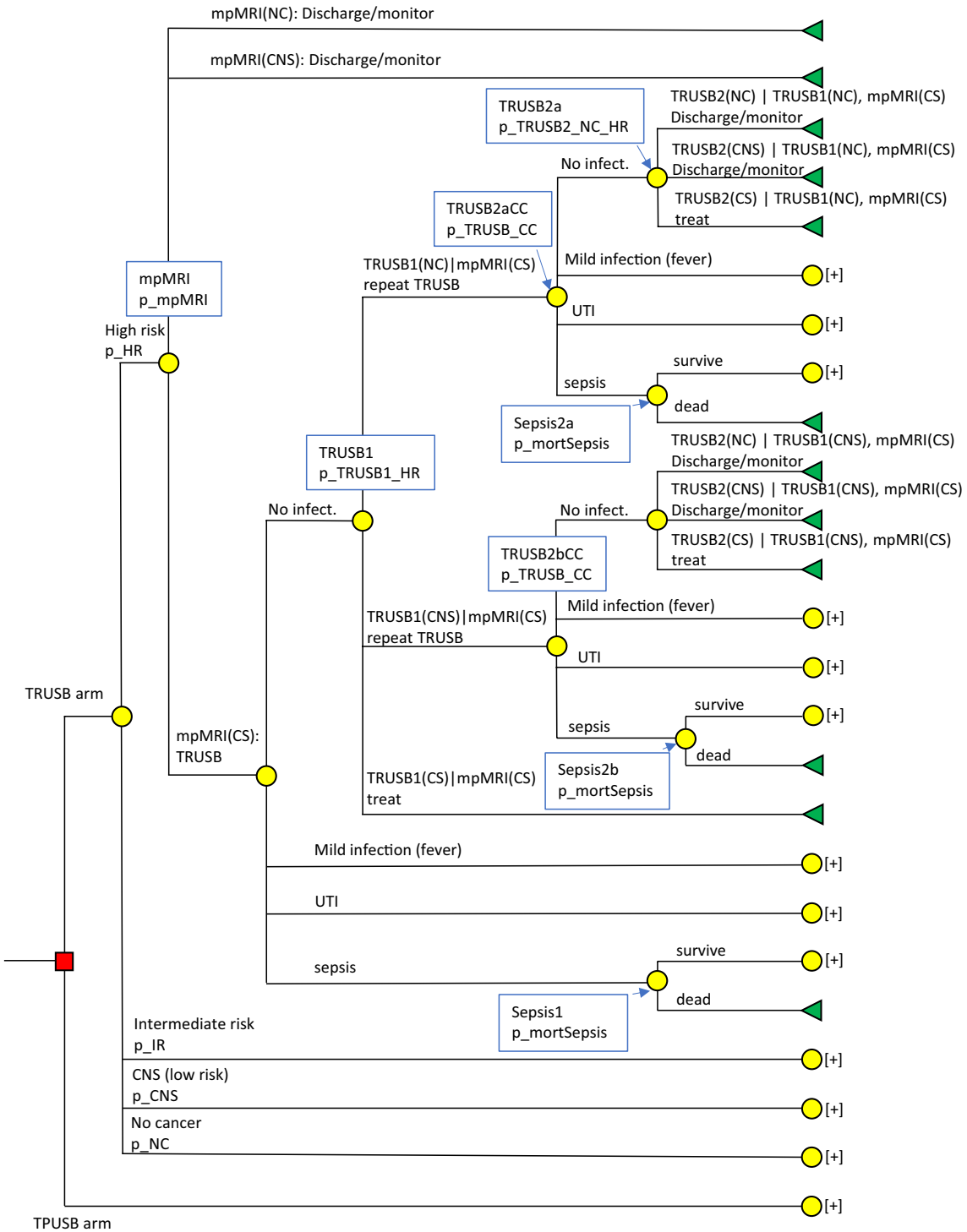


Fig. 1 Decision tree structure. *CNS* clinically non-significant, *CS* clinically significant, *HR* high risk, *IR* intermediate risk, *mpMRI* multi-parametric magnetic resonance imaging, *NC* no cancer, *TPUSBx* transperineal ultrasound-guided biopsy, *TRUSBx* transrectal ultrasound-guided biopsy, *UTI* urinary tract infection

cancer by mpMRI undergoes transrectal ultrasound-guided biopsy (TRUSBx), with an associated risk of fever, urinary tract infection (UTI), sepsis (with risk of death), or no infection. As per mpMRI, the result of the TRUSBx can be either no cancer, clinically non-significant or clinically significant. A man with a clinically significant TRUSBx result enters the treatment pathway, whilst a man with clinically non-significant or no cancer is given a repeat TRUSBx (with

associated infection risks), for which the results can again be no cancer, clinically non-significant or clinically significant.

A man with a positive mpMRI followed by two negative biopsies (either no cancer or clinically non-significant) is discharged to routine follow-up and exits the model. A man with a positive mpMRI, a negative first biopsy (no cancer or clinically non-significant), and a positive second biopsy enters the treatment pathway.

The structure of the model is identical for a man presenting with high, intermediate, low risk or no cancer, but the conditional probabilities (e.g. diagnostic accuracy of TRUSBx) and long-term cost and consequences vary (long-term model described below). Likewise, the structure of the model for the TPUSBx arm is identical, except populated with different probabilities of infection and procedure cost (see model inputs below and Table 1).

Long-term costs and outcomes were calculated from Markov models appended to the terminal nodes dividing disease into 'progression free', 'metastatic disease' and dead (Fig. 2). Transition probabilities, costs and health state utilities were assigned from the literature (Table 1), with a transition period of 1 year. Six possible scenarios were estimated, dependent on the true state of the disease and the subsequent treatment strategy. For men with no cancer, no further monitoring was assumed, and lifetime QALYs calculated based on UK lifetable statistics (scenario 'no cancer'). For men diagnosed with clinically non-significant cancer, a strategy of active surveillance was assumed, comprising one urology follow-up appointment and three PSA tests per annum (scenario 'clinically non-significant'). Transition probabilities reflected the possibility of this becoming metastatic disease in the future (intermediate cancer stages are not explicitly modelled). For men with intermediate-risk and high-risk disease, the treatment strategy could be either active surveillance or radical prostatectomy (scenarios 'intermediate-risk active surveillance', 'intermediate-risk radical prostatectomy', 'high-risk active surveillance' and 'high-risk radical prostatectomy').

