Economic evaluation of trans-perineal devices for local anaesthetic prostate biopsies.

Supplementary Material

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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.
Appendices

Appendix 1: Fitting distributions to probabilities

Sensitivity and specificity of mpMRI and biopsy
As there are four possible disease states (no cancer; NC, clinically non-significant cancer; CNS, intermediate risk; IR and high risk; HR), and three possible diagnoses (NC, CNS and CS where CS includes both IR and HR), the sensitivity and specificity are captured in a 4x3 contingency table, rather than a 2x2 table when there are only two disease states and two diagnoses.

Faria et al.⁹ present mean and 95%CIs for each element (Supplementary tables 6 and 7 for TRUSB and mpMRI respectively). As there are three possible outcomes from a test, a multinomial distribution was required to model these. Using a previously developed search algorithm,¹² Dirichlet, Connor-Mosimann and modified Connor-Mosimann distributions were fitted to the data. This uses an algorithm to find a set of parameters for each distribution that has the lowest sum of the squared deviations between the means and 95%CI bounds. The distribution and set of parameters associated with the lowest sum of squared deviations was selected as the best fitting model.

Long term transition probabilities
Ideally long-term transition probabilities should also be fitted using multinomial distributions. However, as the individual probabilities were ‘low’, independent beta distributions provided a clearer and more expedient approach. The parameters of the betas were calculated from the reported mean and 95% confidence intervals from Table 9, Faria et al.⁹ supplement.
Appendix 2: Microcosting

As part of the prospective case series, a microcosting exercise was undertaken on a sample of CamPROBE and transrectal biopsies (n=17 each). All biopsies were conducted at Cambridge University Hospitals NHS Trust (Addenbrooke’s Hospital).

Data recorded were time to perform biopsy procedure, volume of local anaesthesia used and other consumables and equipment, extracted on to a data collection form (Appendix 3).

A large number of consumables are common to both procedures, and so are excluded from the incremental analysis. However, we present them here for completeness.

Results

Table A2.1 shows a point estimate difference of 4.1 minutes procedure time between CamPROBE and TRUSBx, and a 0.9mL increase in anaesthetic use. Given the small sample size, we do not perform any statistical analysis on these differences, and for the purposes of the decision model, we assume both procedures take the same time and use the same volume of anaesthetic (lidocaine).

|                | CamPROBE (n=17) | TRUSB (n=17) | Difference |
|----------------|-----------------|--------------|------------|
| Procedure time (minutes) | 24.4 (8.88)     | 28.5 (6.8)   | -4.1mins   |
| Anaesthesia (mLs)           | 10.9 (3.1)      | 10 (0)       | +0.9mL     |

Reusable equipment common to both arms are:

- Linear transducer endocavity US probe (CamPROBE)
- Prostate triplane E14C4t US probe (TRUS)
- Ultrasound machine
- Suitable couch and legs

These are not costed as our focus is on the consumables. Common consumables cost £43.49, with TRUSBx-specific consumables costing an extra £19.81, and for CamPROBE £3.10 (Table A2.2). Note importantly, this excludes the cost of the CamPROBE device itself as per the base case analysis (see body text section Methods, Analysis). The difference in cost is therefore -£16.71 per procedure. This can be interpreted as the maximum per-procedure price of CamPROBE for the consumables cost to be equal between the two techniques. As two CamPROBEs are required per procedure, the maximum unit cost would therefore be half of this (£8.36).
Table A2.2: Consumables quantities and cost, mean (SD). 2018-19 prices

| Item                                | Unit Cost   | Unit            | Quantity | Cost  |
|-------------------------------------|-------------|-----------------|----------|-------|
| **Consumables common to both arms** |             |                 |          |       |
| 18 gauge biopsy needle              | £135.00 b   | Box, 5          | 1        | £27.00|
| Condoms                             | £27.77 b    | Box, 500        | 1        | £0.06 |
| Ultrasound lubricant gel            | £3.54 b     | 5L              |          | £0.01 |
| Sterile Gloves                      | £78.60 b    | Case, 50 pairs  | 2 pairs  | £3.14 |
| Dressing Towel                      | £0.20 c     | 1               | 1        | £0.20 |
| Biopsy Cassettes                    | £0.10 c     | 1               | 12       | £1.20 |
| 10mL Syringe                        | £3.72       | Pack, 100       | 2        | £0.07 |
| 1% lignocaine / lidocaine           | £11.00 d    | 20mL            | 20mLs    | £11.00|
| Glycerol Suppositories              | £0.09 d     | 1               | 1        | £0.09 |
| Ciprofloxacin                       | £0.092 d    | 1               | 7x500mg  | £0.64 |
| antiseptic wash                     | £2.59 b,e   | 600mL           | 10mL     | £0.04 |
| Sterile Gloves                      | £3.72 b,f   | 10x100mL        | 10mL     | £0.04 |
| **Total**                           |             |                 |          | £43.49|

| Item                                    | TRUSbx (n=17) | CamPROBE (n=17) | TRUSbx (n=17) | CamPROBE (n=17) |
|-----------------------------------------|---------------|-----------------|---------------|-----------------|
| Clip on needle guide for US transducer | £300.00 b     | Box, 18         | 1             | £17.00          |
| Spinal Needle (Quincke) 22G x 7.00in    | £28.08 b      | Pack, 10        | 1             | £2.81           |
| Cotton Gauze                           | £0.90         | Pack, 100       | ~10           | £0.10           |
| steristrips                            | £7.74         | Pack, 50        | 2             | £0.31           |
| Orange Needles                         | £2.89 b       | Pack, 100       | 2             | £0.06           |
| Green Needles                          | £1.78 b       | Pack, 100       | 2             | £0.04           |
| Sterile Drape with Adhesive            | £111.46 b     | Pack, 50        | 1             | £2.23           |
| Shallow sterile plastic tray           | £18.20 b      | Case, 50        | 1             | £0.36           |
| **Total (technique specific, excluding**|               |                 |               |                 |
| **CamPROBE)**                          |               |                 |               |                 |
| **Total (all consumables, Excl CamPROBE**|               |                 |               |                 |
| **device)**                            |               |                 |               |                 |

