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Study protocol for a single-centre non-inferior randomized controlled trial on a novel three-dimensional matrix positioning based cognitive fusion targeted biopsy, and software-based fusion targeted biopsy for the detection rate of clinically significant prostate cancer in men without a prior biopsy

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4 **Study protocol for a single-centre non-inferior randomized controlled trial**
5 **on a novel three-dimensional matrix positioning based cognitive fusion**
6 **targeted biopsy, and software-based fusion targeted biopsy for the**
7 **detection rate of clinically significant prostate cancer in men without a**
8 **prior biopsy**
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15 **Bi-Ming He ***, **Rong-Bing Li ***, Dong-Yang Li, Li-Qun Huang, Xiao-Fei Wen, Guo-
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45 **Abstract**

46
47 **Introduction**

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49 The classical pathway for diagnosing prostate cancer is systematic 12-core
50 biopsy under the guidance of transrectal ultrasound, which tends to
51 underdiagnosis the clinically significant tumour and overdiagnosis the
52 insignificant disease. Another pathway named targeted biopsy is using
53 multiparametric magnetic resonance imaging to localizing the tumour precisely
54 and then obtain the samples from the suspicious lesions. Targeted biopsy,
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4 which mainly divided into cognitive fusion method and software-based fusion
5 method, is getting prevalent for its good performance in detecting significant
6 cancer. However, the preferred Targeted biopsy technique in detecting
7 clinically significant Prostate cancer between cognitive fusion and software-
8 based fusion is still beyond consensus.
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13 14 15 **Methods and analysis**

16
17 This trial is a prospective, single-centre, randomized controlled, and non-
18 inferiority study in which all men suspicious to have clinically significant prostate
19 cancer. This study aims to determine whether a novel three-dimensional matrix
20 positioning cognitive fusion targeted biopsy is non-inferior to software-based
21 fusion targeted biopsy in the detection rate of clinically significant cancer in men
22 without a prior biopsy. The main inclusion criteria are men with elevated serum
23 PSA above to 4 – 20 ng/ml or with an abnormal DRE and have never had a
24 biopsy before. A sample size of 602 participants allowing for a 10% loss, will be
25 recruited. All patients will undergo a mpMRI examination, and those who fail to
26 be found with a suspicious lesion, with the anticipation of half of the total number,
27 will be dropped. The remaining participants will be randomly allocated to
28 cognitive fusion targeted biopsy (n=137), and software-based fusion targeted
29 biopsy (n=137). The primary outcome is the detection rate of clinically
30 significant prostate cancer for cognitive fusion targeted biopsy, and software-
31 based fusion targeted biopsy in men without a prior biopsy. The clinically
32 significant prostate cancer will be defined as the International Society of
33 Urological Pathology grade group 2 or higher.
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51 52 **Ethics and dissemination**

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54 Ethical approval was obtained from the ethics committee of Shanghai East
55 Hospital, Tongji University School of Medicine, Shanghai, China. The results of
56 the study will be disseminated and published in international peer-reviewed
57 journals.
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registration details

ClinicalTrials.gov: NCT04271527

Strengths and limitations of this study

- ▶ This study is the first trial to compare a novel cognitive fusion targeted biopsy which based on a three-dimensional matrix positioning method, with a software-based fusion targeted biopsy.
- ▶ The study will determine the efficacy of the novel cognitive fusion targeted biopsy in the diagnosis of prostate cancer.
- ▶ Rigorous randomized design and allocation concealment method will reduce bias, which enables the higher reliability of the results.
- ▶ The study performed in the centre that developed the “three-dimensional matrix positioning method” which may overestimate the performance of this method since the operators are experienced.
- ▶ This study takes place in one hospital, hence may making the finding less generalizable.

Introduction

Prostate cancer (PCa) is the second most common cancer worldwide which leads the fifth causes of death among men¹. Men with an elevated serum prostate-specific antigen (PSA) level or an abnormal digital rectal examination (DRE) are usually be considered at risk for PCa and typically be performed a prostate biopsy subsequently to get samples for pathological diagnosis. The common pathway is a systematic 12-core biopsy under the guidance of transrectal ultrasound (TRUS), an approach to randomly get the samples from the whole prostate gland; however, it's blind attribution makes it tends to underdiagnosis the clinically significant tumour and overdiagnosis the clinically insignificant disease^{2, 3}.

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4 Thanks to the development of multiparametric magnetic resonance imaging
5 (mpMRI) in identifying prostate cancer, another pathway named targeted
6 biopsy is getting prevalent. It aims to first perform a mpMRI for localizing the
7 tumour precisely and then obtain the samples from the suspicious lesions,
8 shows more purposeful and less random compared with the systematic biopsy.
9 Several pieces of evidence have proved the superiority of targeted biopsy in
10 detection rates of clinically significant prostate cancer (csPCa) and avoidance
11 of unnecessary biopsy^{4, 5}..

21 Targeted biopsy can be subdivided into three different methods: in-bore MRI,
22 cognitive fusion and software-based fusion. An in-bore MRI-targeted biopsy is
23 described as to perform a targeted biopsy under real-time MRI guidance.
24 Although this method is accurate in locating the targeted lesions, it is a failure
25 to be widely used in clinical practice for its inconvenience and time-consuming⁶.
26 Compared with in-bore MRI-targeted biopsy, another two methods are more
27 acceptable. Cognitive fusion, a procedure of mental located the target of
28 suspicious lesions in the ultrasound image after a review of MRI, is cost saving
29 due to it needs no extra equipment, aside from the essential requirement for a
30 TURS-biopsy. Software-based fusion is an overlap of the real-time ultrasound
31 image and the previous MRI images by software assistance. Although it is
32 widely adopted by urologists or physicians, the barriers of time-consuming, and
33 excessive price and training for the additional equipment cannot be omitted⁷⁻⁹.
34 There is always an interesting topic about whether the ability of cognitive fusion
35 with human brains can achieve the same result as a fusion with intricate fusion
36 software¹⁰. However, evidence from the comparative trials are few^{9, 11-13}.
37 To now, the preferred targeted biopsy technique in detecting csPCa between
38 cognitive fusion and software-based fusion is still beyond consensus.
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We have developed a method named three-dimensional matrix positioning to increase the accuracy of cognitive fusion for targeted biopsy detection of csPCa,

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4 which involves several fiducial axes derived from MRI localization of the region
5 of interest, then transposed onto the ultrasound image to help direct the biopsy
6 needle into the right place¹⁴. This method had shown a reasonable detection
7 rate for clinically significant prostate cancer in a pilot cohort. Hence, we conduct
8 this single-centre randomized controlled trial in order to confirm the finding
9 further.
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18 This trial aims to compare three-dimensional matrix positioning cognitive fusion
19 targeted biopsy and software-based fusion targeted biopsy for the detection
20 rate of clinically significant prostate cancer for men without a prior biopsy
21 localized prostate cancer. The primary objective is to assess whether the
22 cognitive fusion targeted biopsy is non-inferior to software-based fusion
23 targeted biopsy in the detection rate of clinically significant cancer.
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31 **Trial design**