The relevant scenario lifetime costs and outcomes were appended to the terminal nodes of the decision tree: patients with no cancer were discharged back to primary care (scenario 'no cancer'). Patients with clinically non-significant cancer were assigned to the active surveillance strategy (scenario 'clinically non-significant'). Patients with correctly identified intermediate- and high-risk cancers were assigned to the respective radical prostatectomy strategy ('intermediate-risk radical prostatectomy' or 'high-risk radical prostatectomy' scenarios); and those whose cancers were misdiagnosed as clinically non-significant or no cancer were assigned to the intermediate- and high-risk active surveillance strategy/scenarios, respectively.

2.3 Model Inputs

Chance node probabilities and associated hyperparameters as well as health state utilities were replicated from the same sources as Faria et al. [9] (see Table 1). Key inputs included the sensitivity and specificity of mpMRI and first and second TRUSBx, which were extracted from the PROMIS study [10] (published 2017) and a 2015 systematic review [11]. These data suggested the sensitivity of both mpMRI and TRUSBx is 1 in the presence of high-risk cancer; that is, a high-risk cancer will never be misdiagnosed, whilst diagnosis of clinically non-significant cancer and intermediate-risk cancer carries a risk of misdiagnosis as per Table 1. After Faria et al. [9], we assumed perfect specificity of TRUSBx (i.e. a patient with no cancer will always be correctly diagnosed), but imperfect sensitivity as per Table 1. Dirichlet, Connor-Mosimann or modified Connor-Mosimann distributions were fitted [12] to the summary statistics reported in Faria et al. [9], which were then inserted into the model (see Appendix 1 in the Electronic Supplementary Material [ESM]). Note, as there are three possible outcomes from the biopsy (no cancer, clinically non-significant or clinically significant), there is no single measure of 'sensitivity' or 'specificity' as such, but probabilities of one of the three results, conditional on the true disease state. From hereon we refer to these measures as 'diagnostic accuracy'.

We assigned the same probability distributions to the TPUSBx diagnostic accuracy as TRUSBx. The implied assumption of this is that on average we expect there to be no difference between the two methods in these parameters, but as the distributions are modelled independently, the sensitivity and specificity can each vary according to current levels of uncertainty.

The risk of infection associated with TRUSBx was extracted from the treatment arm of a Cochrane systematic review of the effects of antibiotic prophylaxis for TRUSBx [13], and mortality from sepsis was estimated [14] from US Surveillance, Epidemiology and End Results (SEER) data [15]. Our base case assumed a zero risk of infection associated with TPUSBx. This was based on the prospective case series of 40 TPUSBxs from the recent CamPROBE published results [7].

To estimate long-term model transition probabilities, parametric distributions were fitted [12] to the summary statistics reported in Faria et al. [9] (see Appendix 1 in the ESM). Incidence of adverse events following radical prostatectomy and active surveillance were extracted from a randomised controlled trial (RCT) of the two modalities [16], converted to 1-year probabilities.

Unit costs were extracted from routine NHS unit cost sources [17–19] for the price year 2018–19. The unit cost of the TPUSBx and TRUSBx procedures was based on a microcosting exercise (Appendices 2 and 3, see ESM). As this is a small sample from one centre only and the price of

Table 1 Model inputs

Parameter	Parameter name	Mean	LCL	UCL	Dbn	Param1	Param2	Param3	Param4	Source
Prevalence of CaP										
No cancer	prev_CaP	27.94%			D	159	91	301	18	PROMIS [10], as reported in Faria et al. [9] supplementary table 5
Non-clinically significant		15.99%			–					
Intermediate risk		52.90%			–					
High risk		3.16%			–					
mpMRI findings, given true cancer state										
mpMRI(NC)|NC	p_mpMRI_NC	0.33	0.26	0.4	mCM	38.297	85.127	0.063	0.915	PROMIS [10], as reported in Faria et al. [9] supplementary table 7, Definition 2, cutoff 3
mpMRI(CNS)|NC		0.17	0.11	0.23	–	20.928	36.905	0.005	0.681	
mpMRI(CS)|NC		0.5	0.43	0.58	–	0.000	0.000	0.000	0.000	
mpMRI(NC)|CNS	p_mpMRI_CNS	0.28	0.19	0.38	D	22.736	12.718	45.976		
mpMRI(CNS)|CNS		0.16	0.08	0.24	–					
mpMRI(CS)|CNS		0.56	0.46	0.67	–					
mpMRI(NC)|IR	p_mpMRI_IR	0.08	0.05	0.11	mCM	11.902	10.021	0.000	0.148	
mpMRI(CNS)|IR		0.05	0.02	0.07	–	10.734	99.690	0.000	0.504	
mpMRI(CS)|IR		0.87	0.83	0.91	–	0.000	0.000	0.000	0.000	
mpMRI(NC)|HR	p_mpMRI_HR	0	0	0	C	0.000	0.000	1.000		
mpMRI(CNS)|HR		0	0	0	–					
mpMRI(CS)|HR		1	1	1	–					
Complications from TRUSB/TPUSB										
TRUSB—no infection	p_TRUSB_CC1	0.921								Defined as 1-sum (mild, UTI, sepsis)
TRUSB—mild infection	p_TRUSB_CC2	0.042	0.025	0.069	B	13.37	304.99			Zani et al. 2011 [13], P3, SOFT, low risk patients
TRUSB—UTI	p_TRUSB_CC3	0.033	0.020	0.056	B	12.45	364.91			
TRUSB—sepsis	p_TRUSB_CC4	0.004	0.001	0.018	B	0.84	209.99			
TPUSB—no infection	p_TPUSB_CC1	1.000			C	1.000				Assumption
TPUSB—mild infection (fever)	p_TPUSB_CC2	0.000			C	0.000				
TPUSB—UTI	p_TPUSB_CC3	0.000			C	0.000				
TPUSB—sepsis	p_TPUSB_CC4	0.000			C	0.000				
Mortality from sepsis	p_mortSepsis	0.036	0.027	0.052	B	53.19	1424.24			Calculated by Lee et al. 2018 [14] from Loeb et al. 2011 [15]
First mpMRI-targeted TRUSBx and TPUSBx result, given mpMRI result and true cancer state										
T*USB1(NC)|mpMRI(CS),NC	p_T*USB1_NC	1	1	1	C	1.000	0.000	0.000		Assumed perfect specificity as per Faria et al. [9]
T*USB1(CNS)|mpMRI(CS),NC		0	0	0	–					
T*USB1(CS)|mpMRI(CS),NC		0	0	0	–					
T*USB1(NC)|mpMRI(CS),CNS	p_T*USB1_CNS	0.79	0.66	0.89	D	39.815	10.688	0.100		PROMIS [10] & Schoots et al. [11], reported in Faria et al. [9] supplementary table 6, 'test 4 (first biopsy following suspicious mpMRI), definition 2' (row 8 of table)
T*USB1(CNS)|mpMRI(CS),CNS		0.21	0.11	0.34	–					
T*USB1(CS)|mpMRI(CS),CNS		0	0	0	–					