b. Source of unit costs: local prices; c. Source of unit costs: estimate; d. Source of unit costs: Drug Tariff, March 2019 19. e. 600ml bottle = £2.59. f. £3.72 per 10x100ml sachets. g. Base case analysis excludes cost of CamPROBE: see Methods, Analysis in main body for details.
## Appendix 3: Microcosting Data Collection Form

### CamProbe MicroCosting

**V1.0 24/01/19**

| Today's date | Date of procedure | Initials of research nurse |
|--------------|-------------------|----------------------------|
|              |                   |                            |

Please complete the information below as fully as possible. If there are any additional items used please add overleaf. For any further queries please email ed.wilson@uea.ac.uk. Thank you!

### Patient preparation prior to procedure

**Item**

- [ ] Prophylactic antibiotic: Ciprofloxacin
- [ ] Other (please specify): __________
- [ ] None

| Glycerine | Dose |
|-----------|------|
| [ ] Yes   |      |
| [ ] No    |      |

**Other (please specify):**

### During the procedure

**Approx time patient entered room:** __________

**STAFF PRESENT:**

| Type | Grade |
|------|-------|
|      |       |

### CONSUMABLES (approx. number or total ml as appropriate)

| Item            | Qty |
|-----------------|-----|
| Disposable biopsy device |      |
| Biopsy guide    |     |
| Other Needles   |     |
| CamProbe devices|     |
| Anaesthetic (mls) |    |
| Antiseptic wash (mls) | |
| Saline (mls)    |     |

**Other (please tick and/or write in any other items):**

- [ ] Swabs
- [ ] Ultrasound gel
- [ ] Urine pot and dipstick
- [ ] Syringes
- [ ] Sheath
- [ ] Formalin pot
- [ ] Lubricant

**Approx time patient exited procedure room:** __________

### After the procedure

**Post biopsy antibiotic prescribed:**

- [ ] Ciprofloxacin
- [ ] Other (please specify): __________

| Dose |
|------|
|      |
Appendix 4: Definition of population who potentially benefit from further research

In 2018/19, the NHS Schedule of reference costs reports that 39,211 transrectal ultrasound guided biopsies of the prostate were performed in the NHS in England (NHS Reference Costs 2018/19, sheet ‘Total HRGs’, currency code LB76Z [cell C1728]). Given a 10-year time horizon (representing the time for which the information is assumed to be useful), and discounting at 3.5% yields a beneficial population of 337,516.
Appendix 5: Stability testing

The model was run 30 times with increasing numbers of iterations, and the coefficient of variation of the estimate of mean incremental net benefit and of standard error of incremental net benefit calculated. The coefficient of variation of the estimate of mean incremental net benefit is approximately 1.97% at 200,000 iterations, with that of the standard error at 0.28% (Table A5.1). 200,000 iterations were therefore considered to yield sufficiently stable results.

Table A5.1: Coefficient of variation of estimate of mean and standard error of incremental net benefit as a function of number of Monte Carlo simulations

| iterations | Mean    | SE     |
|------------|---------|--------|
| 10         | 2.3996  | 0.2677 |
| 1,000      | 0.2248  | 0.0355 |
| 5,000      | 0.1192  | 0.0150 |
| 10,000     | 0.0773  | 0.0121 |
| 20,000     | 0.0471  | 0.0091 |
| 50,000     | 0.0330  | 0.0044 |
| 100,000    | 0.0264  | 0.0042 |
| 200,000    | 0.0197  | 0.0028 |
| 250,000    | 0.0164  | 0.0021 |
| 500,000    | 0.0119  | 0.0013 |

Incremental Net Benefit calculated at £20,000 per QALY
Appendix 6: Additional data and figures

Figure A6.1: (a) Scatterplot of cost-QALY pairs and (b) Cost-effectiveness acceptability curve (base case)

TR_C = transrectal biopsy; TP_C = transperineal biopsy

Figure A6.2: One-way sensitivity analysis of INB vs risk of infection

Infection risk (x-axis) expressed as a proportion of that of TRUSB. Calculated at a zero price of TPUSBx device.

INB = Incremental Net Benefit (£)
Data for Figure 3a are presented in Table A6.1.