32 This prospective, single-centre, randomized controlled, and non-inferiority
33 study will take place at Shanghai East Hospital, Tongji University School of
34 Medicine, Shanghai, China. The primary objective of this study is to identify
35 whether the three-dimensional matrix positioning cognitive fusion targeted
36 biopsy is non-inferior to software-based fusion targeted biopsy in the detection
37 rate of clinically significant cancer in men without a prior biopsy.
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47 The study flow chart is shown in Fig 1. Patients will be initially screened and
48 recruited by the urologists in outpatient. Those who meet the entry criteria and
49 sign the consent form will go for mpMRI within 2 weeks, and only those whose
50 MRI indicate at least one suspicious lesion will proceed to the randomization.
51 With allocation, men will be assigned to cognitive fusion targeted biopsy or to
52 software-based fusion targeted biopsy in a 1:1 ratio while others will drop out
53 of the trial. Men in both arms will be hospitalized one day before the prostate
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4 biopsy. The biopsy procedure, which usually lasts for less than 30 minutes, will
5 be performed under a local anesthetic block in an operation room. In addition
6 to different targeted biopsy methods, a 20-region template guide prostate
7 biopsy (Fig 2) will be performed after the targeted biopsy in each man, which
8 can be a reference to the different targeted techniques. The samples from the
9 biopsy will send to the pathologic apartment for assessment after the procedure.
10 All participants will schedule dismiss the followed day after the biopsy. The
11 pathological assessment will be reported within 2 weeks of post-biopsy. The
12 details and timeframe of the trial are shown in Table 1.
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23 We chose the randomised trial instead of a paired cohort to reduce bias.
24 Because if two biopsies are performed on the same participant, the progress of
25 one may lead to the bleeding and deformation of the prostate, which will affect
26 the progress of the other.
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33 **Outcomes**

34 The primary outcome is the detection rate of clinically significant prostate
35 cancer for cognitive fusion targeted biopsy, and software-based fusion targeted
36 biopsy in men without a prior biopsy. The clinically significant prostate cancer
37 will be defined as ISUP grade group 2 or higher, according to the 2014 ISUP
38 classification¹⁵.
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48 The main secondary outcomes are as follows:

49 The detection rate of any prostate cancer for cognitive fusion targeted biopsy,
50 and software-based fusion targeted biopsy
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52 The detection rate of clinically significant prostate cancer for each targeted
53 technique combined with a templated guided biopsy
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55 The detection rate of any prostate cancer for each targeted method combined
56 with a templated guided biopsy
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60 The comparison of the results between the two urologists, including the

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4 detection rate of clinically significant prostate cancer and any prostate
5 cancer. The influence of prostate volume on the difference between the two
6 fusion targeted biopsy
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10 **Methods and analysis**

11 **Patient population**

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15 Patients with a suspicion of harbouring prostate cancer and had no previous
16 biopsy will be considered eligible for registration in this trial if they can meet all
17 inclusion criteria and had no any exclusion criteria. The main criteria include
18 men with elevated serum PSA above to 4 – 20 ng/ml or with an abnormal DRE
19 and have never had a biopsy before. The details of inclusion and exclusion
20 criteria are shown in Table 2. All eligible patients will be informed in detail, and
21 only those who sign the consent form can participate in the trial. Men who are
22 ineligible or do not want to participate in the study will be returned to the regular
23 clinical pathway.
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34 **Multi-parametric magnetic resonance imaging**

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37 All participants who sign the informed consent will subsequently undergo a 3.0-
38 Tesla mpMRI (Magnetom Skyra, Siemens Medical Solutions, Erlangen,
39 Germany) with an 18-channel phased-array coil. The sequences of
40 examination mainly included T2-weighted imaging (T2WI), diffusion-weighted
41 imaging (DWI, acquired b-values 0,400,1000 and 2000 seconds per mm²), and
42 dynamic contrast-enhanced imaging (with the setting of temporal resolution
43 less than 7 seconds and 5 minutes acquisition). Images will be evaluated and
44 scored by one of two expert radiologists (20 and 10 yr of experience in prostate
45 MRI) according to Prostate Imaging Reporting and Data System (PI-RADS)
46 version 2.1 criteria. The probability of cancer will be assessed by the score from
47 1 to 5 (1 - Highly unlikely to be clinically significant cancer, 2 - Unlikely to be
48 clinically significant cancer, 3 - equivocal to be clinically significant cancer, 4 -
49 Likely to be clinically significant cancer, 5 - Highly likely to be clinically
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3 significant cancer). The MRI report will only be marked as 'no abnormal' or 'less
4 than 3' when scoring 1 or 2 while a specific score will be recorded at a score 3,
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7 4 or 5.
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10 11 **Randomization**

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13 Only participants with a PI-RADS score 3, 4 or 5 will be allocated 1:1 to
14 cognitive fusion targeted biopsy group or software-based fusion targeted biopsy
15 group by using block-randomization. The random sequence will be generated
16 by PROC PLAN statement of SAS program which keep by one research nurse
17 and blind to other researchers. A random number will be revealed only when
18 one participant being randomising.
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27 **Interventions**

28 29 **Biopsy**

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31 All biopsies in both arms will be performed via the perineum by two urologists
32 (Haifeng Wang with an experience more than 10 years and Biming He with an
33 experience more than 5 years) with an UltraView 800 ultrasound device (BK
34 Ultrasound, USA) and a bi-planar transrectal ultrasound (TRUS) probe (8848,
35 BK Ultrasound) under a local anesthetic block. Before performing the biopsy,
36 one urologist will read the report and the image of MRI to identify the location
37 of target lesions while another one will be blinded to the MRI result.
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47 **Cognitive fusion targeted biopsy arm**

48 Each participant in this arm will undergo a cognitive fusion targeted biopsy first.
49 A novel three-dimensional matrix positioning based cognitive fusion targeted
50 biopsy will be performed under the guidance of a bi-plane TURS probe after
51 reviewing the mpMRI finding. Three cores of biopsy will be taken for each
52 suspicious lesion which is showed in mpMRI that PI-RADS score of 3 to 5. The
53 details of the cognitive fusion targeted biopsy was described in our previous
54 research¹⁴. After the targeted biopsy, a 20-region template guided biopsy will
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4 be subsequently performed by another urologist who blinded to the MRI results
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7 8 9 **Software-based fusion targeted biopsy arm**

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11 The software-based fusion targeted biopsy will be performed with the MIM
12 symphony software by taking two-dimensional (2D) mpMRI images to create a
13 three-dimensional (3D) map then be fused with the ultrasound images. Each
14 suspicious area with a PI-RADS score equal or more than 3 will be performed
15 a 3 cores biopsy by one urologist, which will be followed with a 20-region
16 template guided biopsy by another.
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25 **Histology**