Table 1 (continued)

Parameter	Parameter name	Mean	LCL	UCL	Dbn	Param1	Param2	Param3	Param4	Source
T*USB1(NC)|mpMRI(CS),IR	p_T*USB1_IR	0.15	0.09	0.21	mCM	12.510	31.161	0.009	0.498	PROMIS [10] & Schoots et al. [11], reported in Faria et al. [9] supplementary table 6, 'test 4 (first biopsy following suspicious mpMRI), definition 2' (row 8 of table)
T*USB1(CNS)|mpMRI(CS),IR		0.11	0.06	0.16	–	10.511	43.279	0.000	0.642	
T*USB1(CS)|mpMRI(CS),IR		0.74	0.65	0.84	–	0.000	0.000	0.000	0.000	
T*USB1(NC)|mpMRI(CS),HR	p_T*USB1_HR	0	0	0	C	0.000	0.000	1.000		PROMIS [10] & Schoots et al. [11], reported in Faria et al. [9] supplementary table 6, 'test 4 (first biopsy following suspicious mpMRI), definition 2' (row 8 of table)
T*USB1(CNS)|mpMRI(CS),HR		0	0	0	–					
T*USB1(CS)|mpMRI(CS),HR		1	1	1	–					
Second mpMRI-targeted TRUSBx and TPUSBx result, given first biopsy result, mpMRI result and true cancer state										
T*USB2(NC)|T*USB1(NC),mpMRI(CS),NC	p_T*USB2_NC_NC	1	1	1	C	1.000	0.000	0.000		Assumed perfect specificity as per Faria et al. [9]
T*USB2(CNS)|T*USB1(NC),mpMRI(CS),NC		0	0	0	–					
T*USB2(CS)|T*USB1(NC),mpMRI(CS),NC		0	0	0	–					
T*USB2(NC)|T*USB1(NC),mpMRI(CS),CNS	p_T*USB2_NC_CNS	0.68	0.02	1	mCM	0.818	0.523	0.002	0.991	PROMIS [10] & Schoots et al. [11], reported in Faria et al. [9] supplementary table 6, 'test 5 (second biopsy following negative first biopsy and suspicious mpMRI), definition 2' (row 9 of table)
T*USB2(CNS)|T*USB1(NC),mpMRI(CS),CNS		0.32	0.02	0.91	–	42.340	0.483	0.138	0.944	
T*USB2(CS)|T*USB1(NC),mpMRI(CS),CNS		0	0	0	–	0.000	0.000	0.000	0.000	
T*USB2(NC)|T*USB1(NC),mpMRI(CS),IR	p_T*USB2_NC_IR	0.05	0.02	0.11	D	2.248	4.354	38.923		PROMIS [10] & Schoots et al. [11], reported in Faria et al. [9] supplementary table 6, 'test 5 (second biopsy following negative first biopsy and suspicious mpMRI), definition 2' (row 9 of table)
T*USB2(CNS)|T*USB1(NC),mpMRI(CS),IR		0.08	0.03	0.18	–					
T*USB2(CS)|T*USB1(NC),mpMRI(CS),IR		0.87	0.71	0.95	–					
T*USB2(NC)|T*USB1(NC),mpMRI(CS),HR	p_T*USB2_NC_HR	0.05	0.02	0.11	D	2.185	4.150	37.427		PROMIS [10] & Schoots et al. [11], reported in Faria et al. [9] supplementary table 6, 'test 5' (second biopsy following negative first biopsy and suspicious mpMRI), definition 2' (row 9 of table)
T*USB2(CNS)|T*USB1(NC),mpMRI(CS),HR		0.08	0.03	0.18	–					
T*USB2(CS)|T*USB1(NC),mpMRI(CS),HR		0.87	0.71	0.95	–					

Table 1 (continued)

Parameter	Parameter name	Mean	LCL	UCL	Dbn	Param1	Param2	Param3	Param4	Source
T*USB2(NC)|T*USB1(CNS),mpMRI(CS),NC	p_T*USB2_CNS_NC	1	1	1	C-	1.000	0.000	0.000		Assumed perfect specificity as per Faria et al. [9]
T*USB2(CNS)|T*USB1(CNS),mpMRI(CS),NC		0	0	0	–					
T*USB2(CS)|T*USB1(CNS),mpMRI(CS),NC		0	0	0	–					
T*USB2(NC)|T*USB1(CNS),mpMRI(CS),CNS	p_T*USB2_CNS_CNS	0.68	0.02	1	mCM	0.826	0.521	0.000	0.991	Assumed as per NC findings above—see note 6, p8 of Faria et al. [9] supplement
T*USB2(CNS)|T*USB1(CNS),mpMRI(CS),CNS		0.32	0.02	0.91	–	18.384	0.295	0.035	0.946	
T*USB2(CS)|T*USB1(CNS),mpMRI(CS),CNS		0	0	0	–	0.000	0.000	0.000	0.000	
T*USB2(NC)|T*USB1(CNS),mpMRI(CS),IR	p_T*USB2_CNS_IR	0.05	0.02	0.11	D	2.297	4.083	38.111		Assumed as per NC findings above—see note 6, p8 of Faria et al. [9] supplement
T*USB2(CNS)|T*USB1(CNS),mpMRI(CS),IR		0.08	0.03	0.18	–					
T*USB2(CS)|T*USB1(CNS),mpMRI(CS),IR		0.87	0.71	0.95	–					
T*USB2(NC)|T*USB1(CNS),mpMRI(CS),HR	p_T*USB2_CNS_HR	0.05	0.02	0.11	D	2.278	3.985	37.545		Assumed as per NC findings above—see note 6, p8 of Faria et al. [9] supplement
T*USB2(CNS)|T*USB1(CNS),mpMRI(CS),HR		0.08	0.03	0.18	–					
T*USB2(CS)|T*USB1(CNS),mpMRI(CS),HR		0.87	0.71	0.95	–					

Table 1 (continued)