Table A6.1: One-way sensitivity analysis on price of TPUSBx device

| Price* | TRUSBx | Cost | QALYs | TPUSBx | Cost | QALYs | Increments | Net Benefit** |
|--------|--------|------|-------|--------|------|-------|------------|--------------|
| 0      | 5051.523 | 10.291 | 5021.911 | 10.292 | -29.612 | 0.001 | 58.87979 |
| 10     | 5051.523 | 10.291 | 5029.165 | 10.292 | -22.358 | 0.001 | 51.62605 |
| 20     | 5051.523 | 10.291 | 5036.418 | 10.292 | -15.105 | 0.001 | 44.3723 |
| 30     | 5051.523 | 10.291 | 5043.672 | 10.292 | -7.851 | 0.001 | 37.11856 |
| 40     | 5051.523 | 10.291 | 5050.926 | 10.292 | -0.597 | 0.001 | 29.86481 |
| 40.1   | 5051.523 | 10.291 | 5050.998 | 10.292 | -0.525 | 0.001 | 29.79228 |
| 40.2   | 5051.523 | 10.291 | 5051.071 | 10.292 | -0.452 | 0.001 | 29.71974 |
| 40.3   | 5051.523 | 10.291 | 5051.144 | 10.292 | -0.379 | 0.001 | 29.6472 |
| 40.4   | 5051.523 | 10.291 | 5051.216 | 10.292 | -0.307 | 0.001 | 29.57467 |
| 40.5   | 5051.523 | 10.291 | 5051.289 | 10.292 | -0.234 | 0.001 | 29.50213 |
| 40.6   | 5051.523 | 10.291 | 5051.361 | 10.292 | -0.162 | 0.001 | 29.42959 |
| 40.7   | 5051.523 | 10.291 | 5051.434 | 10.292 | -0.089 | 0.001 | 29.35705 |
| 40.8   | 5051.523 | 10.291 | 5051.506 | 10.292 | -0.017 | 0.001 | 29.28452 |
| 40.81  | 5051.523 | 10.291 | 5051.514 | 10.292 | -0.009 | 0.001 | 29.27726 |
| 40.82  | 5051.523 | 10.291 | 5051.521 | 10.292 | -0.002 | 0.001 | 29.27001 |
| 40.83  | 5051.523 | 10.291 | 5051.528 | 10.292 | 0.005 | 0.001 | 29.26725 |
| 40.84  | 5051.523 | 10.291 | 5051.535 | 10.292 | 0.012 | 0.001 | 29.2555 |
| 40.85  | 5051.523 | 10.291 | 5051.543 | 10.292 | 0.037 | 0.001 | 29.24825 |
| 40.86  | 5051.523 | 10.291 | 5051.551 | 10.292 | 0.073 | 0.001 | 29.24099 |
| 40.87  | 5051.523 | 10.291 | 5051.557 | 10.292 | 0.349 | 0.001 | 29.23734 |
| 40.88  | 5051.523 | 10.291 | 5051.564 | 10.292 | 0.514 | 0.001 | 29.22649 |
| 40.89  | 5051.523 | 10.291 | 5051.572 | 10.292 | 0.685 | 0.001 | 29.21923 |
| 40.9   | 5051.523 | 10.291 | 5051.579 | 10.292 | 0.857 | 0.001 | 29.21198 |
| 41     | 5051.523 | 10.291 | 5051.651 | 10.292 | 1.028 | 0.001 | 29.13944 |
| 42     | 5051.523 | 10.291 | 5052.377 | 10.292 | 1.200 | 0.001 | 28.41407 |
| 43     | 5051.523 | 10.291 | 5053.102 | 10.292 | 1.372 | 0.001 | 27.68869 |
| 44     | 5051.523 | 10.291 | 5053.827 | 10.292 | 1.544 | 0.001 | 26.96332 |
| 45     | 5051.523 | 10.291 | 5054.553 | 10.292 | 1.716 | 0.001 | 26.23794 |
| 46     | 5051.523 | 10.291 | 5055.278 | 10.292 | 1.888 | 0.001 | 25.51257 |
| 47     | 5051.523 | 10.291 | 5056.004 | 10.292 | 2.060 | 0.001 | 24.78719 |
| 48     | 5051.523 | 10.291 | 5056.729 | 10.292 | 2.232 | 0.001 | 24.06182 |
| 49     | 5051.523 | 10.291 | 5057.454 | 10.292 | 2.404 | 0.001 | 23.33645 |
| 50     | 5051.523 | 10.291 | 5058.180 | 10.292 | 2.576 | 0.001 | 22.61107 |
| 60     | 5051.523 | 10.291 | 5065.433 | 10.292 | 3.134 | 0.001 | 15.35733 |
| 70     | 5051.523 | 10.291 | 5072.687 | 10.292 | 3.692 | 0.001 | 8.10358 |
| 80     | 5051.523 | 10.291 | 5079.941 | 10.292 | 4.251 | 0.001 | 0.84984 |
| 81     | 5051.523 | 10.291 | 5080.666 | 10.292 | 4.810 | 0.001 | 0.124466 |
| 81.1   | 5051.523 | 10.291 | 5080.739 | 10.292 | 5.523 | 0.001 | 0.051928 |
| 81.11  | 5051.523 | 10.291 | 5080.746 | 10.292 | 5.906 | 0.001 | 0.044674 |
| 81.12  | 5051.523 | 10.291 | 5080.753 | 10.292 | 5.917 | 0.001 | 0.037421 |
| 81.13  | 5051.523 | 10.291 | 5080.761 | 10.292 | 5.928 | 0.001 | 0.030167 |
| 81.14  | 5051.523 | 10.291 | 5080.768 | 10.292 | 5.939 | 0.001 | 0.022913 |
Table A6.2 shows the EVPI and EVPPI for groups of parameters at both a zero and maximum cost-effective price of CamPROBE, where the groups represent individual model parameters that would logically be collected together in a future clinical trial. The individual constituent model parameters are shown in Tables A6.3 (zero price of CamPROBE) and A6.4 (max price).