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27 A pathology group, which blind to all clinical data including the technique of
28 biopsy, will evaluate the samples. The pathologic finding will be reported within
29 2 weeks post biopsy. Clinically significant cancer defined as the International
30 Society of Urological Pathology grade group 2 or higher.
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37 **Statistical analysis**

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39 Continuous variables will be reported by using means with standard deviations
40 (SD) or median with interquartile range (IQR), while categorical variables will
41 be shown by using frequencies with proportions.
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44 The primary analysis in this trial will follow the intention-to-treat principle,
45 including all patients who have undergone randomization. The primary outcome
46 is the detection rate of clinically significant prostate cancer for cognitive fusion
47 targeted biopsy and software-based fusion targeted biopsy. The absolute
48 difference between these two arms will be calculated with a 95% confidence
49 interval (CI) by estimating with a generalized linear model. The cognitive fusion
50 targeted biopsy will be described as non-inferior if the lower bound of the 95%CI
51 of the difference in the clinically significant cancer detection rate of the cognitive
52 fusion targeted biopsy arm compared with the software-based fusion targeted
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4 biopsy arm (cognitive fusion arm minus software-based arm) is higher than -
5 10%.
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9 The second outcomes will be analysed with 95%CI and Pearson chi-square
10 test. All reported P values were two-sided in this trial.
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13 **Sample size**

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15 A retrospective data review for cognitive fusion targeted biopsy performed at
16 our institution during 2017 showed a clinically significant cancer detection rate
17 of 52.8%¹⁹ while a literature from Germany revealed a clinically significant
18 cancer detection rate of 45% for software-based fusion targeted biopsy. The
19 patients with PI-RADS score ≥ 3 account for 60.6% in all patients who had
20 undergone a mpMRI examination at our institution.
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29 For the non-inferiority hypothesis, using a 10% noninferiority margin, using 80%
30 power and 5% one-sided α , assuming a detection rate of clinically significant
31 cancer for cognitive fusion targeted biopsy of 50% and a detection rate for
32 software-based fusion targeted biopsy of 45%, using allocation ratio of 1:1, 137
33 men per arm will be required. Assuming that 50% has at least one suspicious
34 lesion on mpMRI, 548 men are needed. Account for 10% withdraw/loss, a total
35 of 602 participants are required for inclusion.
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45 **Harms and adverse events**

46 A research nurse will record all harms or adverse events relevant or not relevant
47 to the procedure of biopsy. Adverse events will be assessed by Common
48 Terminology Criteria for Adverse Events (CTCAE). The serious adverse events
49 include (1) death; (2) life-threatening; (3) hospitalization and (4) disability or
50 permanent damage will be recorded immediately and then sent to the ethics
51 committee and the monitoring board within 24 hours. All harms and adverse
52 events will be recorded from the registration to one-week after the biopsy.
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Data collection

The data will be collected from the patient/relative of a patient at registration, and the medical record on two weeks and six weeks. The demographic information (age, height, weight, BMI), PSA, and family history will be recorded on registration, as well as the digital rectal examination will be performed. On two weeks after the registration, an MRI result will be recorded, including a PI-RADS score, prostate volume, and suspicious lesion volume. Both prostate volume and suspicious lesion volume will be measured by mpMRI on the T2WI sequence. The data of pathological assessment will be recorded on six weeks (two weeks post-biopsy) including an overall Gleason score and a separate Gleason score for each biopsy core. Besides, the length and percent of tumour in each biopsy core will also be reported.

Monitoring

A team of independent clinical research associate (CRA) with all more than five years of experiences is responsible for being familiar with the trial protocol and monitoring all researchers and all participants involved in the whole processes of this trial. The CRA's role is to (1) monitoring the trial plan, the record forms, and the case report form before the start of the trial; (2) monitoring participants' informed consent and enrolment rates; (3) monitor the compliance of participants and investigators with the protocol, and monitoring data quality and authenticity.

Ethics and dissemination

Ethical approval was obtained from the ethics committee of Shanghai East Hospital. The results of this study will be disseminated for international peer-reviewed journal and disseminated for presentation at international or national academic conference.

Trial status

This RCT was first registered online at ClinicalTrials.gov on 13 February 2020.

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4 The study is expected to start on 1 September 2020. Recruitment is anticipated
5 to continue until 1 September 2021 with 6-week follow-up to be completed in
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7 November 2020.
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10 11 **Patient and public involvement**

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13 This trial protocol was written without patient or public involvement. The
14 participants were not involved in the contribution of the design, recruitment or
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at follow-up and received a summary of the main finding at the end of the trial.

Authors' contributions

Conceptualization: He B, Li R and Wang H.

Data curation: He B, Li R, Li D, Huang L and Wang H.

Formal analysis: He B, Li R, Li D and Huang L.

Investigation: He B, Li R, Li D, Huang L and Wang H

Supervision: Wen X and Yang G

Original draft: He B and Wang H

Review and editing: Li R, Wen X and Yang G.

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Declaration of interests

None of the authors have any conflicts of interest to declare.

Table 1. Participant timeline in the study

	Contact with patient			
	Vist 1	Vist 2	Vist 3	Vist 4
	0	0~2 weeks	2~4 weeks	5~6 weeks
Consent	×			
Screening	×			
Baseline characteristic	×			
PSA	×			
MRI		×		
Randomization		×		
Prostate biopsy			×	
Cognitive fusion targeted biopsy + 20 region templated guide biopsy (cognitive fusion arm)			×	
Software fusion targeted biopsy + 20 region templated guide biopsy (Software fusion arm)			×	
Pathological assessment				×
Withdrawal		Complete as required at any time following registration		
SAE		Complete as required at any time following registration		

Table 2. Patients inclusion and exclusion criteria

Inclusion criteria

Age over 18 years old

PSA increase to 4–20 ng/ml and/or abnormal DRE;

Without previous prostate biopsy

Fully understand the clinical trial protocol and sign the informed consent

Exclusion criteria

Previous history of prostate biopsy

Evidence of acute or chronic prostatitis

Contraindications to prostate biopsy (e.g. fever, evidence of urinary tract infection)

Contraindications to MRI (e.g. metal implant, contrast agent allergy)

