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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med. DOI: 10.1056/NEJMoa1801993

Supplementary Appendix

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Section S1: Collaborators

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Section S2: Further details on statistical methods

We used Stata version 15 and SAS version 9.4 for the analyses of primary and secondary outcomes. We conducted intention-to-treat analyses for all secondary outcomes as outlined below (see list of outcomes in Table S6).

Proportion of men with clinically insignificant cancer detected
Clinically insignificant cancer was defined as Gleason grade 3+3 disease. We fitted a generalized linear mixed model with the clinically insignificant cancer binary outcome as the dependent variable, arm as an independent variable and center as a random effect. We used this model to estimate an adjusted absolute difference in detection rates (i.e. risk difference) by using an identity link function with a binomial distribution.

Proportion of men in the MRI±TB arm who avoid biopsy
We calculated the number of men in the MRI±TB arm in whom there was no suspicion of clinically significant cancer (PIRADSv2 score ≤2 and so biopsy avoided) divided by the total number of men in the arm.

Proportion of men in whom the PIRADSv2 score for suspicion of clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was detected
We calculated the proportion of men who underwent biopsy in the MRI±TB arm but in whom no clinically significant cancer was detected.

Proportion of men who go on to definitive local or systemic treatment
Treatment for prostate cancer may include:

- Active surveillance
- Radical prostatectomy
- Radical radiotherapy
- Radical brachytherapy
- Focal therapy
- Hormone therapy

We calculated the proportion of men in each arm who underwent each treatment.

Proportion of Gleason grade upgrading in men undergoing radical prostatectomy
Of the men who underwent radical prostatectomy, the proportion of men who had cancer upgraded from the biopsy histopathology to the radical prostatectomy histopathology in each arm was calculated and tabulated.

Proportion of men with post-biopsy adverse events
Immediate post-biopsy discomfort and pain were characterized by intensity using the numerical analogue score and scores for each arm were summarised. 30-day biopsy specific complications and adverse events were characterized according to their presence, absence, duration and how much of a problem the symptoms caused the participant. Whether the participant had contact with health care was also recorded. The proportion of individuals experiencing each symptom, proportion in whom the symptom caused a problem and proportion who had contact with healthcare were ascertained. The biopsy specific complications that were assessed included pain, urinary retention, fever, pain, erectile

dysfunction, urinary incontinence, haematuria, haematochezia and haemotospermia. Any post-biopsy complications up to 30 days post biopsy procedure was tabulated and listed by duration and management.

Cancer core length of the most involved biopsy core

The mean maximum cancer core length from each arm was compared using mixed effects linear regression with maximum cancer core length as the dependent variable, arm as an independent variable and center as a random effect.

Health-related quality of life scores

EQ-5D-5L descriptive domain summary indices and visual analogue scores were assessed at baseline, and 24 hours and 30 days post intervention. Scores from the 5 domains of the questionnaire were converted to EQ-5D descriptive scores using the value set for the United Kingdom. To estimate mean differences between arms, each outcome was analysed using a repeated-measures mixed model with adjustment for baseline levels of the outcome variable. Only men who fully completed a questionnaire were included in the analyses.

Section S3: Adjustment for multiple secondary outcomes

In post-hoc analyses following NEJM guidance, the Bonferroni correction was used to adjust the standard threshold for statistical significance for the three secondary outcomes: proportion of clinically insignificant cancer, maximum core length and health-related quality of life. A two-sided P value of less than 0.017(i.e., 0.05/3) was used to indicate statistical significance instead of the conventional 0.05 value.

Using the 0.05 threshold the difference in health-related quality of life between MRI±TB and TRUS biopsy was not statistically significant at 24 hours and 30 days post intervention (Table S10) and so inferences remain unchanged after adjustment for multiplicity.

Similarly, for the difference in maximum cancer core length, the P value was 0.053 (see Table 2) and is not statistically significant either at the standard critical value of 0.05 or the adjusted value of 0.017.

For the difference in clinically insignificant cancer, the results remain statistically significant ($P<0.001$) whichever threshold it was compared to.

Figure S1: Trial Schema[1]