**Table A6.2: Expected Value of Perfect Information**

| Parameter(s) | Per Person | SE** | % of total | EVPPI for England over 10 years* |
|--------------|------------|------|------------|----------------------------------|
|              | EVPPI*     |      |            |                                  |
| At zero price of CamPROBE |             |      |            |                                  |
| diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is IR cancer | £136.96 | £3.43 | 82% | £46,225,000 |
| EVPI | £167.00 | -- | 100% | £56,366,000 |

**At maximum price of CamPROBE (£81.17)**

diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is IR cancer

| EVPPI* | £162.15 | £3.42 | 83.66% | £54,730,000 |

* Per procedure price of TPUSBx device. **Net benefit calculated at £20,000 per QALY.
| Parameter                                                                 | EVPI  | SE** | % of total EVPI | EVPPI for England over 10 years* |
|------------------------------------------------------------------------|-------|------|----------------|----------------------------------|
| Probability of infection with TRUSB                                    | £14.99| £0.69| 7.73%          | £5,060,000                        |
| Long term prognosis                                                    | £13.06| £3.02| 6.74%          | £4,410,000                        |
| Diagnostic accuracy of 1st TR & TP biopsy when true state is IR cancer  | £8.93 | £2.93| 4.61%          | £3,010,000                        |
| Diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is NC, and true state is HR cancer | £9.44 | £3.29| 4.87%          | £3,190,000                        |
| Diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is HR cancer | £7.31 | £3.15| 3.77%          | £2,470,000                        |
| Diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is NC, and true state is IR cancer | £8.25 | £3.16| 4.25%          | £2,780,000                        |
| Diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is CNS cancer | £8.67 | £3.01| 4.47%          | £2,930,000                        |
| Diagnostic accuracy of 1st TR & TP biopsy when true state is CNS cancer | £5.49 | £2.77| 2.83%          | £1,850,000                        |
| Prevalence of varying severity of CaP                                  | £1.84 | £0.52| 0.95%          | £620,000                          |
| Diagnostic accuracy of mpMRI when true state is CNS                   | £1.84 | £0.52| 0.95%          | £620,000                          |
| Risk of death from sepsis                                              | £1.64 | £0.57| 1.00%          | £552,000                          |
| EVPI                                                                   | £193.80 |     | 100%           | £65,416,000                       |

*note EVPI ≠ ΣEVPPI (and thus also % of total EVPI ≠ 100%) due to interactions and correlations between input parameters. **Standard error of per person EVPPI arises due to the SAVI approximation method. Figures shown for groups of parameters with EVPPI>£500,000

Table A6.3: Full EVPPI by model parameter and groups of parameters (at zero price of TPUSBx device)
EVPPI of individual parameters with EVPPI over £100,000. Explanation of parameter names: the group of six parameters, p_TPUSB2_CNS_IR3 to p_TRUSB2_CNS_IR1 relate to the sensitivity and specificity of the second TP or TR biopsy in patients with intermediate risk (IR) cancer, following a first biopsy result of ‘clinically non-significant’ (CNS). Suffix 1 = outcome of NC, 2 = CNS, 3 = CS. Thus p_TPUSB2_CNS_IR3 = probability of the second TP biopsy giving a result of clinically significant cancer following a first (TP) biopsy result of CNS, when the true state of the patient is intermediate risk cancer. The EVPPI of the group together represents the value of eliminating uncertainty in second biopsy results following a first biopsy result of CNS, when the true state is intermediate risk cancer, and is the figure reported in Table A6.

Table A6.4: Full EVPPI by model parameter and groups of parameters (at max price of TPUSBx device (£81.17))

| Parameter | Per Person EVPPI (£) | Standard Error | %total EVPI | EVPPI for England (£) |
|-----------|----------------------|----------------|-------------|-----------------------|
| p_TRUSB2_CNS_IR3 | 91.78 | 0.69 | 0.55 | 30,980,000 |
| p_TRUSB2_CNS_IR2 | 70.54 | 0.6 | 0.42 | 23,810,000 |
| p_TRUSB2_CNS_IR1 | 63.88 | 0.69 | 0.38 | 21,560,000 |
| p_TPUSB2_CNS_IR1 | 46.12 | 0.64 | 0.28 | 15,570,000 |
| p_TRUSB2_CNS_IR2 | 37.03 | 0.78 | 0.22 | 12,500,000 |
| Group | 136.9562 | 3.43005 | 0.82 | 46,224,920 |
| EVPI | 167.00 | -- | 100% | 56,366,000 |

EVPPI of the group represents the value of eliminating uncertainty in second biopsy results following a first biopsy result of CNS, when the true state is intermediate risk cancer, and is the figure reported in Table A6.2.

diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is IR cancer

| Parameter | Per Person EVPPI (£) | Standard Error | %total EVPI | EVPPI for England (£) |
|-----------|----------------------|----------------|-------------|-----------------------|
| p_TRUSB2_CNS_IR1 | 67.21 | 0.67 | 0.350 | 22,690,000 |
| p_TRUSB2_CNS_IR2 | 94.05 | 0.60 | 0.490 | 31,740,000 |
| p_TRUSB2_CNS_IR3 | 121.39 | 0.55 | 0.630 | 40,970,000 |
| p_TRUSB2_CNS_IR1 | 67.69 | 0.67 | 0.350 | 22,850,000 |
| p_TRUSB2_CNS_IR2 | 93.78 | 0.59 | 0.480 | 31,650,000 |
| p_TRUSB2_CNS_IR3 | 121.41 | 0.57 | 0.630 | 40,980,000 |
| probability of infection with TRUSB | 14.99 | 0.69 | 0.077 | 5,060,000 |
| p_PF_dead_IRww | 0.12 | 0.26 | 0.000 | 41,330 |
| p_PF_dead_IRRp | 0.17 | 0.27 | 0.000 | 56,010 |
| p_mets_dead_IRww | 1.16 | 0.48 | 0.010 | 390,300 |
| p_PF_mets_IRww | 0.92 | 0.43 | 0.000 | 309,900 |
| p_PF_dead_CNS | 0.16 | 0.28 | 0.000 | 53,320 |
| p_PF_mets_CNS | 0.65 | 0.40 | 0.000 | 219,900 |
| p_PF_mets_HRrp | 0.48 | 0.33 | 0.000 | 161,700 |
| p_mets_dead_HRrp | 0.13 | 0.26 | 0.000 | 42,760 |
| p_PF_mets_IRrp | 0.28 | 0.28 | 0.000 | 95,910 |
### Long Term Prognosis