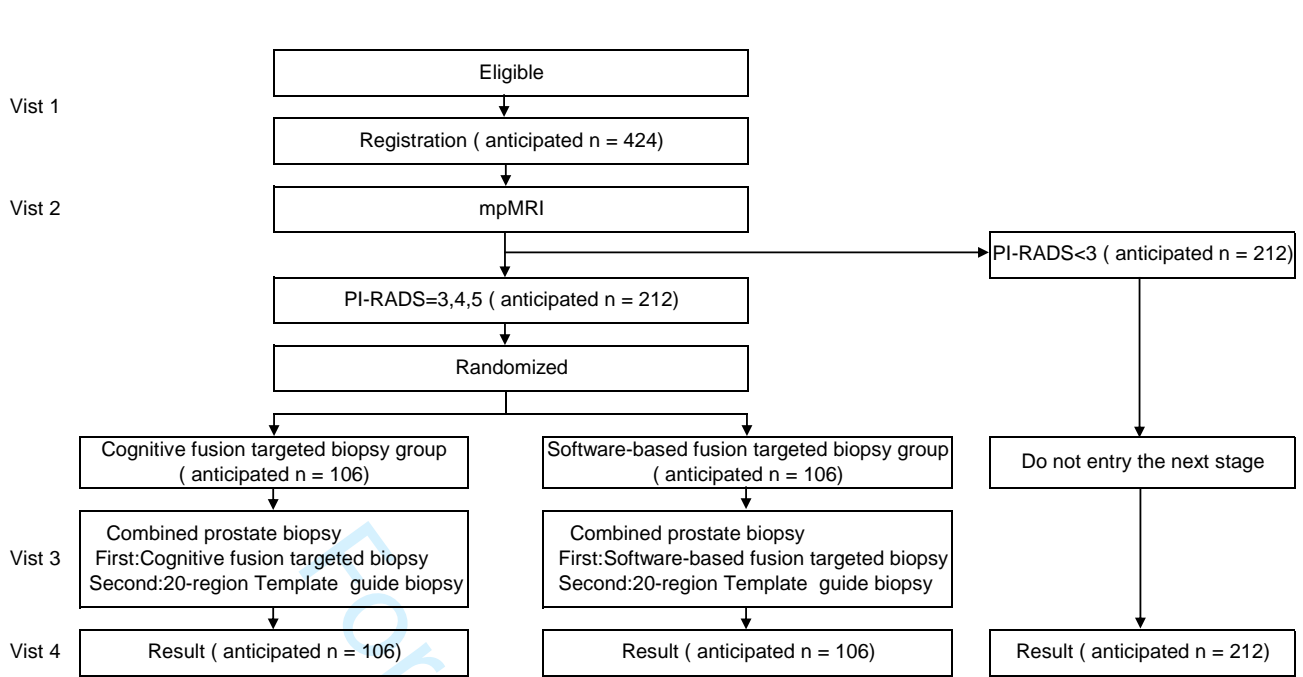
The investigator judges that patients who are not suitable for this clinical trial

Any other conditions that investigator judges that participations who are not suitable for this trial

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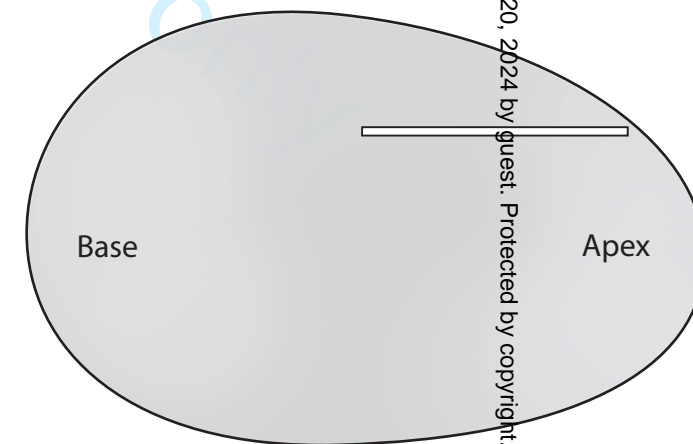
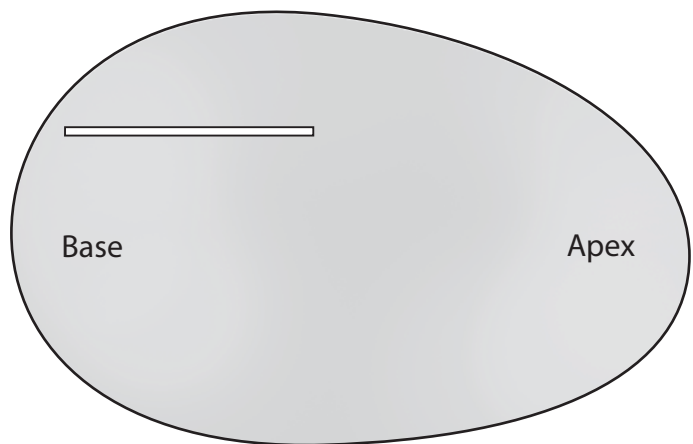
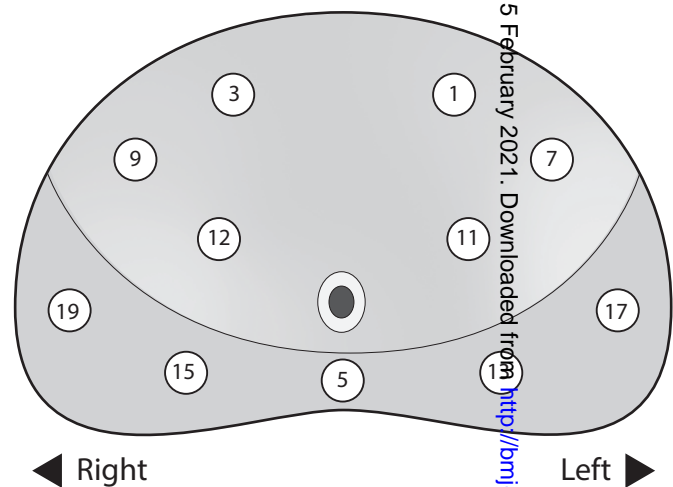
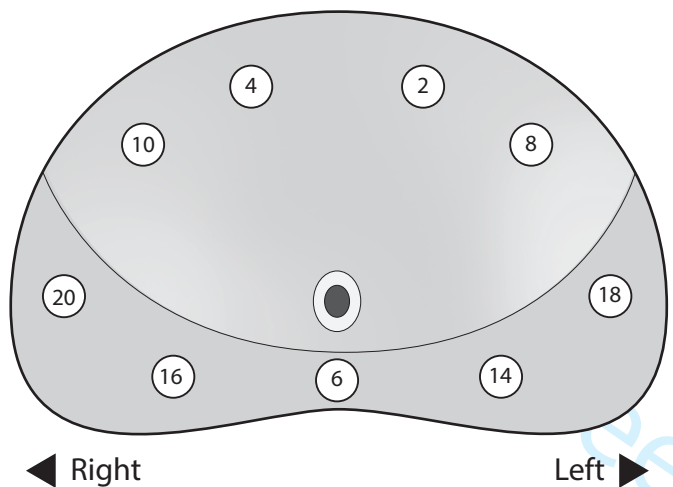
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BMJ Open

Study protocol for a single-centre non-inferior randomized controlled trial on a novel three-dimensional matrix positioning based cognitive fusion targeted biopsy, and software-based fusion targeted biopsy for the detection rate of clinically significant prostate cancer in men without a prior biopsy