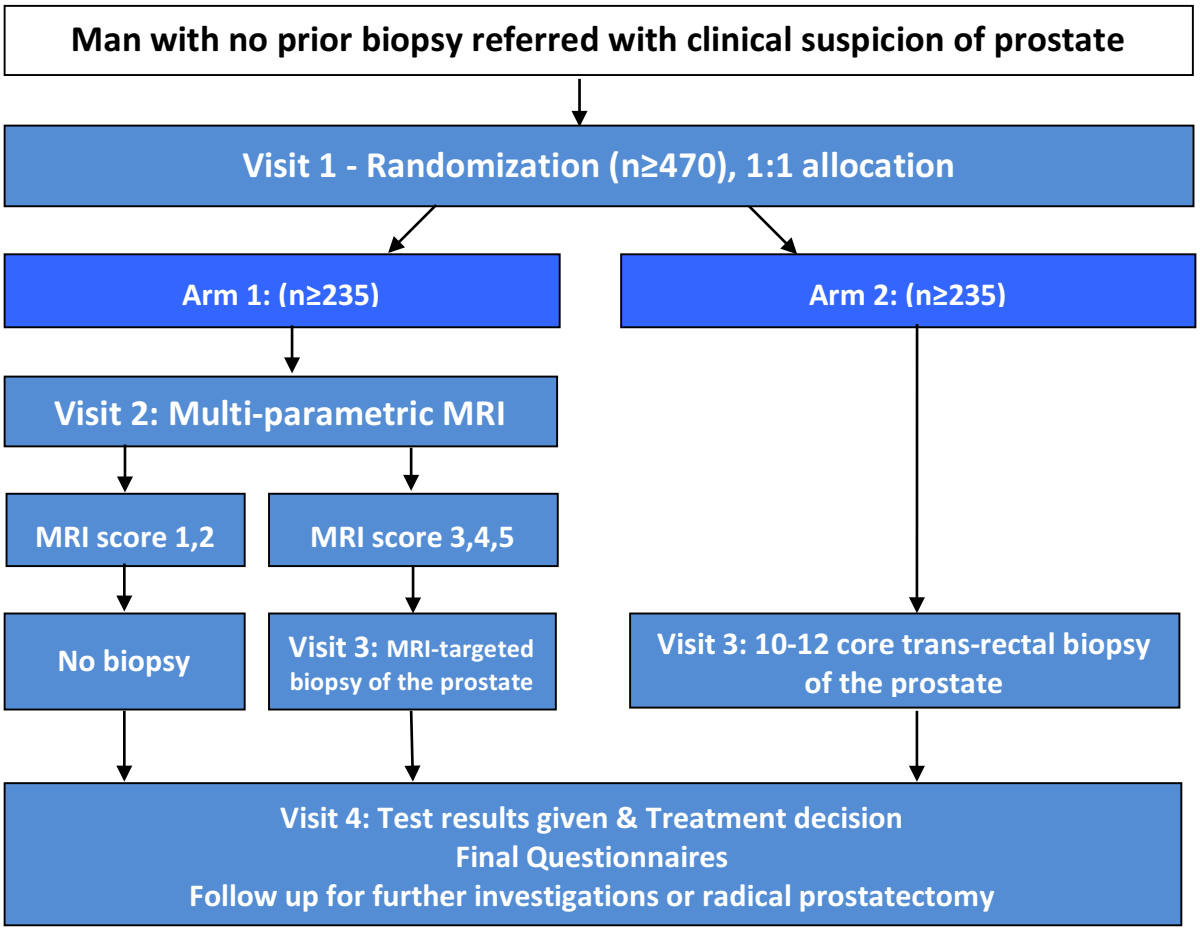

Table S1: Recruitment by site

Table 8: Recruitment by centre

Centre	MRI±TB	TRUS-biopsy	Total
Helsinki University Hospital, Finland	37	37	74
Centro de Urologia CDU, Argentina	31	33	64
Sapienza University, Italy	31	30	61
Mayo clinic, Rochester, Minnesota, USA	27	27	54
Oulu University Hospital, Finland	27	26	53
San Raffaele Hospital, Italy	26	25	51
University College London Hospitals NHS Foundation Trust, UK	10	11	21
Martini Klinik, Hamburg, Germany	10	10	20
London North West Healthcare NHS Trust, UK	7	6	13
Erasmus University Medical Center, Rotterdam, the Netherlands	6	6	12
Hampshire Hospitals NHS Foundation Trust, UK	6	6	12
CHU Lille, France	4	5	9
University of Chicago, USA	5	4	9
Whittington Health NHS Trust, UK	5	4	9
Jewish General Hospital, Montreal, Canada	4	4	8
Ghent University Hospital, Belgium	3	2	5
Bordeaux Pellegrin University Hospital, France	2	2	4
Princess Alexandra Hospital NHS Trust, UK	2	2	4
RadboudUMC, the Netherlands	2	2	4
Royal Free London NHS Foundation Trust, UK	2	2	4
University Hospital Bern, Switzerland	2	2	4
University Hospital Heidelberg, Germany	2	1	3
Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, France	1	1	2
Weill Cornell Medicine New York-Presbyterian Hospital, USA	0	0	0
Hospices Civils de Lyon of the Hôpital Edouard Herriot, France	0	0	0
Total	**252**	**248**	**500**

Table S2: Eligibility criteria for enrollment[1]

Inclusion criteria:
1. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy 2. Serum PSA ≤ 20ng/ml 3. Suspected stage ≤ T2 on rectal examination (suspected organ-confined prostate cancer) 4. Fit to undergo all procedures listed in protocol 5. Able to provide written informed consent
Exclusion criteria:
1. Prior prostate biopsy 2. Prior treatment for prostate cancer 3. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤ 50mls/min) 4. Contraindication to prostate biopsy 5. Men in whom artefact would reduce the quality of the MRI 6. Previous hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work 7. Unfit to undergo any procedures listed in protocol