|                          | 13.06 | 3.02 | 0.067 | 4,410,000 |
|--------------------------|-------|------|-------|-----------|
| p_TRUSB1_IR1             | 0.56  | 0.37 | 0.000 | 188,800   |
| p_TRUSB1_IR2             | 0.48  | 0.35 | 0.000 | 162,700   |
| p_TRUSB1_IR3             | 0.10  | 0.28 | 0.000 | 33,520    |
| p_TPUSB1_IR1             | 0.39  | 0.33 | 0.000 | 130,100   |
| p_TPUSB1_IR2             | 0.38  | 0.32 | 0.000 | 127,400   |
| p_TPUSB1_IR3             | 0.04  | 0.24 | 0.000 | 12,490    |

**Diagnostic Accuracy of 1st TR & TP Biopsy when True State is IR Cancer**

|                          | 8.93  | 2.93 | 0.046 | 3,010,000 |
|--------------------------|-------|------|-------|-----------|
| p_TRUSB2_NC_HR1          | 0.25  | 0.27 | 0.000 | 83,700    |
| p_TRUSB2_NC_HR2          | 0.90  | 0.45 | 0.000 | 303,300   |
| p_TRUSB2_NC_HR3          | 0.68  | 0.40 | 0.000 | 229,700   |
| p_TPUSB2_NC_HR1          | 0.02  | 0.23 | 0.000 | 6,839     |
| p_TPUSB2_NC_HR2          | 0.19  | 0.27 | 0.000 | 63,810    |
| p_TPUSB2_NC_HR3          | 0.13  | 0.25 | 0.000 | 43,650    |

**Diagnostic Accuracy of 2nd TR & TP Biopsy when 1st Biopsy Result is NC, and True State is HR Cancer**

|                          | 9.44  | 3.29 | 0.049 | 3,190,000 |
|--------------------------|-------|------|-------|-----------|
| p_TPUSB2_CNS_HR1         | 3.37  | 0.64 | 0.020 | 1,137,000 |
| p_TPUSB2_CNS_HR2         | 4.56  | 0.61 | 0.020 | 1,539,000 |
| p_TPUSB2_CNS_HR3         | 6.00  | 0.61 | 0.030 | 2,025,000 |
| p_TRUSB2_CNS_HR1         | 3.90  | 0.64 | 0.020 | 1,318,000 |
| p_TRUSB2_CNS_HR2         | 4.41  | 0.60 | 0.020 | 1,489,000 |
| p_TRUSB2_CNS_HR3         | 6.18  | 0.65 | 0.030 | 2,087,000 |

**Diagnostic Accuracy of 2nd TR & TP Biopsy when 1st Biopsy Result is CNS, and True State is HR Cancer**

|                          | 7.31  | 3.15 | 0.038 | 2,470,000 |
|--------------------------|-------|------|-------|-----------|
| p_TRUSB2_CNS_CNS1        | 1.05  | 0.51 | 0.010 | 463,700   |
| p_TRUSB2_CNS_CNS2        | 1.37  | 0.51 | 0.010 | 463,700   |
| p_TRUSB2_CNS_CNS3        | 0.08  | 0.24 | 0.000 | 25,350    |
| p_TRUSB2_CNS_CNS1        | 0.70  | 0.41 | 0.000 | 236,000   |

**Diagnostic Accuracy of 2nd TR & TP Biopsy when 1st Biopsy Result is NC, and True State is IR Cancer**

|                          | 8.25  | 3.16 | 0.043 | 2,780,000 |
|--------------------------|-------|------|-------|-----------|
| p_TPUSB2_CNS_IR1         | 0.80  | 0.47 | 0.000 | 268,700   |
| p_TPUSB2_CNS_IR2         | 0.76  | 0.47 | 0.000 | 255,200   |
| p_TPUSB2_CNS_IR3         | 0.80  | 0.43 | 0.000 | 269,700   |
| p_TRUSB2_CNS_IR1         | 1.05  | 0.51 | 0.010 | 355,300   |
| p_TRUSB2_CNS_IR2         | 0.92  | 0.48 | 0.000 | 310,500   |
| p_TRUSB2_CNS_IR3         | 0.74  | 0.41 | 0.000 | 248,200   |
diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is CNS cancer  

| Parameter         | p  | q  | c   | V    |
|-------------------|----|----|-----|------|
| p_TPUSB1_CNS1     | 0.69 | 0.40 | 0.000 | 233,100 |
| p_TPUSB1_CNS2     | 0.75 | 0.43 | 0.000 | 253,500 |
| p_TPUSB1_CNS3     | 0.37 | 0.28 | 0.000 | 123,600 |
| p_TRUSB1_CNS1     | 0.59 | 0.37 | 0.000 | 199,300 |
| p_TRUSB1_CNS2     | 0.69 | 0.40 | 0.000 | 232,900 |
| p_TRUSB1_CNS3     | 0.56 | 0.31 | 0.000 | 188,200 |

diagnostic accuracy of 1st TR & TP biopsy when true state is CNS cancer  

| Parameter         | p  | q  | c   | V    |
|-------------------|----|----|-----|------|
| p_TPUSB1_CNS1     | 0.69 | 0.40 | 0.000 | 233,100 |
| p_TPUSB1_CNS2     | 0.75 | 0.43 | 0.000 | 253,500 |
| p_TPUSB1_CNS3     | 0.37 | 0.28 | 0.000 | 123,600 |
| p_TRUSB1_CNS1     | 0.59 | 0.37 | 0.000 | 199,300 |
| p_TRUSB1_CNS2     | 0.69 | 0.40 | 0.000 | 232,900 |
| p_TRUSB1_CNS3     | 0.56 | 0.31 | 0.000 | 188,200 |