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4 **Study protocol for a single-centre non-inferior randomized controlled trial**
5 **on a novel three-dimensional matrix positioning based cognitive fusion**
6 **targeted biopsy, and software-based fusion targeted biopsy for the**
7 **detection rate of clinically significant prostate cancer in men without a**
8 **prior biopsy**
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15 **Bi-Ming He ***, **Rong-Bing Li ***, **Dong-Yang Li**, **Li-Qun Huang**, **Xiao-Fei Wen**, **Guo-**
16 **Sheng Yang** and **Hai-Feng Wang**
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45 **Abstract**

46
47 **Introduction**

48
49 The classical pathway for diagnosing prostate cancer is systematic 12-core
50 biopsy under the guidance of transrectal ultrasound, which tends to
51 underdiagnosis the clinically significant tumour and overdiagnosis the
52 insignificant disease. Another pathway named targeted biopsy is using
53 multiparametric magnetic resonance imaging to localizing the tumour precisely
54 and then obtain the samples from the suspicious lesions. Targeted biopsy,
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4 which mainly divided into cognitive fusion method and software-based fusion
5 method, is getting prevalent for its good performance in detecting significant
6 cancer. However, the preferred Targeted biopsy technique in detecting
7 clinically significant Prostate cancer between cognitive fusion and software-
8 based fusion is still beyond consensus.
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13 14 15 **Methods and analysis**

16
17 This trial is a prospective, single-centre, randomized controlled, and non-
18 inferiority study in which all men suspicious to have clinically significant prostate
19 cancer. This study aims to determine whether a novel three-dimensional matrix
20 positioning cognitive fusion targeted biopsy is non-inferior to software-based
21 fusion targeted biopsy in the detection rate of clinically significant cancer in men
22 without a prior biopsy. The main inclusion criteria are men with elevated serum
23 PSA above to 4 – 20 ng/ml or with an abnormal DRE and have never had a
24 biopsy before. A sample size of 602 participants allowing for a 10% loss, will be
25 recruited. All patients will undergo a mpMRI examination, and those who fail to
26 be found with a suspicious lesion, with the anticipation of half of the total number,
27 will be dropped. The remaining participants will be randomly allocated to
28 cognitive fusion targeted biopsy (n=137), and software-based fusion targeted
29 biopsy (n=137). The primary outcome is the detection rate of clinically
30 significant prostate cancer for cognitive fusion targeted biopsy, and software-
31 based fusion targeted biopsy in men without a prior biopsy. The clinically
32 significant prostate cancer will be defined as the International Society of
33 Urological Pathology grade group 2 or higher.
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51 52 **Ethics and dissemination**

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54 Ethical approval was obtained from the ethics committee of Shanghai East
55 Hospital, Tongji University School of Medicine, Shanghai, China. The results of
56 the study will be disseminated and published in international peer-reviewed
57 journals.
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registration details

ClinicalTrials.gov: NCT04271527

Strengths and limitations of this study

- ▶ This study is the first trial to compare a novel cognitive fusion targeted biopsy which based on a three-dimensional matrix positioning method, with a software-based fusion targeted biopsy.
- ▶ The study will determine the efficacy of the novel cognitive fusion targeted biopsy in the diagnosis of prostate cancer.
- ▶ Rigorous randomized design and allocation concealment method will reduce bias, which enables the higher reliability of the results.
- ▶ This study takes place in one hospital, hence may making the finding less generalizable.
- ▶ The study is performed in the centre that developed the guiding method, which may over-estimate its performance as compared to less experienced readers.

Introduction

Prostate cancer (PCa) is the second most common cancer worldwide which leads the fifth causes of death among men¹. Men with an elevated serum prostate-specific antigen (PSA) level or an abnormal digital rectal examination (DRE) are usually be considered at risk for PCa and typically be performed a prostate biopsy subsequently to get samples for pathological diagnosis. The common pathway is a systematic 12-core biopsy under the guidance of transrectal ultrasound (TURS), an approach to randomly get the samples from the whole prostate gland; however, it's blind attribution makes it tends to underdiagnosis the clinically significant tumour and overdiagnosis the clinically insignificant disease^{2, 3}.

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6 Thanks to the development of multiparametric magnetic resonance imaging
7 (mpMRI) in identifying prostate cancer, another pathway named targeted
8 biopsy is getting prevalent. It aims to first perform a mpMRI for localizing the
9 tumour precisely and then obtain the samples from the suspicious lesions,
10 shows more purposeful and less random compared with the systematic biopsy.
11 Several pieces of evidence have proved the superiority of targeted biopsy in
12 detection rates of clinically significant prostate cancer (csPCa) and avoidance
13 of unnecessary biopsy^{4, 5}..

23 Targeted biopsy can be subdivided into three different methods: in-bore MRI,
24 cognitive fusion and software-based fusion. An in-bore MRI-targeted biopsy is
25 described as to perform a targeted biopsy under real-time MRI guidance.
26 Although this method is accurate in locating the targeted lesions, it is a failure
27 to be widely used in clinical practice for its inconvenience and time-consuming⁶.
28 Compared with in-bore MRI-targeted biopsy, another two methods are more
29 acceptable. Cognitive fusion, a procedure of mental located the target of
30 suspicious lesions in the ultrasound image after a review of MRI, is cost saving
31 due to it needs no extra equipment, aside from the essential requirement for a
32 TURS-biopsy. Software-based fusion is an overlap of the real-time ultrasound
33 image and the previous MRI images by software assistance. Although it is
34 widely adopted by urologists or physicians, the barriers of time-consuming, and
35 excessive price and training for the additional equipment cannot be omitted⁷⁻⁹.
36 There is always an interesting topic about whether the ability of cognitive fusion
37 with human brains can achieve the same result as a fusion with intricate fusion
38 software¹⁰. However, evidence from the comparative trials are few^{9, 11-13}.
39 To now, the preferred targeted biopsy technique in detecting csPCa between
40 cognitive fusion and software-based fusion is still beyond consensus.
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We have developed a method named three-dimensional matrix positioning to

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4 increase the accuracy of cognitive fusion for targeted biopsy detection of csPCa,
5 which involves several fiducial axes derived from MRI localization of the region
6 of interest, then transposed onto the ultrasound image to help direct the biopsy
7 needle into the right place¹⁴. This method had shown a reasonable detection
8 rate for clinically significant prostate cancer in a pilot cohort. Hence, we conduct
9 this single-centre randomized controlled trial in order to confirm the finding
10 further.
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20 This trial aims to compare three-dimensional matrix positioning cognitive fusion
21 targeted biopsy and software-based fusion targeted biopsy for the detection
22 rate of clinically significant prostate cancer for men without a prior biopsy
23 localized prostate cancer. The primary objective is to assess whether the
24 cognitive fusion targeted biopsy is non-inferior to software-based fusion
25 targeted biopsy in the detection rate of clinically significant cancer.
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33 **Trial design**