Table S3: MRI protocols

Site	1	2	3	4	5	6	7	7	8
MRI manufacturer	Philips	Philips	GE	GE	Siemens	Philips	Siemens	Philips	Philips
MRI Model	Achieva	Ingenia	Discovery	Discovery	Skyra	Achieva	Avanto	Achieva	Ingenia
Field Strength	3T	3T	3T	3T	3T	1.5T	1.5T	3T	3T
Coils	PPA	PPA	PPA & ER	PPA	PPA	PPA & ER	PPA	PPA	PPA
Sequences used	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE
T2 sequence details									
Planes acquired	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal	Axial, coronal	Axial, coronal, sagittal
Slice Thickness (axial)	3mm	3mm	3mm	3mm	3mm	3mm	3mm	3mm	3mm
Voxel size (axial)	0.389 x 0.389 x 3 mm	0.352 x 0.352 x 3 mm	0.435 x 0.435 x 3 mm	0.469 x 0.469 x 3 mm	0.521 x 0.521 x 3.3mm	0.312 x 0.312 x 3 mm	0.391 x 0.391 x 3.45 mm	0.375 x 0.375 x 3.3mm	0.37x0.37x3mm
DCE sequence details									
Temporal resolution	6.91 s	10 s	5 s	6.5 s	7.4 s	9 s	11 s	11 s	3.2s
Model used for post-processing	DynaCAD	DynaCAD	genIQ	DynCAD	NR	NR	No	No	DynaCAD
Slice Thickness	4mm	3 mm	1.5 mm	3mm	3.6mm	3mm	3mm	3mm	3mm
Voxel size	0.75 x 0.75 x 4mm	1.3 x 1.3 x 3mm	1.02 x 1.02 x 1.5mm	0.859 x 0.859 x 3mm	1.35 x 1.35 x 3.6mm	0.625 x 0.625 x 3mm	0.677 x 0.677 x 3mm	0.938 x 0.938 x 3mm	1.02 x 1.02 x3mm
Power Injector	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gadolinium contrast	Dotarem	Gadovist	Gadovist	Dotarem	Dotarem	Gadobutrol	Dotarem	Dotarem	Dotarem
Injection rate	3mls/s	1ml/s	3mls/s	3mls/s	2.5mls/s	2mls/s	3mls/s	3mls/s	NR
Flush given after	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR
Fat saturation (FS)/subtraction(SUB)	Yes (FS)	No	Yes (FS)	No	No	Yes (FS)	Yes (FS)	Yes (FS)	No
DWI sequence details									
B-values used	0,100,800, 2000	0,800,1600	0,500,1000, 3000	100,1000,1600	50,400,800, 1500, 3000	50,800,1600	0,150,500, 1000,1400	0,150,500, 1000,2000	0,50,1200
ADC threshold applied?	No	No	Yes	No	No	No	Yes	Yes	No
DWI combinations	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value & ADC
Slice Thickness	3mm	3mm	3mm	6mm	5mm	3mm	5mm	5mm	3mm
Voxel size	0.893 x 0.893 x 3mm	1.47 x 1.47 x 3mm	0.892 x 0.892 x 3 mm	1.02 x 1.02 x 6 mm	1.98 x 1.98 x 5.2 mm	1.25 x 1.25 x 3.3 mm	1.51 x 1.51 x 5 mm	0.98 x 0.982 x 5 mm	1.02x1.02x3mm
Bowel Relaxant	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

PPA = pelvic phased array, ER = endorectal, Res. = resolution, DCE = dynamic contrast enhanced, DWI = diffusion weighted imaging, s = second, NR = not reported

Table S3: MRI protocols (continued…)

Site	9	10	11	12	13	14	15	16
MRI manufacturer	Philips	GE	Siemens	Philips	Philips	Philips	Siemens	Siemens
MRI Model	Achieva	Discovery	Aera	Ingenia	Ingenia	Achieva	Skyra	Trio
Field Strength	1.5T	3T	1.5T	1.5T	3T	1.5T	3T	3T
Coils	PPA	PPA	PPA	PPA	PPA & ER	PPA	PPA	PPA
Sequences used	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE
T2 sequence details								
Planes acquired	Axial, coronal, sagittal	Axial, sagittal	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal	Axial,coronal, sagittal	Axial, coronal, sagittal	Axial,coronal, sagittal
Slice Thickness (axial)	3mm	3mm	3mm	3mm	3 mm	3mm	3mm	3mm
Voxel size (axial)	0.417x0.417x 3.3mm	0.371 x 0.371 x3.3mm	0.781x0.781x 3.3mm	0.511x0.511 x3mm	0.45x0.45 x3mm	0.703x0.703 x3.3mm	0.625x0.625 x3mm	0.512x0.512 x3mm
DCE sequence details								
Temporal resolution	18s	4-5s	17s	15s	7s	12 s	9.2s	9s
Model used for post-processing	NR	No	No	Tofts	No	No	No	No
Slice Thickness	1.5mm	4mm	3mm	3mm	1.5mm	3mm	3mm	3.6mm
Voxel size	0.488x0.488 x1.25mm	1.33x1.33 x1.5mm	0.875x0.875x 3mm	0.625x.0.625 x3mm	0.994x0.994 x1.5mm	1.45x1.45 x3mm	1.25x1.25x3.1mm	1.35x1.88x3.6mm
Power Injector	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Gadolinium contrast	Dotarem	Dotarem	Dotarem	Gadovist/Dotarem	Multihance/Dotarem	Gadovist	Optimark/Omniscan	Omniscan
Injection rate	3mls/s	3mls/s	3mls/s	2mls/s	2mls/s	3mls/s	2.5mls/s	3mls/sec
Flush given after	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Fat saturation (FS)/subtraction(SUB)	Yes (FS)	Yes (FS)	Yes (FS)	No	Yes (FS)	Yes (FS)	Yes (FS)	No
DWI sequence details								
B-values used	0,500,1000, 1400	50,400,800	0,150,500, 1000, 1400	1,150,1000,2000	0,50,150,990,1500	0,100,500, 1000,1400	50 ,1400	50,400,800, 1200,1600
ADC threshold applied?	No	Yes	Yes	No	No	Yes	No	No
DWI combinations	Multi-b value, ADC & high b	Multi-b value & ADC	Multi-b value, ADC & high b	Multi-b value & ADC	Multi-b value & ADC	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b
Slice Thickness	4.5mm	3mm	5mm	4mm	3mm	5mm	4mm	3mm
Voxel size	0.977x0.977x 4.5 mm	0.703x0.703x 3.3mm	1.72x1.72x 5mm	1.39x1.39x 4mm	1.12x1.12x3mm	1.3x1.3 x5.5mm	1.69x1.69x4mm	1.62x2.14x3mm
Bowel Relaxant	No	Yes	Yes	Yes	Yes	Yes	No	Yes