Prevalence of varying severity of CaP  

| Parameter         | p  | q  | c   | V    |
|-------------------|----|----|-----|------|
| prev_CaP1         | 1.16 | 0.51 | 0.010 | 390,900 |
| prev_CaP2         | 1.09 | 0.49 | 0.010 | 369,200 |
| prev_CaP3         | 0.12 | 0.23 | 0.000 | 39,320  |
| prev_CaP4         | 0.72 | 0.41 | 0.000 | 242,800 |

Diagnostic accuracy of mpMRI when true state is CNS cancer  

| Parameter         | p  | q  | c   | V    |
|-------------------|----|----|-----|------|
| p_mpMRI_CNS1      | 0.29 | 0.29 | 0.000 | 98,350  |
| p_mpMRI_CNS2      | 0.11 | 0.27 | 0.000 | 37,030  |
| p_mpMRI_CNS3      | 0.17 | 0.26 | 0.000 | 58,270  |

EVPPPI of individual parameters where population EVPPPI > £100,000. Explanation of parameter names: Prefix p_ = probability, prev = prevalence, q = long term QALYs accrued, c= long term accrued costs. TRUSB = trans-rectal ultrasound guided biopsy. TPUSB = trans-perineal ultrasound-guided biopsy. mpMRI = multiparametric magnetic resonance imaging. Suffix 1 = outcome of NC, 2 = CNS, 3 = CS. Thus p_TPUSB2_CNS_IR3 = probability of the second TP biopsy giving a result of clinically significant cancer following a first (TP) biopsy result of CNS, when the true state of the patient is intermediate risk cancer. CC1 = no infection from biopsy; CC2 = mild infection, CC3 = urinary tract infection, CC4 = sepsis. CaP1 = prevalence of no cancer, CaP2 = prevalence of CNS cancer, CaP3 = prevalence of intermediate risk cancer, CaP4 = prevalence of high risk cancer. As = Active surveillance. Rp = radical prostatectomy.
One-way sensitivity analysis on diagnostic accuracy of TP vs TR biopsy in patients with intermediate risk cancer.

As there are three possible outcomes from the biopsy (no cancer, clinically non-significant and clinically significant), a one-way sensitivity analysis on the relative diagnostic accuracy of TP vs TR is not straightforward. For this analysis we focus only on patients whose true disease state is intermediate risk cancer, and explore the impact of changing the probability of a ‘clinically significant’ (CS) diagnosis with a TP biopsy as a proportion of that of the TR. In other words, the relative risk of the TP biopsy giving a CS result when the patient has IR cancer, compared with a TR biopsy. This requires adjustment of the probabilities of a no-cancer or clinically non-significant result proportionately so that the probabilities sum to 1.

For example, in patients with intermediate risk cancer, the probability of a first TR biopsy giving a result of no cancer, clinically non-significant or clinically significant result which we denote Pa, Pb and Pc is 15%, 11% and 74% respectively.

To test the impact of assuming the probability of a TP biopsy being only 90% of the sensitivity of the TR, which we define as Pc(1) the formula is:

\[ \text{Pc(1)} = \text{Pc(0)} \times \text{RR} = 74\% \times 0.9 = 66.6\% \]

Pa and Pb are then adjusted according to the formulae:

\[ \text{Pa(1)} = \left( 1 - \text{Pc(1)} \right) \times \frac{\text{Pa(0)}}{\text{Pa(0)} + \text{Pb(0)}} \]
\[ \text{Pb(1)} = \left( 1 - \text{Pc(1)} \right) \times \frac{\text{Pb(0)}}{\text{Pa(0)} + \text{Pb(0)}} \]

An illustrative example calculated on the mean probabilities is shown in Table A6.5.

| RR    | p(NC) | p(CNS) | p(CS) |
|-------|-------|--------|-------|
| Base value (TR Bx) | 15.00% | 11.00% | 74.00% | 100.00% |
| 0.1   | 53.42% | 39.18% | 7.40%  | 100.00% |
| 0.2   | 49.15% | 36.05% | 14.80% | 100.00% |
| 0.3   | 44.88% | 32.92% | 22.20% | 100.00% |
| 0.4   | 40.62% | 29.78% | 29.60% | 100.00% |
| 0.5   | 36.35% | 26.65% | 37.00% | 100.00% |
| 0.6   | 32.08% | 23.52% | 44.40% | 100.00% |
| 0.7   | 27.81% | 20.39% | 51.80% | 100.00% |
| 0.8   | 23.54% | 17.26% | 59.20% | 100.00% |
| 0.9   | 19.27% | 14.13% | 66.60% | 100.00% |
| 1     | 15.00% | 11.00% | 74.00% | 100.00% |

This approach was applied to the first and second biopsies simultaneously (parameters p_TPUSB1_IR, p_TPUSB2_NC_IR and p_TPUSB2_CNS_IR) to all the sampled values in the PSA. At a zero price of CamPROBE, the sensitivity must be no less than 98.8% that of the trans-rectal biopsy for it to be cost-effective (Table A6.6). At the maximum cost-effective price CamPROBE must be no less than 99.97% of the sensitivity of the trans-rectal biopsy for it to be cost-effective (Table A6.7).
Note this is not the required absolute sensitivity of CamPROBE, but the sensitivity relative to trans-rectal biopsy.