34 This prospective, single-centre, randomized controlled, and non-inferiority
35 study will take place at Shanghai East Hospital, Tongji University School of
36 Medicine, Shanghai, China. The primary objective of this study is to identify
37 whether the three-dimensional matrix positioning cognitive fusion targeted
38 biopsy is non-inferior to software-based fusion targeted biopsy in the detection
39 rate of clinically significant cancer in men without a prior biopsy.
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49 The study flow chart is shown in Fig 1. Patients will be initially screened and
50 recruited by the urologists in outpatient. Those who meet the entry criteria and
51 sign the consent form will go for mpMRI within 2 weeks, and only those whose
52 MRI indicate at least one lesion with a PI-RADS v2.1 ≥ 3 will proceed to the
53 randomization. With allocation, men will be assigned to cognitive fusion
54 targeted biopsy using the three-dimensional matrix positioning method or to
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4 software-based fusion targeted biopsy using the MIM symphony software in a
5 1:1 ratio while others will drop out of the trial. Men in both arms will be
6 hospitalized one day before the prostate biopsy. The biopsy procedure, which
7 usually lasts for less than 30 minutes, will be performed under a local anesthetic
8 block in an operation room. In addition to different targeted biopsy methods, a
9 20-region template guide prostate biopsy (Fig 2) will be performed after the
10 targeted biopsy in each man, which can be a reference to the different targeted
11 techniques. The samples from the biopsy will send to the pathologic department
12 for assessment after the procedure. All participants will schedule dismiss the
13 followed day after the biopsy. The pathological assessment will be reported
14 within 2 weeks of post-biopsy. The details and timeframe of the trial are shown
15 in Table 1.
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29 We chose the randomised trial instead of a paired cohort to reduce bias.
30 Because if two biopsies are performed on the same participant, the progress of
31 one may lead to the bleeding and deformation of the prostate, which will affect
32 the progress of the other.
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39 **Outcomes**

40 The primary outcome is the detection rate of clinically significant prostate
41 cancer for cognitive fusion targeted biopsy, and software-based fusion targeted
42 biopsy in men without a prior biopsy. The clinically significant prostate cancer
43 will be defined as ISUP grade group 2 or higher, according to the 2014 ISUP
44 classification¹⁵.
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52 The main secondary outcomes are as follows:

53 The detection rate of any prostate cancer for cognitive fusion targeted biopsy,
54 and software-based fusion targeted biopsy
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57 The detection rate of clinically significant prostate cancer for each targeted
58 technique combined with a templated guided biopsy
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4 The detection rate of any prostate cancer for each targeted method combined
5 with a templated guided biopsy
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7 The comparison of the results between the two urologists, including the
8 detection rate of clinically significant prostate cancer and any prostate cancer
9 in the targeted biopsy, template biopsy and combined biopsy
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12 The influence of prostate volume on the difference between the two fusion
13 targeted biopsy
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16 17 18 19 **Methods and analysis**

20 21 **Patient population**

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23 Patients with a suspicious of harbouring prostate cancer and had no previous
24 biopsy will be considered eligible for registration in this trial if they can meet all
25 inclusion criteria and had no any exclusion criteria. The main criteria include
26 men with elevated serum PSA above to 4 – 20 ng/ml or with an abnormal DRE
27 and have never had a biopsy before. The details of inclusion and exclusion
28 criteria are shown in Table 2. All eligible patients will be informed in detail, and
29 only those who sign the consent form can participate in the trial. Men who are
30 ineligible or do not want to participate in the study will be returned to the regular
31 clinical pathway.
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42 43 **Multi-parametric magnetic resonance imaging**

44 All participants who sign the informed consent will subsequently undergo a 3.0-
45 Tesla mpMRI (Magnetom Skyra, Siemens Medical Solutions, Erlangen,
46 Germany) with an 18-channel phased-array coil. The sequences of
47 examination mainly included T2-weighted imaging (T2WI), diffusion-weighted
48 imaging (DWI, acquired b-values 0,400,1000 and 2000 seconds per mm²), and
49 dynamic contrast-enhanced imaging (with the setting of temporal resolution
50 less than 7 seconds and 5 minutes acquisition). Images will be evaluated and
51 scored by one of two expert radiologists (20 and 10 yr of experience in prostate
52 MRI) according to Prostate Imaging Reporting and Data System (PI-RADS)
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4 version 2.1 criteria¹⁶. The probability of cancer will be assessed by the score
5 from 1 to 5 (1 - Highly unlikely to be clinically significant cancer, 2 - Unlikely to
6 be clinically significant cancer, 3 - equivocal to be clinically significant cancer,
7 4 - Likely to be clinically significant cancer, 5 - Highly likely to be clinically
8 significant cancer). The MRI report will only be marked as 'no abnormal' or 'less
9 than 3' when scoring 1 or 2 while a specific score will be recorded at a score 3,
10 4 or 5.
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19 **Randomization**

20 Only participants with a PI-RADS score 3, 4 or 5 will be allocated 1:1 to
21 cognitive fusion targeted biopsy group or software-based fusion targeted biopsy
22 group by using block-randomization. The random sequence will be generated
23 by PROC PLAN statement of SAS program which keep by one research nurse
24 and blind to other researchers. A random number will be revealed only when
25 one participant being randomising.
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35 **Interventions**

36 **Biopsy**

37 All biopsies in both arms will be performed via the perineum by two urologists
38 (Haifeng Wang with an experience more than 10 years and Biming He with an
39 experience more than 5 years) with an UltraView 800 ultrasound device (BK
40 Ultrasound, USA) and a bi-planar transrectal ultrasound (TRUS) probe (8848,
41 BK Ultrasound) under a local anesthetic block. Before performing the biopsy,
42 one urologist will read the report and the image of MRI to identify the location
43 of target lesions while another one will be blinded to the MRI result.
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54 **Cognitive fusion targeted biopsy arm**

55 Each participant in this arm will undergo a cognitive fusion targeted biopsy first.
56 A novel three-dimensional matrix positioning based cognitive fusion targeted
57 biopsy will be performed under the guidance of a bi-plane TURS probe after
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4 reviewing the mpMRI finding. Three cores of biopsy will be taken for each
5 suspicious lesion which is showed in mpMRI that PI-RADS score of 3 to 5. The
6 details of the cognitive fusion targeted biopsy was described in our previous
7 research¹⁴. After the targeted biopsy, a 20-region template guided biopsy will
8 be subsequently performed by another urologist who blinded to the MRI results
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reviewing the mpMRI finding. Three cores of biopsy will be taken for each suspicious lesion which is showed in mpMRI that PI-RADS score of 3 to 5. The details of the cognitive fusion targeted biopsy was described in our previous research¹⁴. After the targeted biopsy, a 20-region template guided biopsy will be subsequently performed by another urologist who blinded to the MRI results¹⁷. The urologist who performs the targeted biopsy will be determined by a random number generated by PROC PLAN statement of SAS program.