PPA = pelvic phased array, ER = endorectal, Res. = resolution, DCE = dynamic contrast enhanced, DWI = diffusion weighted imaging, s = second, NR = not reported

Table S3: MRI protocols (continued…)

Site	17	18	19	20	21	22	23
MRI manufacturer	Siemens	Siemens	Siemens	Philips	Siemens	Siemens	GE
MRI Model	Avanto	Avanto	Skyra	Ingenia	Skyra	Prisma	Discovery
Field Strength	1.5T	1.5T	3T	1.5T	3T	3T	3T
Coils	PPA	PPA	PPA	PPA	PPA	PPA	PPA
Sequences used	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE
T2 sequence details							
Planes acquired	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial,coronal, sagittal	Axial,coronal, sagittal	Axial, coronal	Axial,coronal, sagittal	Axial, sagittal
Slice Thickness (axial)	3.5mm	3mm	3mm	3mm	3 mm	3mm	3mm
Voxel size (axial)	0.5x0.5x3.5mm	0.43x0.43 x3.3mm	0.5x0.5 x3.6mm	0.45x0.45 x3.3mm	0.43x0.43x3 mm	0.312x0.312 x3mm	0.43x0.43x 3mm
DCE sequence details							
Temporal resolution	9.6s	14s	3.27s	3.3s	3.47s	4.42s	6s
Model used for post- processing	NR	No	proCAD	No	No	Tofts	No
Slice Thickness	3.5mm	3.5mm	3mm	2mm	3.5mm	1.2mm	3mm
Voxel size	1.3x1.0x3.5mm	1.4x1.0x3.5mm	0.857x0.857 x3mm	1.42x1.42x2mm	1.38x1.38x 3.5mm	1.19x1.19 x1.2mm	0.938x0.938 x3mm
Power Injector	Yes	Yes	Yes	Yes	Yes	No	Yes
Gadolinium contrast	Dotarem/Gadovist	Dotarem	Dotarem	Dotarem	Multihance	Gadovist	Gadoterate
Injection rate	3mls/s	3mls/s	2.5mls/s	3mls/s	2.5mls/s	3mls/s	3mls/s
Flush given after	Yes	Yes	Yes	Yes	Yes	No	Yes
Fat saturation (FS)/subtraction(SUB)	Yes (FS)	NR	No	Yes (FS)	No	Yes (FS)	Yes (FS)
DWI sequence details							
B-values used	0,100,800,1500	50,500,1000, 1350	400,800,1400	0,50,400, 800,1200	0,500,1000, 2000	0,50,100,150, 200,250,800, 1000,1500,4000	1,50,150,300, 800, 2000
ADC threshold applied?	Yes	No	No	No	Yes	No	No
DWI combinations	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value & ADC	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value & ADC
Slice Thickness	3.5mm	4mm	3mm	6mm	4mm	3mm	3mm
Voxel size	1.8x1.4x3.5mm	2.45x2.45x4mm	2.0x2.0x3.6mm	1.89x1.89x6mm	3.1x3.1x4mm	3x3x3mm	1.4x1.4x3mm
Bowel Relaxant	Yes	Yes	Yes	No	Yes	Yes	Yes

PPA = pelvic phased array, ER = endorectal, Res. = resolution, DCE = dynamic contrast enhanced, DWI = diffusion weighted imaging, s = second, NR = not reported

Table S4: Clinician experience

The following table details the experience of the clinicians involved in PRECISION trial procedures at the start of the trial