Parameter	Parameter name	Mean	LCL	UCL	Dbn	Param1	Param2	Param3	Param4	Source
Long-term transition probabilities										
PF to mets|CNS (low risk)	p_PF_mets_CNS	0.008	0.004	0.013	B	12.04	1492.49			Fit from figures reported in Faria et al. [9] Table 9
PF to dead|CNS (low risk)	p_PF_dead_CNS	0.05	0.043	0.058	B	162.15	3080.87			
mets to dead|CNS (low risk)	p_mets_dead_CNS	0.139	0.058	0.226	B	8.92	55.24			
PF to mets|IR, active surveillance	p_PF_mets_IRas	0.018	0.01	0.026	B	19.08	1040.92			
PF to dead|IR, active surveillance	p_PF_dead_IRas	0.064	0.049	0.078	B	69.99	1023.55			
mets to dead|IR, active surveillance	p_mets_dead_IRas	0.145	0.071	0.223	B	11.81	69.64			
PF to mets|HR, active surveillance	p_PF_mets_HRas	0.022	0.011	0.034	B	13.73	610.27			
PF to dead|HR, active surveillance	p_PF_dead_HRas	0.08	0.058	0.101	B	48.85	561.81			
mets to dead|HR, active surveillance	p_mets_dead_HRas	0.157	0.087	0.226	B	16.37	87.89			
PF to mets|IR, radical prostatectomy	p_PF_mets_IRrp	0.007	0.003	0.011	B	11.68	1656.26			
PF to dead|IR, radical prostatectomy	p_PF_dead_IRrp	0.054	0.045	0.063	B	130.78	2290.99			
mets to dead|IR, radical prostatectomy	p_mets_dead_IRrp	0.142	0.062	0.226	B	9.74	58.87			
PF to mets|HR, radical prostatectomy	p_PF_mets_HRrp	0.008	0.002	0.014	B	6.77	839.09			
PF to dead|HR, radical prostatectomy	p_PF_dead_HRrp	0.07	0.053	0.085	B	68.31	907.59			
mets to dead|HR, radical prostatectomy	p_mets_dead_HRrp	0.148	0.071	0.225	B	11.94	68.76			
Adverse events following radical prostatectomy										
Sexual dysfunction		34.56%								Wilt et al. [16] incidence over 2 years converted to 1-year probability as per Faria et al. [9]
Urinary incontinence		8.20%								
Bowel dysfunction		5.94%								
Adverse events following active surveillance										
Sexual dysfunction		20.05%								Wilt et al. [16] incidence over 2 years converted to 1-year probability as per Faria et al. [9]
Urinary incontinence		3.12%								
Bowel dysfunction		5.52%								
Unit costs										
Cost mpMRI	c_mpMRI	217			C	217				NHS Ref Costs 2018/19 [17], Imaging: Outpatient, RD03Z, MRI imaging scan of one area, with pre and post-contrast. Sheets("IMAG")!F26. As per Faria et al. [9] Table S12
Cost TRUSB	c_TRUSB	16.71			C	16.71				Entered as difference in cost between TP AND TR (Note excludes cost of Cam-PROBE device, see Appendix 2)
Cost TPUSB	c_TPUSB	0			C	0				

Table 1 (continued)

Parameter	Parameter name	Mean	LCL	UCL	Dbn	Param1	Param2	Param3	Param4	Source
Cost fever	c_fever	39.63			C	39.63				GP visit, 3-day trimethoprim (see 'components for compound costs' below)
Cost UTI	c_UTI	46.16			C	46.16				GP visit, urinalysis, 7-day trimethoprim (see 'components for compound costs' below)
Cost sepsis	c_sepsis	2206			C	2206				NHS Ref Costs 2018/19 [17], Total HRGs, weighted average WJ06A to WJ06J
Cost, watchful wait, pa	c_watchwait	123			C	123				1× FU urology OP + 3× PSA test PA (see 'components for compound costs' below)
Cost, radical prostatectomy	c_radProstatectomy	6667			C	6667				Surgery + 1× initial OP + 2× OP FU (see 'components for compound costs' below)
Cost, AE post radical prostatectomy, pa	c_AEradProst	207			C	207				Weighted average of 1-year probabilities
Cost, metastatic disease, pa	c_mets	1990			C	1990				As calculated by Faria et al. [9] (from Lord et al. [20]), adjusted to 2018/19
Components for compound costs										
Radical prostatectomy surgery		6330								NHS Ref Costs 2018/19 [17], EL, weighted average LB21A, LB21B, LB22Z (see 'additional calculations' sheet). As per Faria et al. [9] Table S12
Surgical consultation pre surgery		127								NHS Ref Costs 2018/19 [17], CL, WF01B, service code 101, urology. Row 153. After Faria et al. [9] Table S12
Surgical consultation follow-up		105								NHS Ref Costs 2018/19 [17], CL, WF01A, service code 101, urology. Row 7. After Faria et al. [9] Table S12
Primary care PSA test		6								NHS Ref Costs 2018/19 [17], DAPS, DAPS09, Direct access pathology, other. Row 14. After Faria et al. [9] Table S12
Sexual dysfunction management		217								NHS Ref Costs 2018/19 [17], Total HRGs, LB43Z, cell D1669. After Faria et al. [9] Table S12
Urinary incontinence management		296								Inflated to 2018/19 from Faria et al. [9] Table S12 (itself based on NICE Prostate Cancer CG 2014)
Bowel dysfunction management		1810								Inflated to 2018/19 from Faria et al. [9] Table S12 (itself based on mean weighted cost of sigmoidoscopy, laser therapy, enemas and blood transfusion, from NICE Clinical Guideline 2014, inflated from 2008–09 to 2014–15)
GP visit		39.23								PSSRU 2019 [18], P120

Table 1 (continued)

Parameter	Parameter name	Mean	LCL	UCL	Dbn	Param1	Param2	Param3	Param4	Source
Trimethoprim, 3d		0.40								Drug Tariff, March 2019 [19]. Trimethoprim 200 mg 6 tabs
Trimethoprim, 7d		0.93								Drug Tariff, March 2019 [19]. Trimethoprim 200 mg 14 tabs
Urinalysis		6								Assumed same as PSA test
Health state utilities										
QALY loss fever	Qloss_fever	0.0008			C	0.00082				Based on assumption of 0.1 decrement × 3 days symptomatic duration
QALY loss UTI	Qloss_UTI	0.0058			C	0.00584				Based on 0.2894 decrement (reported in Barry et al. 1997 [21])
QALY loss sepsis	Qloss_sepsis	0.0403			C	0.04027				(Note is stock QALY loss not utility decrement)
Utility of progression free	u_pf				Age-dependent					Faria et al. [9] Table s10—age dependent
Disutility of metastatic disease	du_mets				C	0.137				Faria et al. [9] Table s10