Software-based fusion targeted biopsy arm

The software-based fusion targeted biopsy will be performed with the MIM symphony software by taking two-dimensional (2D) mpMRI images to create a three-dimensional (3D) map then be fused with the ultrasound images. Each suspicious area with a PI-RADS score equal or more than 3 will be performed a 3 cores biopsy by one urologist, which will be followed with a 20-region template guided biopsy by another. Also, who performs the targeted biopsy will be randomized.

Histology

A pathology group, which blind to all clinical data including the technique of biopsy, will evaluate the samples. The pathologic finding will be reported within 2 weeks post biopsy. Clinically significant cancer defined as the International Society of Urological Pathology grade group 2 or higher.

Statistical analysis

Continuous variables will be reported by using means with standard deviations (SD) or median with interquartile range (IQR), while categorical variables will be shown by using frequencies with proportions.

The primary analysis in this trial will follow the intention-to-treat principle, including all patients who have undergone randomization. The primary outcome is the detection rate of clinically significant prostate cancer for cognitive fusion

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4 targeted biopsy and software-based fusion targeted biopsy. The absolute
5 difference between these two arms will be calculated with a 95% confidence
6 interval (CI) by estimating with a generalized linear model. The cognitive fusion
7 targeted biopsy will be described as non-inferior if the lower bound of the 95%CI
8 of the difference in the clinically significant cancer detection rate of the cognitive
9 fusion targeted biopsy arm compared with the software-based fusion targeted
10 biopsy arm (cognitive fusion arm minus software-based arm) is higher than -
11 10%.
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21 The second outcomes will be analysed with 95%CI and Pearson chi-square
22 test. All reported P values were two-sided in this trial.
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27 **Sample size**

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29 A retrospective data review for cognitive fusion targeted biopsy performed at
30 our institution during 2017 showed a clinically significant cancer detection rate
31 of 52.8%¹⁸ while a literature from Germany revealed a clinically significant
32 cancer detection rate of 45%¹⁹ for software-based fusion targeted biopsy. The
33 patients with PI-RADS score ≥ 3 account for 60.6% in all patients who had
34 undergone a mpMRI examination at our institution.
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42 For the non-inferiority hypothesis, using a 10% noninferiority margin, using 80%
43 power and 5% one-sided α , assuming a detection rate of clinically significant
44 cancer for cognitive fusion targeted biopsy of 50% and a detection rate for
45 software-based fusion targeted biopsy of 45%, using allocation ratio of 1:1, 137
46 men per arm will be required. Assuming that 50% has at least one suspicious
47 lesion on mpMRI, 548 men are needed. Account for 10% withdraw/loss, a total
48 of 602 participants are required for inclusion.
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58 **Harms and adverse events**

59 A research nurse will record all harms or adverse events relevant or not relevant
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4 to the procedure of biopsy. Adverse events will be assessed by Common
5 Terminology Criteria for Adverse Events (CTCAE). The serious adverse events
6 include (1) death; (2) life-threatening; (3) hospitalization and (4) disability or
7 permanent damage will be recorded immediately and then sent to the ethics
8 committee and the monitoring board within 24 hours. All harms and adverse
9 events will be recorded from the registration to one-week after the biopsy.
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17 **Data collection**

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19 The data will be collected from the patient/relative of a patient at registration,
20 and the medical record on two weeks and six weeks. The demographic
21 information (age, height, weight, BMI), PSA, and family history will be recorded
22 on registration, as well as the digital rectal examination will be performed. On
23 two weeks after the registration, an MRI result will be recorded, including a PI-
24 RADS score, prostate volume, and suspicious lesion volume. Both prostate
25 volume and suspicious lesion volume will be measured by mpMRI on the T2WI
26 sequence. The data of pathological assessment will be recorded on six weeks
27 (two weeks post-biopsy) including an overall Gleason score and a separate
28 Gleason score for each biopsy core. Besides, the length and percent of tumour
29 in each biopsy core will also be reported.
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43 **Monitoring**

44 A team of independent clinical research associate (CRA) with all more than five
45 years of experiences is responsible for being familiar with the trial protocol and
46 monitoring all researchers and all participants involved in the whole processes
47 of this trial. The CRA's role is to (1) monitoring the trial plan, the record forms,
48 and the case report form before the start of the trial; (2) monitoring participants'
49 informed consent and enrolment rates; (3) monitor the compliance of
50 participants and investigators with the protocol, and monitoring data quality and
51 authenticity.
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Ethics and dissemination

Ethical approval was obtained from the ethics committee of Shanghai East Hospital. The results of this study will be disseminated for international peer-reviewed journal and disseminated for presentation at international or national academic conference.

Trial status

This RCT was first registered online at ClinicalTrials.gov on 13 February 2020. The study is expected to start on 1 September 2020. Recruitment is anticipated to continue until 1 September 2021 with 6-week follow-up to be completed in November 2021.

Patient and public involvement

This trial protocol was written without patient or public involvement. The participants were not involved in the contribution of the design, recruitment or conduction of the study. Each participant will be informed of the latest results at follow-up and received a summary of the main finding at the end of the trial.

Authors' contributions

Conceptualization: He B, Li R and Wang H.

Data curation: He B, Li R, Li D, Huang L and Wang H.

Formal analysis: He B, Li R, Li D and Huang L.

Investigation: He B, Li R, Li D, Huang L and Wang H

Supervision: Wen X and Yang G

Original draft: He B and Wang H

Review and editing: Li R, Wen X and Yang G.

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Declaration of interests

None of the authors have any conflicts of interest to declare.

Table 1. Participant timeline in the study

	Contact with patient			
	Vist 1	Vist 2	Vist 3	Vist 4
	0	0~2 weeks	2~4 weeks	5~6 weeks
Consent	×			
Screening	×			
Baseline characteristic	×			
PSA	×			
MRI		×		
Randomization		×		
Prostate biopsy			×	
Cognitive fusion targeted biopsy + 20 region templated guide biopsy (cognitive fusion arm)			×	
Software fusion targeted biopsy + 20 region templated guide biopsy (Software fusion arm)			×	
Pathological assessment				×
Withdrawal	Complete as required at any time following registration			
SAE	Complete as required at any time following registration			

Table 2. Patients inclusion and exclusion criteria

Inclusion criteria

Age over 18 years old

PSA increase to 4–20 ng/ml and/or abnormal DRE;

Without previous prostate biopsy

Fully understand the clinical trial protocol and sign the informed consent

Exclusion criteria

Previous history of prostate biopsy

Evidence of acute or chronic prostatitis

Contraindications to prostate biopsy (e.g. fever, evidence of urinary tract infection)

Contraindications to MRI (e.g. metal implant, contrast agent allergy)

The investigator judges that patients who are not suitable for this clinical trial

Any other conditions that investigator judges that participations who are not suitable for this trial