Clinician category	Total number in study	Experience of individual clinicians prior to starting study	
		Descriptor of experience	Median number, n (IQR)
Transrectal ultrasound guided (TRUS) biopsy operators	38	Number of TRUS biopsies previously performed	750 (300-1000)
		Number of TRUS biopsies performed per year	100 (50-190)
MRI-targeted biopsy operators	33	Number of MRI-targeted biopsies previously performed	100 (28-250)
		Number of MRI-targeted biopsies performed per year	60 (25-100)
Radiologists reporting MRI	37	Number of prostate MRIs reported per year	300 (200-500)
		Number of years of experience	5 (4.5-10)
Pathologists reporting prostate specimens	39	Number of patient's prostate specimens analyzed/year	230 (100-350)
		Number of years of experience	11 (8-20)

Table S5: Techniques used by sites for MRI-targeted prostate biopsy

Site	No. of men randomized to MRI±TB arm	Access route	Registration used	Name of software assisted system (where applicable)
1	37	Transrectal	Visual & Software-assisted	Philips UroNav
2	31	Transrectal	Visual & Software-assisted	UC-Care Medical Systems
3	31	Transrectal	Software-assisted	Koelis Urostation
4	27	Transrectal	Software-assisted	Philips UroNav
5	27	Transrectal	Software-assisted	Koelis Urostation
6	26	Transrectal	Software-assisted	BK Biojet
7	10	Transperineal	Visual	N/A
8	10	Transrectal	Software-assisted	Koelis Urostation
9	7	Transrectal	Visual	N/A
10	6	Transrectal	Software-assisted	Koelis Urostation
11	6	Transperineal	Visual	N/A
12	4	Transrectal	Software-assisted	Vnav Esaote
13	5	Transrectal	Visual & Software-assisted	Philips UroNav
14	5	Transperineal	Visual	N/A
15	4	Transrectal	Software-assisted	Koelis Urostation
16	3	Transrectal	Visual	N/A
17	2	Transrectal	Software-assisted	Philips EPIQ
18	2	Transperineal	Visual	N/A
19	2	Transrectal	Software-assisted	Toshiba Medical Aplio 500
20	2	Transrectal	Software-assisted	Philips UroNav
21	2	Transrectal	Software-assisted	Eigen Artemis
22	2	Transperineal	Software-assisted	Medcom BiopSee
23	1	Transrectal	Software-assisted	Koelis Urostation

MRI±TB = MRI±targeted biopsy; Software-assisted = MRI/US fusion

Table S6: Secondary outcomes in the study[1]

Outcome	Time frame for assessment & further details
Proportion of men with clinically insignificant cancer (Gleason grade 3+3)	When histology results available, at an expected average of 30 days post-intervention
Proportion of men in MPMRI arm who avoid biopsy	When MRI results available, at an expected average of 30 days post-MRI
Proportion of men in whom MPMRI score for suspicion of clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was detected	When histology results available, at an expected average of 30 days post-biopsy
Proportion of men who go on to definitive local treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g. hormone therapy, chemotherapy)	After treatment decision, at an expected average of 30 days post-biopsy
Cancer core length of the most involved biopsy core (maximum cancer core length, mm)	When histology results available, at an expected average of 30 days post-intervention
Proportion of men with post-biopsy adverse events	30 days post-biopsy
Health related quality of life	Baseline, 24 hours post intervention and 30 days post intervention
Proportion Gleason grade upgrading in men undergoing radical prostatectomy	An expected average of 90 days post-biopsy
Cost per diagnosis of cancer	An NHS health services perspective was taken for a cost-effectiveness analysis assessing the within-arm costs of the diagnostic tests, staging tests and health care contacts within 30-days in relation to numbers of clinically significant and insignificant cancers detected within that arm

Table S7a,b,c: Derivation of the Intention to treat, modified intention to treat and per protocol analyses of the primary outcome

These tables were derived in the statistical analysis plan, finalised prior to obtaining the data from the study

Table S7a: Randomized allocation and analysis group for intention-to-treat analysis

Test allocated	Test received	Analysis group
TRUS biopsy	TRUS biopsy	TRUS biopsy
TRUS biopsy	MRI (score 1 or 2) and no biopsy	TRUS biopsy
TRUS biopsy	MRI (score 3, 4 or 5) and MRI-TB	TRUS biopsy
TRUS biopsy	Other	TRUS biopsy
MRI±TB	TRUS biopsy	MRI
MRI±TB	MRI (score 1 or 2) and no biopsy	MRI
MRI±TB	MRI (score 3, 4 or 5) and MRI-TB	MRI
MRI±TB	Other	MRI

MRI±TB = MRI±targeted biopsy, TRUS = Transrectal ultrasound guided

Table S7b: Comparisons of intention-to-treat, modified intention-to-treat and per-protocol analyses for TRUS biopsy arm. Conditions for excluding patients based on deviations from the protocol.