Interpretation of complex parameters: Example 1: T*USB1(NC)|mpMRI(CS), NC: denotes the probability of a first TPUSBx or TRUSBx yielding a result of no cancer following an mpMRI result of no cancer when the true state of the patient's disease is no cancer (this equates to the specificity). Example 2: T*USB2(CNS)|T*USB1(NC),mpMRI(CS), IR: denotes the probability of a TPUSBx or TRUSBx yielding a result of clinically significant cancer given a first biopsy result of no cancer, an mpMRI result of clinically significant cancer, and the true state of the patient's disease is intermediate-risk cancer

AE adverse event, *C* constant, *CaP* cancer of the prostate, *CNS* clinically non-significant, *CS* clinically significant, *B* beta, *D* Dirichlet, *Dbn* parametric distribution, *FU* Follow-up, *HR* high risk, *HRG* Health Resource Group, *IR* intermediate risk, *LCL, UCL* lower/upper 95% confidence limit, *mCM* modified Connor Mosimann, *mpMRI* multi-parametric magnetic resonance imaging, *NC* no cancer, *OP* Outpatient, *PA* per annum, *Param1–Param4* hyperparameters of respective distribution, *PF* progression free, *PSA* prostate-specific antigen, *PSSRU* Personal Social Services Research Unit, *TP* transperineal, *TPUSBx* transperineal ultrasound-guided biopsy, *TR* transrectal, *TRUSBx* transrectal ultrasound-guided biopsy, *T*USB* transrectal or transperineal biopsy (used where same distributions are used for both biopsy modes), *UTI* urinary tract infection

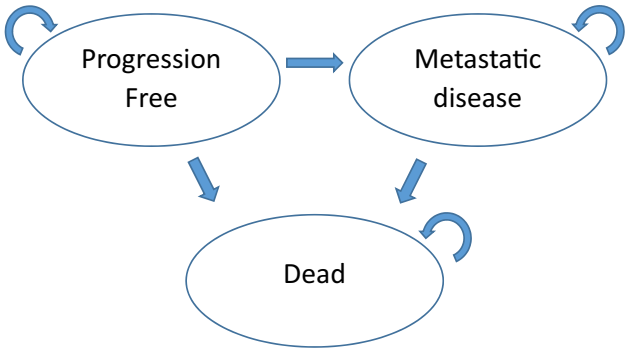


Fig. 2 Long-term model structure

the TPUSBx device itself is unknown, our base-case analysis assumes equal procedure time and a zero price for the TPUSBx device: We explore the various price points in sensitivity analysis. Other cost inputs were based on previously described treatment regimens [20]. Health state utilities were extracted from relevant previous reports and sources [9, 21] (Table 1).

2.4 Analysis

The model and inputs were reviewed for face validity and clinical plausibility by the clinical lead (VG). Internal validity checks were conducted to test for bugs and errors (details and model code available from corresponding author). Analysis was based on a 50-year-old male and run for 30 years, representing the expected life span of the individual. Future costs and QALYs were discounted at the UK recommended rate of 3.5% [22]. Analysis was conducted probabilistically via Monte Carlo simulation, repeatedly running the model with sets of inputs drawn from their respective distributions. Stability testing determined the appropriate number of simulations, with a coefficient of variation of estimates of (a) mean incremental net benefit and (b) standard error of mean incremental net benefit below 2% declared stable.

We reported mean cost and QALYs associated with TRUSBx and TPUSBx, increments and 95% credibility intervals, incremental cost-effectiveness ratios and incremental net benefit (INB) at a threshold of £20,000 per QALY. As no price is currently set for the model TPUSBx device (CamPROBE), our base case assumes a zero price, and we draw readers' attention to our sensitivity analyses:

1. We present a one-way sensitivity analysis on the price of the TPUSBx device, identifying the price associated with an ICER of £20,000.
2. Our base case assumes the risk of infection with TPUSBx is zero, thus we present a one-way sensitivity analysis on risk of infection with TPUSBx, varying the risk between 0 and 100% of that of TRUSBx. The base-case price for CamPROBE is assumed in this analysis.
3. As the reduction in risk of infection is considered the primary benefit of TPUSBx, we present a two-way sensitivity analysis showing the maximum cost-effective per-procedure price of the TPUSBx device as a function of the infection risk.

Finally, we present a VoI, estimating the expected value of perfect information (EVPI) and expected value of perfect parameter information (EVPPI) to help guide future research efforts to where they will be of most value. VoI parameters are calculated for the relevant patient population of England over a time horizon of 10 years (337,516; Appendix 4, see ESM). As the value for further information is dependent on the point estimate cost effectiveness, which itself is dependent on the price of the TPUSBx device, we present two analyses: one at the base case zero price and one at the maximum cost-effective price. At this price, the expected

Table 2 Point estimate cost effectiveness at equal procedure cost, and maximum cost-effective per-procedure price for TPUSBx device, mean (95% credible interval [CrI])

Intervention	Cost (£)	QALYs	Net benefit (£)*	ICER	P(CE) (%)
TRUSBx	5051.52 (4518.29–5593.38)	10.291 (9.909–10.671)	200,762.00 (193,082.06–208,393.78)		
Zero price of TPUSBx device					
TPUSBx	5021.91 (4489.16–5560.88)	10.292 (9.911–10.672)	200,820.90 (193,140.36–208,448.03)		
Increment	− 29.61 (− 501.54 to 441.68)	0.0015 (− 0.081 to 0.084)	58.88 (− 1192.63 to 1322.16)	Dominant**	59
Max price of TPUSBx device (£81.17)					
TPUSBx	5080.79	10.292	200,758.70 (193,080.17 to 208,389.23)		
Increment	29.27 (− 442.72 to 500.51)	0.0015 (− 0.081 to 0.084)	0.0012*** (− 1251.59 to 1262.89)	£19,999***	50

ICER incremental cost-effectiveness ratio, *INB* incremental net benefit, *P(CE)* Probability ICER is below £20,000 per QALY, *TPUSBx* transperineal ultrasound-guided biopsy, *TRUSBx* transrectal ultrasound-guided biopsy