Table A6.6: One-way sensitivity analysis of relative sensitivity of TP vs TR biopsy (zero price of CamPROBE)

| RR*   | Cost  | QALYs       | TRUSbx | Cost  | QALYs       | TPUSBx | Increments |
|-------|-------|-------------|--------|-------|-------------|--------|------------|
| 0.00  | 5051.523 | 10.291      | 2290.034 | 9.905 | -2761.49    | -0.386 | -4957.67   |
| 0.1   | 5051.523 | 10.291      | 2563.298 | 9.943 | -2488.23    | -0.348 | -4455.84   |
| 0.2   | 5051.523 | 10.291      | 2836.561 | 9.982 | -2214.96    | -0.309 | -3954.01   |
| 0.3   | 5051.523 | 10.291      | 3109.824 | 10.021 | -1941.7     | -0.27  | -3452.17   |
| 0.4   | 5051.523 | 10.291      | 3383.088 | 10.06 | -1668.44    | -0.231 | -2950.34   |
| 0.5   | 5051.523 | 10.291      | 3656.351 | 10.098 | -1395.17    | -0.193 | -2448.5    |
| 0.6   | 5051.523 | 10.291      | 3929.615 | 10.137 | -1121.91    | -0.154 | -1946.67   |
| 0.7   | 5051.523 | 10.291      | 4202.878 | 10.176 | -848.645    | -0.115 | -1444.84   |
| 0.8   | 5051.523 | 10.291      | 4476.142 | 10.215 | -575.381    | -0.076 | -943.005   |
| 0.9   | 5051.523 | 10.291      | 4749.405 | 10.254 | -302.118    | -0.037 | -441.171   |
| 0.91  | 5051.523 | 10.291      | 4776.732 | 10.257 | -274.791    | -0.034 | -390.988   |
| 0.92  | 5051.523 | 10.291      | 4804.058 | 10.261 | -247.465    | -0.03  | -340.805   |
| 0.93  | 5051.523 | 10.291      | 4831.384 | 10.265 | -220.139    | -0.026 | -290.621   |
| 0.94  | 5051.523 | 10.291      | 4858.711 | 10.269 | -192.812    | -0.022 | -240.438   |
| 0.95  | 5051.523 | 10.291      | 4886.037 | 10.273 | -165.486    | -0.018 | -190.255   |
| 0.96  | 5051.523 | 10.291      | 4913.363 | 10.277 | -138.16     | -0.014 | -140.071   |
| 0.97  | 5051.523 | 10.291      | 4940.69  | 10.281 | -110.833    | -0.01  | -89.888    |
| 0.98  | 5051.523 | 10.291      | 4968.016 | 10.285 | -83.507     | -0.006 | -39.7047   |
| 0.981 | 5051.523 | 10.291      | 4970.749 | 10.285 | -80.774     | -0.006 | -34.6863   |
| 0.982 | 5051.523 | 10.291      | 4973.481 | 10.285 | -78.042     | -0.006 | -29.668    |
| 0.983 | 5051.523 | 10.291      | 4976.214 | 10.286 | -75.309     | -0.005 | -24.6497   |
| 0.984 | 5051.523 | 10.291      | 4978.947 | 10.286 | -72.576     | -0.005 | -19.6313   |
| 0.985 | 5051.523 | 10.291      | 4981.679 | 10.286 | -69.844     | -0.005 | -14.613    |
| 0.986 | 5051.523 | 10.291      | 4984.412 | 10.287 | -67.111     | -0.004 | -9.59466   |
| 0.987 | 5051.523 | 10.291      | 4987.144 | 10.287 | -64.379     | -0.004 | -4.57633   |
| 0.9871 | 5051.523 | 10.291 | 4987.418 | 10.287 | -64.105     | -0.004 | -4.0745    |
| 0.9872 | 5051.523 | 10.291 | 4987.691 | 10.287 | -63.832     | -0.004 | -3.57266   |
| 0.9873 | 5051.523 | 10.291 | 4987.964 | 10.287 | -63.559     | -0.004 | -3.07083   |
| 0.9874 | 5051.523 | 10.291 | 4988.238 | 10.287 | -63.285     | -0.004 | -2.569     |
| 0.9875 | 5051.523 | 10.291 | 4988.511 | 10.287 | -63.012     | -0.004 | -2.06716   |
| 0.9876 | 5051.523 | 10.291 | 4988.784 | 10.287 | -62.739     | -0.004 | -1.56533   |
| 0.9877 | 5051.523 | 10.291 | 4989.057 | 10.287 | -62.466     | -0.004 | -1.0635    |
| 0.9878 | 5051.523 | 10.291 | 4989.331 | 10.288 | -62.192     | -0.003 | -0.56166   |
| 0.9879 | 5051.523 | 10.291 | 4989.604 | 10.288 | -61.919     | -0.003 | -0.05983   |
| 0.988  | 5051.523 | 10.291 | 4989.877 | 10.288 | -61.646     | -0.003 | 0.442004   |