Randomization arm	Diagnostic test received	Action for ITT analysis	Action for modified ITT	Action for per-protocol analysis
TRUS biopsy	Other diagnostic test	Include	Include	Exclude
TRUS biopsy	MRI (score 1 or 2) and no biopsy	Include	Include	Exclude
TRUS biopsy	MRI (score 3, 4 or 5) and MRI-TB	Include	Include	Exclude
TRUS biopsy	MRI (score 1 or 2) but still has other biopsy	Include	Include	Exclude
TRUS biopsy	MRI (score 3, 4 or 5) but other biopsy	Include	Include	Exclude
TRUS biopsy	TRUS biopsy but with deviation in biopsy core number greater than ± 10%	Include	Include	Exclude
TRUS biopsy	Withdrawn prior to any fully completed diagnostic test	Include	Exclude	Exclude

ITT, intention-to-treat; MRI±TB = MRI±targeted biopsy, TRUS = Transrectal ultrasound guided

Table S7c: Comparisons of intention-to-treat, modified intention-to-treat and per protocol analyses for MRI±TB arm. Conditions for excluding patients based on deviations from the protocol.

Randomization arm	Diagnostic test received	Action for ITT analysis	Action for modified ITT	Action for per-protocol analysis
MRI±TB	TRUS biopsy	Include	Include	Exclude
MRI±TB	Other biopsy test	Include	Include	Exclude
MRI±TB	Attempted but incomplete MRI (e.g. because patient could not tolerate full MRI) followed by TRUS biopsy or other biopsy test	Include	Include	Exclude
MRI±TB	MRI±TB but MRI not multi-parametric (e.g. contrast or diffusion weighted sequences not taken)	Include	Include	Exclude
MRI±TB	MRI (score 3, 4 or 5) and MRI-TB but with deviation in biopsy core number greater than ± 10%	Include	Include	Exclude
MRI±TB	MRI (score 3, 4 or 5) and MRI-TB but with additional biopsy test at same sitting	Include	Include	Exclude
MRI±TB	MRI (score 3, 4 or 5) and MRI-TB but where not all of MRI-suspicious areas were targeted e.g. 3 suspicious areas identified but only 1 targeted	Include	Include	Exclude
MRI±TB	MRI (score 3, 4 or 5) but no biopsy	Include	Exclude	Exclude
MRI±TB	MRI (score 3, 4 or 5) but other type of biopsy	Include	Include	Exclude
MRI±TB	Withdrawn prior to any fully completed diagnostic test	Include	Exclude	Exclude

ITT, intention-to-treat; MRI±TB = MRI±targeted biopsy, TRUS = Transrectal ultrasound guided

Table S8: MPMRI features

Characteristic	MRI±TB (N = 246)*
Field strength of magnet — no. (%)	
1.5T	62 (25.2)
3.0T	184 (74.8)
MRI suspicion score — no. (%)	
1–2	71 (28.9)
3, 4 or 5	175 (71.1)
Suspicious lesions per patient — no. (%)†	
1 lesion	107 (61.1)
2 lesions	44 (25.1)
3 lesions	24 (13.7)
Highest MRI score for men with suspicious lesions‡ — no. (%)	
Score 3	51 (29.1)
Score 4	70 (40.0)
Score 5	54 (30.9)
MRI volume of prostate§ — mls	
Median (IQR)	46.0 (34.9 to 62.0)
Problems with MR quality — no. (%)	13 (5.3)
Median maximum lesion diameter (lesion-based)Δ — mm	
Median (IQR)	12 (8 to 15)
Median lesion volume (lesion-based)Δ — mls	
Median (IQR)	0.6 (0.3 to 1.2)

MRI = Multiparametric MRI, MRI±TB = MRI±targeted biopsy

*Six of the patients in the MRI arm were protocol violators with no MRI data. Therefore, the number of patients is 246 unless indicated otherwise.

†Percentages are based on the 175 men with MRI suspicion score of 3, 4, or 5.

‡Each patient may have more than one suspicious lesion. The highest MRI score for each of the 175 patients with at least one suspicious lesion was included so that each patient contributed only one score.

§Prostate volume was unknown for one man and so the results are based on 245 men.

ΔCalculated using all lesions for each patient (lesion-based).

Table S9: Biopsy characteristics for men undergoing MRI-TB and TRUS biopsy

	MRI-TB (N = 169)	**TRUS biopsy (N = 228)**
TRUS volume of prostate — mls		
Median (IQR)	40.5 (32.0–54.8)	43.7 (33.3–60.0)
Number of biopsies taken		
Median (IQR)	4 (3 to 7)	12 (12 to 12)
Length of procedure — mins*		
Median (IQR)	15 (10 to 25)	10 (9 to 15)
Anaesthetic — no. (%)		
Local	114 (67.5)	196 (86.0)
Sedation/general anaesthetic/spinal	55 (32.5)	32 (14.0)

*Length of procedure based on time from when TRUS probe inserted prior to procedure to when TRUS probe removed at end of procedure

MRI-TB = MRI-targeted biopsy, TRUS = Transrectal ultrasound guided

Table S10: Health-related quality of life at baseline, 24 hours post intervention and 30 days post intervention

Variable	Baseline		24 hours		Mean difference (95% CI)	P value	30 days		Mean difference (95% CI)	P value
	MRI±TB* (N = 245)	TRUS-biopsy (N = 238)	MRI±TB* (N = 215)	TRUS-biopsy (N = 200)			MRI±TB* (N = 200)	TRUS-biopsy (N = 192)		
EQ-5D descriptive score	0.909±0.137	0.907±0.123	0.907±0.126	0.894±0.159	0.006 (-0.017 to 0.029)	0.61	0.917±0.124	0.921±0.126	-0.004 (-0.028 to 0.020)	0.72
EQ-5D VAS score	85.6±11.8	85.5±10.2	84.8±10.8	84.2±11.3	0.61 (-0.95 to 2.18)	0.44	84.6±11.9	85.7±10.3	-0.27 (-1.88 to 1.33)	0.74

Plus–minus values are means ±SD. MRI±TB = MRI±targeted biopsy, TRUS = Transrectal ultrasound guided.