*Calculated at £20,000 per QALY

**TPUSBx dominates TRUSBx

***Price of TPUSBx device rounded to the nearest 1p, hence ICER is slightly below £20,000 and INB slightly above £0

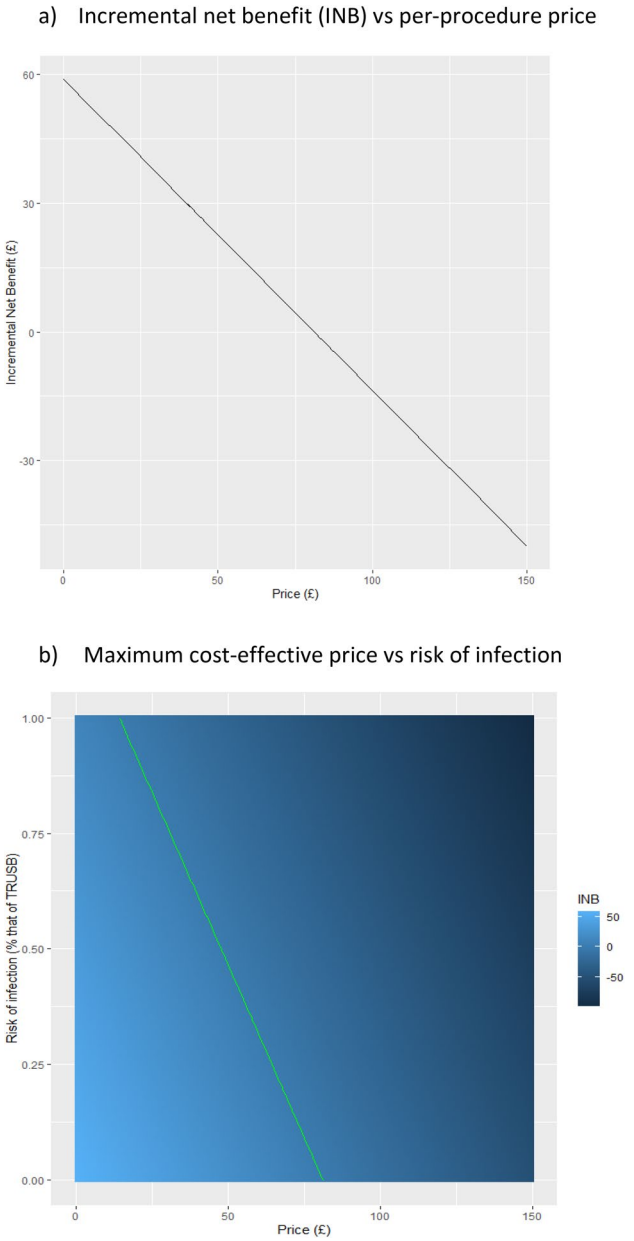


Fig. 3 Sensitivity analyses on **a** price and **b** price vs risk of infection. **a** INB vs per-procedure price. Price expressed as per procedure price of TPUSBx, not per unit (e.g. if two units required, then the unit price is half that stated). Data reported in Appendix 6, Table A6.1 (see ESM). **b** Maximum cost-effective price vs risk of infection. Shading shows INB; lighter shading indicates higher INB. Solid line shows locus of points yielding an INB of £0 (= ICER of £20,000), and thus shows the maximum cost-effective price as a function of the infection risk. Risk of infection is expressed as a proportion of the risk associated with TRUSBx (i.e. relative risk, so risk = 1 means same probability of infection, risk = 0.5 means 50% probability of infection). Price is expressed as per procedure price; thus, if TPUSBx requires 2 units, the max unit cost is half the stated price. Points to the south-west of the line yield an INB > £0 (ICER < £20,000), those to the north-east yield an INB < £0 (ICER > £20,000). One-way sensitivity analysis against risk of infection alone is shown in Appendix 6, Fig A6.2 (see ESM). *INB* incremental net benefit, *ESM* electronic supplementary material, *ICER* incremental cost-effectiveness ratio, *TPUSBx* transperineal ultrasound-guided biopsy, *TRUSBx* transrectal ultrasound-guided biopsy

ICER is £20,000/expected INB is £0 and so decision uncertainty is maximised. This thus represents an absolute upper bound to the value of further information.

3 Results

Stability testing suggested that 200,000 iterations were sufficient for purpose (Appendix 5, see ESM).

At a zero price of the TPUSBx device, there is a 59% probability that it is cost effective compared with TRUSBx (Table 2 and Appendix 6, Table A6.1 [see ESM]). The cost-neutral per-procedure price (i.e. the price yielding a zero incremental cost) is £40.82. The maximum cost-effective price (yielding an ICER of £20,000 per QALY) is £81.17 (Fig. 3a). At this price there is a 50% probability of cost effectiveness. Note, this is the per-procedure price; thus, for the example of CamPROBE where two devices are required, the maximum cost effective price is £40.59.

The above prices assume a zero infection risk with TPUSBx. As the risk of infection approaches that of TRUSBx, the maximum per-procedure cost-effective price falls to approximately £14.50 (Fig. 3b).

Value of information analysis suggests the overall value of eliminating all decision uncertainty is worth between £56 m and £65 m to the population of England, depending on the price of TPUSBx (Fig. 4 and Appendix 6, Tables A6.2–A6.4, see ESM). This is particularly focused on the diagnostic accuracy of a second transperineal or transrectal biopsy following a first biopsy result of 'clinically non-significant cancer', when the true disease state is intermediate-risk cancer (group EVPPI £46.2 m to £54.7 m, depending on the price of TPUSBx). There may also be value in reducing uncertainty in the probability of infection with TRUSBx (up to £5.0 m), long-term prognosis (£4.4 m) and the diagnostic accuracy of biopsy in patients with a true disease state of anything other than no cancer (between £1.8 m and £3.2 m each). However, this is only true when the price for CamPROBE is towards the upper end of its maximum cost-effective price; at a lower price for CamPROBE, there is minimal value in reducing uncertainty in these parameters.

4 Discussion

4.1 Interpretation of Results

Given current information, a per-procedure price for a TPUSBx device of up to £81.17 is expected to yield an incremental cost-effectiveness ratio at or below £20,000 per QALY gained. This price is derived from both the differences in consumables required between the procedures and

the assumed elimination of risk of infection associated with TRUSBx, which both averts loss of QALYs and reduces health system cost. We also assumed that on average, TRUSBx and TPUSBx had the same diagnostic accuracy.

At this maximum price, decision uncertainty is also maximised, with a 50% probability that TPUSBx is cost effective. At a zero price, there is a 59% probability of TPUSBx being cost effective. This decision uncertainty is reflected in an EVPI of £56 m or £65 m (at zero or £81.17 per-procedure price, respectively). This represents the opportunity loss due to uncertainty and can be equally expressed as 2818 or 3271 QALYs foregone to patients in England.