| 0.989  | 5051.523 | 10.291 | 4992.61  | 10.288 | -58.913     | -0.003 | 5.460338   |
| 0.99   | 5051.523 | 10.291 | 4995.342 | 10.288 | -56.181     | -0.003 | 10.47867   |
| 1.0    | 5051.523 | 10.291 | 5022.669 | 10.292 | -28.854     | 0.001 | 60.66201   |
| RR* | Cost  | QALYs | Cost  | QALYs | Cost  | QALYs | Cost  | QALYs | Cost  | QALYs | Cost  | QALYs | Cost  | QALYs | Increments | Net Benefit** |
|-----|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------------|--------------|
| 0.01 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | -0.386 | -5016.55 |
| 0.1  | 5051.523 | 10.291 | 2348.913 | 9.905 | -2702.61 | -0.348 | -4514.72 |
| 0.2  | 5051.523 | 10.291 | 2895.44 | 9.982 | -2156.08 | -0.309 | -4012.88 |
| 0.3  | 5051.523 | 10.291 | 3168.703 | 10.021 | -1882.82 | -0.27 | -3511.05 |
| 0.4  | 5051.523 | 10.291 | 3441.967 | 10.06 | -1609.56 | -0.231 | -3009.22 |
| 0.5  | 5051.523 | 10.291 | 3715.23 | 10.098 | -1336.29 | -0.193 | -2507.38 |
| 0.6  | 5051.523 | 10.291 | 3988.493 | 10.137 | -1063.03 | -0.154 | -2005.55 |
| 0.7  | 5051.523 | 10.291 | 4261.757 | 10.176 | -789.766 | -0.115 | -1503.72 |
| 0.8  | 5051.523 | 10.291 | 4535.02 | 10.215 | -516.503 | -0.076 | -1001.88 |
| 0.9  | 5051.523 | 10.291 | 4808.284 | 10.254 | -243.239 | -0.037 | -500.05 |
| 0.91 | 5051.523 | 10.291 | 4835.61 | 10.257 | -215.913 | -0.034 | -449.867 |
| 0.92 | 5051.523 | 10.291 | 4862.937 | 10.261 | -188.586 | -0.03 | -399.683 |
| 0.93 | 5051.523 | 10.291 | 4890.263 | 10.265 | -161.26 | -0.026 | -349.5 |
| 0.94 | 5051.523 | 10.291 | 4917.589 | 10.269 | -133.934 | -0.022 | -299.317 |
| 0.95 | 5051.523 | 10.291 | 4944.916 | 10.273 | -106.607 | -0.018 | -249.133 |
| 0.96 | 5051.523 | 10.291 | 4972.242 | 10.277 | -79.281 | -0.014 | -198.95 |
| 0.97 | 5051.523 | 10.291 | 4999.568 | 10.281 | -51.955 | -0.01 | -148.767 |
| 0.98 | 5051.523 | 10.291 | 5026.895 | 10.285 | -24.628 | -0.006 | -98.5833 |
| 0.99 | 5051.523 | 10.291 | 5054.221 | 10.288 | 2.698 | -0.003 | -48.4 |
| 0.991 | 5051.523 | 10.291 | 5056.954 | 10.289 | 5.431 | -0.002 | -43.3816 |
| 0.992 | 5051.523 | 10.291 | 5059.686 | 10.289 | 8.163 | -0.002 | -38.3633 |
| 0.993 | 5051.523 | 10.291 | 5062.419 | 10.29 | 10.896 | -0.001 | -33.345 |
| 0.994 | 5051.523 | 10.291 | 5065.152 | 10.29 | 13.629 | -0.001 | -28.3266 |
| 0.995 | 5051.523 | 10.291 | 5067.884 | 10.29 | 16.361 | -0.001 | -23.3083 |
| 0.996 | 5051.523 | 10.291 | 5070.617 | 10.29 | 19.094 | 0 | -18.29 |
| 0.997 | 5051.523 | 10.291 | 5073.349 | 10.29 | 21.826 | 0 | -13.2716 |
| 0.998 | 5051.523 | 10.291 | 5076.082 | 10.29 | 24.559 | 0 | -8.25329 |
| 0.999 | 5051.523 | 10.291 | 5078.815 | 10.29 | 27.292 | 0.001 | -3.23496 |
| 0.9991 | 5051.523 | 10.291 | 5079.088 | 10.29 | 27.565 | 0.001 | -2.73313 |
| 0.9992 | 5051.523 | 10.291 | 5079.361 | 10.29 | 27.838 | 0.001 | -2.23129 |
| 0.9993 | 5051.523 | 10.291 | 5079.635 | 10.29 | 28.112 | 0.001 | -1.72946 |
| 0.9994 | 5051.523 | 10.291 | 5079.908 | 10.29 | 28.385 | 0.001 | -1.22763 |
| 0.9995 | 5051.523 | 10.291 | 5080.181 | 10.29 | 28.658 | 0.001 | -0.72579 |
| 0.9996 | 5051.523 | 10.291 | 5080.454 | 10.29 | 28.931 | 0.001 | -0.22396 |
| 0.9997 | 5051.523 | 10.291 | 5080.728 | 10.29 | 29.205 | 0.001 | 0.277873 |
| 0.9998 | 5051.523 | 10.291 | 5081.001 | 10.29 | 29.478 | 0.001 | 0.779707 |
| 0.9999 | 5051.523 | 10.291 | 5081.274 | 10.29 | 29.751 | 0.001 | 1.28154 |
| 1    | 5051.523 | 10.291 | 5081.547 | 10.29 | 30.024 | 0.001 | 1.783374 |