*If the patient only underwent MRI and did not undergo biopsy, the 24-hour and 30-day post intervention questionnaires refer to the post MRI questionnaires. If the patient underwent MRI and targeted biopsy, the questionnaires refer to the post-biopsy questionnaires. Scores from the domains of the European Quality of Life 5 Dimensions 5-Level (EQ-5D-5L) Questionnaire were converted to EQ-5D descriptive scores using the value set for the United Kingdom. Scores from the EQ visual analogue scale (VAS) were also summarised. Higher EQ-5D scores indicate better quality of life. For the comparison of the two arms, mean differences (value in the MRI±TB arm minus value in the TRUS biopsy arm) were estimated using repeated measures mixed models with adjustment for baseline levels.

Table S11: Post-intervention patient-reported complications

	MRI±TB*	TRUS biopsy
Immediate post-intervention complications†	**(N = 224)**	**(N = 222)**
Discomfort		
Median (IQR)	2 (0–4)	3 (2–5)
Pain		
Median (IQR)	1 (0–3)	2 (1–4)
30-day post-intervention complications	**(N = 212)**	**(N = 206)**
	No. of patients (%)	
Fever	9 (4.2)	9 (4.4)
Blood in the urine	64 (30.2)	129 (62.6)
Blood in the semen	68 (32.1)	123 (59.7)
Blood in the stools or from the back passage	30 (14.2)	45 (21.8)
Acute urinary retention	3 (1.4)	2 (1.0)
Erectile dysfunction	23 (10.8)	32 (15.5)
Urinary incontinence	13 (6.1)	10 (4.9)
Urinary tract infection	5 (2.4)	2 (1.0)
Pain at site of procedure	27 (12.7)	48 (23.3)
Men for whom another procedure would be a major problem	2 (0.9)	10 (4.9)

MRI±TB = MRI±targeted biopsy, TRUS = Transrectal ultrasound guided

*If the patient only underwent MRI and did not undergo biopsy, the immediate intervention questionnaire refers to the post MRI questionnaire. If the patient underwent MRI and biopsy, the questionnaire refers to the post-biopsy questionnaire.

†Based on a numerical analogue scale ranging from 0 to 10, with higher scores indicating greater intensity of symptoms.

Table S12: Investigator-reported adverse events

Characteristic	MRI±TB (N = 252) N (%)	TRUS biopsy (N = 248) N (%)
Number of adverse events		
Serious adverse events	4 (1.6)	5 (2.0)
Adverse events	2 (0.8)	3 (1.2)
Adverse events related to intervention		
Sepsis	1 (0.4)	4 (1.6)
Haematuria	0 (0)	1 (0.4)
Prostatitis	3 (1.2)	0 (0)
Adverse events unrelated to intervention		
Fatigue	0 (0)	1 (0.4)
Runny nose and cough	0 (0)	1 (0.4)
Myocardial infarction	0 (0)	1 (0.4)
Pulmonary embolism	1 (0.4)	0 (0)
Death (secondary to pulmonary metastasis of known squamous cell carcinoma)	1 (0.4)	0 (0)

MRI±TB = MRI±targeted biopsy, TRUS = Transrectal ultrasound guided

Table S13: Proportion of men undergoing definitive treatment

Treatment decision	MRI±TB[†] (N =252) N (%)	TRUS biopsy (N = 248) N (%)
Discharge patient, no treatment or follow up required	13 (5.2)	15 (6.0)
PSA monitoring	104 (41.3)	74 (29.8)
Active Surveillance	29 (11.5)	29 (11.7)
Radical treatment	70 (27.0)	60 (24.2)
Radical prostatectomy	34 (13.5)	30 (12.1)
Radiotherapy ± neoadjuvant hormone therapy	35 (13.9)	26 (10.5)
Brachytherapy	1 (0.4)	4 (1.6)
Focal therapy	1 (0.4)	0 (0)
Hormone therapy ± chemotherapy	2 (0.8)	2 (0.8)
Watchful waiting	1 (0.4)	2 (0.8)
Other treatment decisions	11 (4.4)	7 (2.8)
Unknown	14 (5.6)	20 (8.1)
Further diagnostic tests ordered from treatment decision visit	7 (2.7)	39 (15.7)
MPMRI for diagnosis	3 (1.2)	38 (15.3)
Patient choice	0	1
Clinician choice	3	37
Immediate further prostate biopsies	4 (1.6)	1 (0.4)
Patient choice	1	0
Clinician choice	3	1
Further staging tests*		
MRI for staging	2 (0.8)	39 (15.7)
Bone scan	52 (20.6)	37 (14.9)
CT	33 (13.1)	31(12.5)
PET-CT	0 (0)	1 (0.4)
PET-MRI	0 (0)	1 (0.4)

MPMRI = Multiparametric MRI, MRI±TB = MRI±targeted biopsy, TRUS = Transrectal ultrasound guided

*A patient can have more than one type of staging scan. Therefore, the percentages were calculated by dividing the number of patients who received the scan by the total number in the arm.