The interpretation of this result is that at or below the maximum price, TPUSBx is on average the cost-effective option, but this is uncertain, and if wrong there is a loss to society in terms of foregone health gain: either a TRUSBx would have been better for diagnosing prostate cancer or TPUSBx is overpriced leading to a net loss of health gain as excessive resources are diverted to TPUSBx. The probability of being wrong (incurring an opportunity loss) is around 41% (50% at maximum price). So, in 41 (50) of 100 possible realisations of the world, TPUSBx is not cost effective. The expected loss due to uncertainty (= 41% * loss or = 50% * loss) is around 2818 (3271) QALYs, or £56 m (£65 m) when each QALY is valued at £20,000. This represents the maximum amount that should be paid for research to eliminate uncertainty. At the cost-neutral price of £40.82, the EVPI is £61 m, or 3034 QALYs.

Exploring further, the parameters responsible for the greatest opportunity loss due to uncertainty are those relating to the diagnostic accuracy of a second biopsy (whether TP or TR), following a first biopsy result of clinically non-significant cancer, when the true health state is intermediate-risk cancer (EVPPI = £46m or £55m, accounting for 82% or 84% of the entire EVPI, Appendix 6, Table A6.2, see ESM). There is also some value in reducing uncertainty in the probability of infection with TRUSBx, long-term prognosis from different management strategies, and diagnostic accuracy of the entire biopsy pathway (both first and second biopsy) in patients with a true state of high-risk cancer or clinically non-significant cancer.

These recommendations for research are for very specific subpopulations of those men undergoing prostate biopsy and must be considered within the context of the overall assumptions of the model. In our base case we assumed (1) a zero risk of infection with TPUSBx, (2) on average equal sensitivity and specificity between TRUSBx and TPUSBx, (3) perfect specificity and (4) perfect sensitivity in high risk disease. Whilst recent systematic reviews do not contradict these assumptions [23, 24] (see Sect. 4.3), this may not always be the case in every-day practice. The EVPPI of £46 m to £55 m represents the upper limit for a trial budget that would eliminate uncertainty. A trial of finite sample size can only reduce, and not eliminate uncertainty, so the expected value of sample information (EVSI), which is a function of the sample size, will be lower than this. Calculation of EVSI is extremely computationally expensive. Several statistical approximation methods are available [25], but unfortunately due to the nature of our data we were unable to generate solutions to the EVSI parameters.

Taking the EVPPI results, sensitivity analyses and base-case assumptions into account, a suitably powered comparative study of the risk of infection and diagnostic accuracy associated with TRUSBx devices versus TPUSBx may be warranted. Diagnostic accuracy can be established with patients acting as their own controls and/or in those whose disease status is already known, if they are willing to undergo both procedures, whereas establishing risk of infection may require an RCT design. Consideration should be given to enriching the enrolled population in these studies with men with a diagnosis of, or high prior probability of intermediate-risk cancer.

4.2 Strengths and Weaknesses

Our analysis presents a synthesis of current evidence on the cost and consequences of transperineal in place of transrectal ultrasound-guided biopsy in the diagnosis of cancer of the prostate. The conduct and reporting of our analysis conforms to best practice in economic evaluation [22, 26]. However, there are a number of limitations.

Any decision model is only as reliable as its assumptions. Our estimate of the maximum price is based on differences in consumables cost and elimination of infection risk. The quality of the data (reflecting the stage of development of the model device) must be considered when addressing the generalisability of our results. For example, the observed difference in consumables cost is driven by replacing the transrectal biopsy needle and guide with the CamPROBE device and based on a small sample of biopsies conducted in one centre (a large research-intensive teaching hospital). Consideration must be given as to whether this is generalisable to other settings; we provide full microcosting data in Appendix 2 to assist this (see ESM).

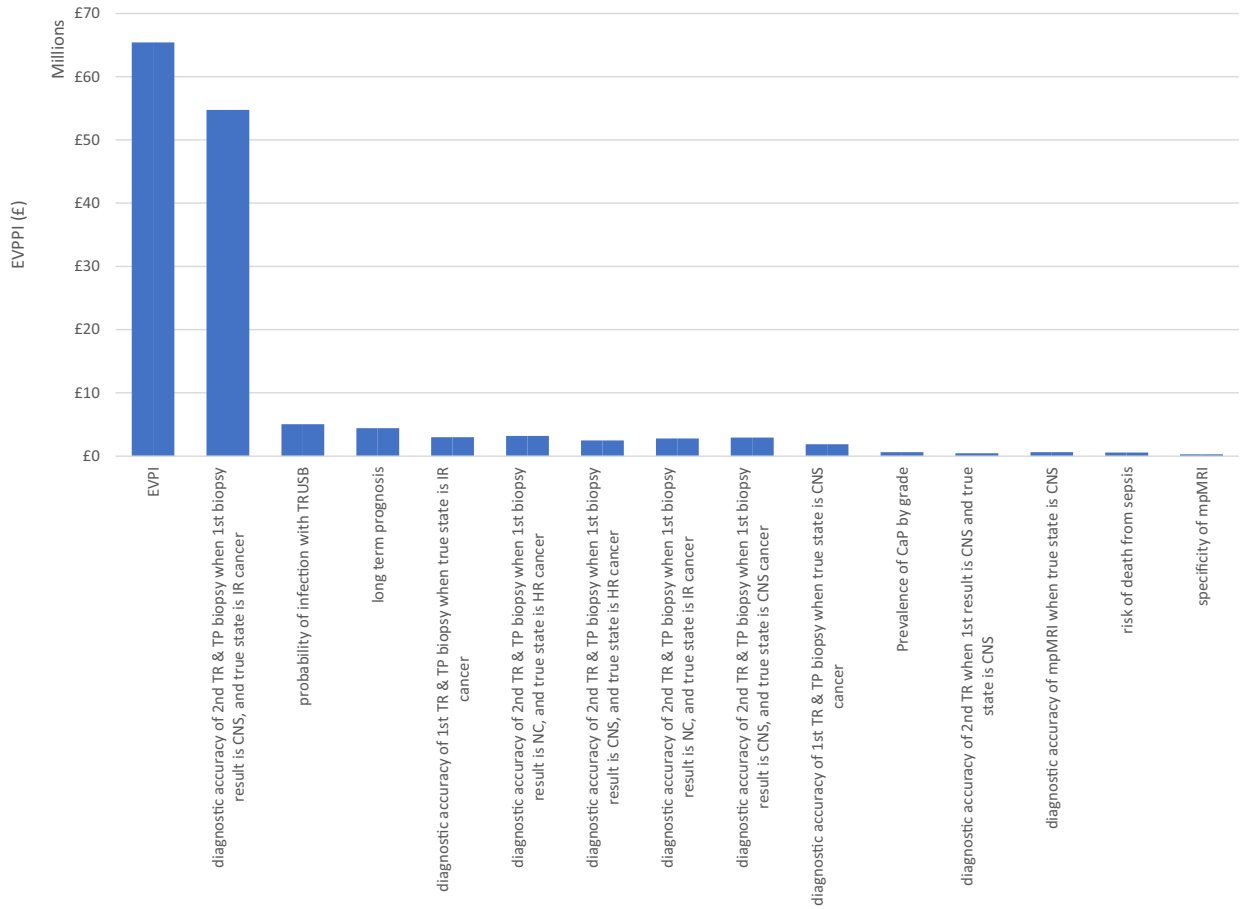
The other major component of value is the reduction in biopsy-associated infection. Indeed, this is the major anticipated benefit. Whilst we feel the estimates of QALY loss and health service cost associated with infections are plausible, the biggest uncertainty is the probability of infection itself. Data and budgetary limitations prevented us from assigning a plausible probability distribution for this (e.g. by conducting a formal expert elicitation process), so we addressed this by conducting a two-way sensitivity analysis, showing the maximum price as a function of the risk of infection, but stress the need for good quality comparative data to establish the difference in infection rate.