[†]Of the 71 men with negative MRI and no biopsy, 3 (4.2%) were discharged, 62 (87.3%) were referred for PSA monitoring, 3 (4.2%) underwent further prostate biopsies (all were negative), 1 have further MPMRI and 2 have missing information.

Table S14: Outcomes of men undergoing further diagnostic procedures following initial protocol test

Characteristic	MRI±TB	TRUS biopsy
Further MPMRI following treatment decision — no.	3	38
MPMRI identified suspicious areas scoring 3 or greater — no. (%)		
Yes	0 (0)	18 (47.4)
No	3 (100)	20 (52.6)
MPMRI with post-biopsy artefact — no. (%)	0 (0)	7 (18.4)
MPMRI led to further biopsy — no.	0 (0)	8
Further biopsies following treatment decision — no.(%)	4	9
Transperineal template biopsy	0 (0)	1 (11.1)
10-12 core transrectal biopsy	3 (75.0)	0 (0)
MRI-targeted prostate biopsy	1 (25.0)	8 (88.9)
Overall Gleason grade from further biopsy — no. (%)		
Benign	3 (75.0)	5 (55.6)
ASAP	1 (25.0)	0 (0)
3+3	0 (0)	1 (11.1)
3+4	0 (0)	3 (33.3)
Maximum cancer core length — mm		
Median (IQR)	NA	6.5 (4.0 to 8.5)

NA = not applicable, MPMRI = Multiparametric MRI, MRI±TB = MRI±targeted biopsy, TRUS = Transrectal ultrasound guided

Table S15: Gleason grade concordance with original biopsy after radical prostatectomy

Number of cases	Concordant	Upgraded	Downgraded
MRI±TB arm - no. (%)	19 (63.3)	5 (16.7)	6 (20.0)
TRUS biopsy arm - no. (%)	19 (70.4)	4 (14.8)	4 (14.8)

MRI±TB = MRI±targeted biopsy, TRUS = Transrectal ultrasound guided. Results of radical prostatectomy were available for 30 of the 34 men in the MRI±TB arm and 27 of the 30 men in the TRUS biopsy arm. The remainder were lost to follow up.

Table S16a,b,c: Quality control results

Table S16a: Agreement in PIRADSv2 score for MPMRI scans between site reading and central quality control reading:

		PIRADSv2 score for MRI as reported centrally*					
		1	2	3	4	5	TOTAL
PIRADSv2 score for MRI reported by local site radiologist	1	10	-	1	4	-	11
	2	-	5	-	1	-	10
	3	1	6	2	1	1	11
	4	1	-	-	8	5	14
	5	-	-	1	2	15	18
	TOTAL	12	11	4	16	21	64

*25% of the MRIs from every site were chosen at random and were reported blinded to the original report by two expert uro-radiologists in consensus at the coordinating centre (one with 15 years of experience and one with 5 years of experience in reporting prostate MRI, both reporting approximately 1000 scans per year)

Key:

Concordant scores, where management decision to perform biopsy would not have changed

Discordant scores, where management decision to perform biopsy would have changed

Agreement by concordant biopsy decision: 50/64 = 78%

Table S16b: Agreement in Gleason grade score for men undergoing biopsy between site reading and central quality control reading:

		Overall Gleason grade by central pathology review*							
		Benign	Gleason 3+3	Gleason 3+4	Gleason 3+5	Gleason 4+3	Gleason 4+4	Gleason 4+5	TOTAL
Overall Gleason grade as reported by local site pathologist	Benign	26	1	1	-	-	-	-	27
	Gleason 3+3	-	8	1	-	-	-	-	9
	Gleason 3+4	-	1	13	-	-	-	-	15
	Gleason 3+5	-	-	-	1	-	-	-	0
	Gleason 4+3	-	-	1	-	1	-	-	2
	Gleason 4+4	-	-	-	-	1	1	-	2
	Gleason 4+5	-	-	-	-	-	-	3	3
	Gleason 5+4	-	-	-	-	-	-	1	1
	TOTAL	25	10	16	1	2	1	4	60

*15% of biopsy slides from every site were chosen at random and reported centrally blinded to the original report by one of 4 uro-pathologists based at the coordinating centre. The central pathologist's experience in reporting prostate specimens was 23, 14, 8 and 3 years, reporting 100, 100, 100 and 250 prostate specimens per year, respectively)

Table S16c: Summary table of central pathology review outcome:

	In Agreement	Upgraded	Downgraded
Number of cases	53/60 (88%)	3/60 (5%)	4/60 (7%)

References

1. Kasivisvanathan V, Jichi F, Klotz L, et al. A multicentre randomised controlled trial assessing whether MRI-targeted biopsy is non-inferior to standard transrectal ultrasound guided biopsy for the diagnosis of clinically significant prostate cancer in men without prior biopsy: a study protocol. BMJ Open 2017;7:e017863.