We also assumed an on-average equal diagnostic accuracy for transrectal and transperineal biopsies. We conducted an additional one-way sensitivity analysis on the probability of a true positive in patients with intermediate-risk cancer, concluding that transperineal biopsies remained cost effective as long as the relative probability was at least 98.8–99.97% that of transrectal, depending on the price of the transperineal biopsy device, with a higher price giving less 'room' for a reduction in relative diagnostic accuracy (Appendix 6, Tables A6.6 and A6.7, see ESM). Note, the figures quoted above are for the relative true-positive rate, not the absolute.

Finally, we did not include any costs for training or the impact of any learning curve effect in the analysis. In the experience of our clinical lead (and inventor of CamPROBE, VG), transferring from transrectal to transperineal biopsies is relatively straightforward with minimal training requirements. So whilst our analysis could be regarded as a 'steady state', assuming surgeons are fully competent in the transperineal technique, any additional training costs should be minor.

4.3 Comparison with Other Studies

We are not aware of any other economic evaluations comparing the cost effectiveness of transrectal and transperineal ultrasound-guided devices for local anaesthetic biopsies. Several transperineal biopsy devices have recently entered the market; a 2020 systematic review [23] comparing transrectal and transperineal methods identified 14 studies enrolling approximately 2000 patients. However, all but one



**Assuming maximum cost-effective price for CamPROBE (£81.17). Figure shows EVPI and EVPPI associated with various groups of parameters. TR = transrectal; TP = transperineal; IR = intermediate risk; NC = no cancer; HR = high risk; CNS = clinically non-significant; CaP = Cancer of the prostate.*

Fig. 4 Expected value of perfect (parameter) information (EVPPI) to England, assuming maximum cost-effective price for CamPROBE (£81.17). Figure shows EVPI and EVPPI associated with various groups of parameters. *CaP* cancer of the prostate, *CNS* clinically non-significant, *HR* high risk, *IR* intermediate risk, *NC* no cancer, *TP* transperineal, *TR* transrectal

of these were single-arm cohort studies. The one comparative study compared both techniques in the same patients [27]. The review concluded that both techniques were of similar sensitivity and specificity, although the diagnostic odds ratio may favour the transrectal approach [23]. Another (2019) systematic review [24] identified four RCTs (and a number of observational studies), concluding there was no evidence of a difference between transrectal and transperineal biopsies, although this review did not distinguish between GA-based template and non-template LA transperineal biopsy and did not explore sensitivity and specificity, instead reporting the ratio of cancer detection rates. However, the authors noted that TPUSBx was associated with a lower risk of fever and rectal bleeding. High-quality comparative data specifically comparing infection rates with the two techniques are somewhat limited, although a number of smaller single-centre and retrospective database analyses suggest an effective zero rate of sepsis with transperineal biopsy [4, 28–32].

The most influential economic study on UK prostate biopsy policy is the Faria et al. [9] model, drawing on the PROMIS study [10], on which UK guidelines are largely based. Other economic studies support the use of mpMRI first line [33–36] and newer biomarker tests appear cost effective compared with a first-line biopsy [37, 38]. However, comparison with mpMRI first line is unknown.

5 Conclusion

Transperineal ultrasound-guided biopsies have the potential to be cost effective with a device priced at up to £81.17 per procedure. This price must be divided by the number of units required per procedure to obtain the maximum unit price: if two devices are used, this equates to £40.59 per unit. A cost-neutral price to the NHS is £40.82 per procedure. The greatest value of further research is in the diagnostic accuracy of TPUSBx versus traditional transrectal prostate biopsy, and in the risk of infection associated with the two biopsy modes. Consideration should be given to enriching the enrolled patient population with men with either known or a high prior probability of intermediate-risk disease. New biomarkers are showing potential to assist in the diagnosis of prostate cancer, which may change the prevalence of disease in those eventually referred for biopsy, and hence the cost effectiveness of different diagnostic pathways. Future economic modelling aimed at informing the next revision of guidelines and clinical pathways should consider both (non-template) transperineal biopsy procedures as well as biomarker tests.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s41669-021-00277-4.

Acknowledgements The authors would like to thank Dr Rita Faria, University of York for very helpful discussions and responses to queries during development of this analysis. Any errors or omissions are the authors' own. We acknowledge infrastructure support from the NIHR Cambridge Biomedical Research Centre and Cancer Research UK Cambridge Centre. We are particularly grateful for the support from the Cambridge Clinical Research Centre and Ms Caroline Saunders. We acknowledge the support of the Cambridge Clinical Trials Unit (Cancer theme) in delivering the NIHR i4i CamPROBE study and especially the critical role of Mr Richard Skells (trial co-ordinator) and Dr Jerome Wulff (trial statistician).

Declarations

Funding The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study/project is funded by an NIHR i4i Product Development Award (II-LB-0716-20001). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Ethical approval Ethical approval was not required for the decision model component of the NIHR award reported here. However, the clinical study was reviewed and received favourable ethical opinion by the East of England—Cambridge Central Ethics Committee (REC 18/EE/0272, IRAS Project ID: 242948).

Conflicts of interest/Competing interests VJG is the inventor and patent holder of the CamPROBE device. All other authors confirm they have no conflicts of interest to declare.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material (data transparency) Not applicable.

Code availability (software application or custom code) Model code is available on request from the corresponding author.

Authors' contributions EW developed and analysed the model and led drafting, editing and review of the manuscript. AW conducted the microcosting and revised and edited the manuscript. PT revised and edited the manuscript. KL revised and edited the manuscript. HB revised and edited the manuscript. VJG contributed to development of the model and drafting, editing and review of the manuscript.

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