Figure legend

Fig 1 Trial flow chart

Fig 2 20-region template guided prostate biopsy

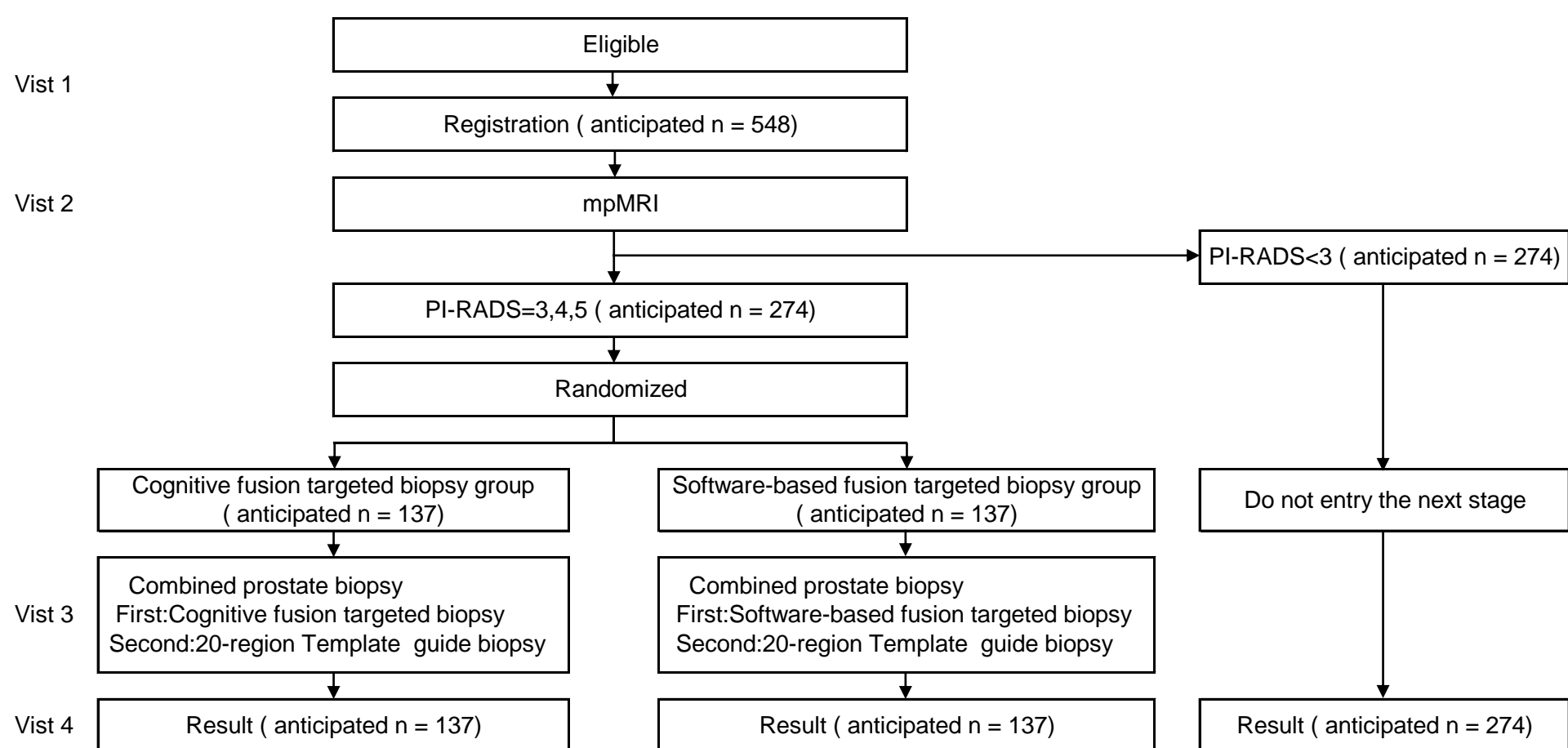
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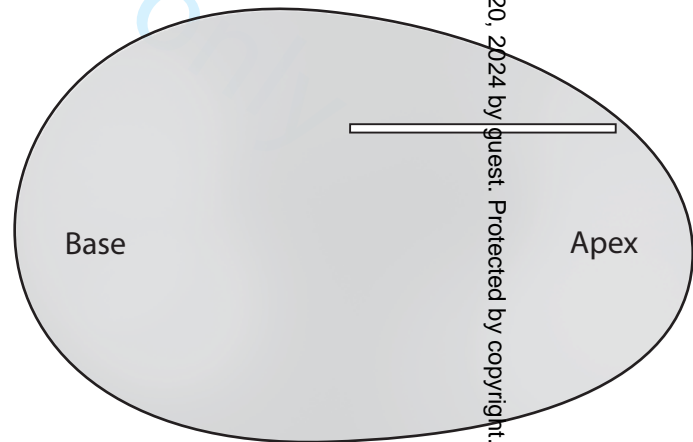
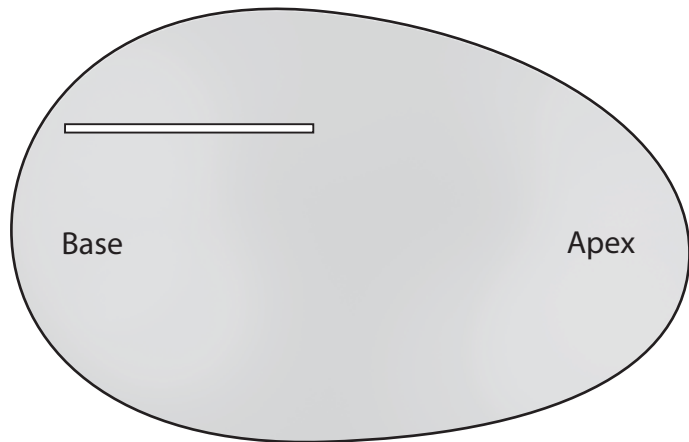
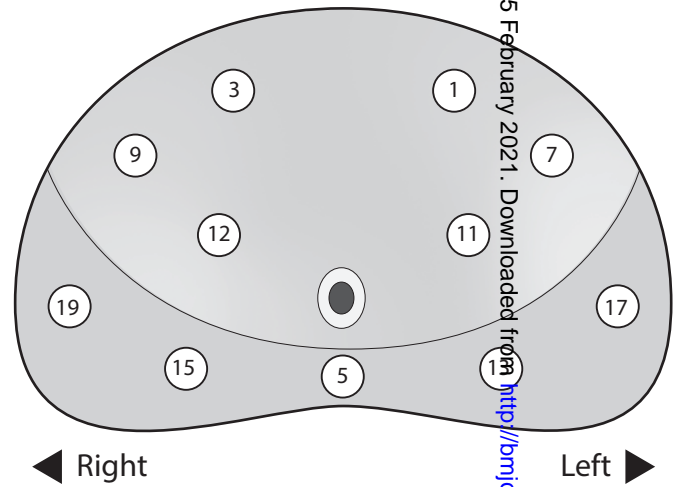
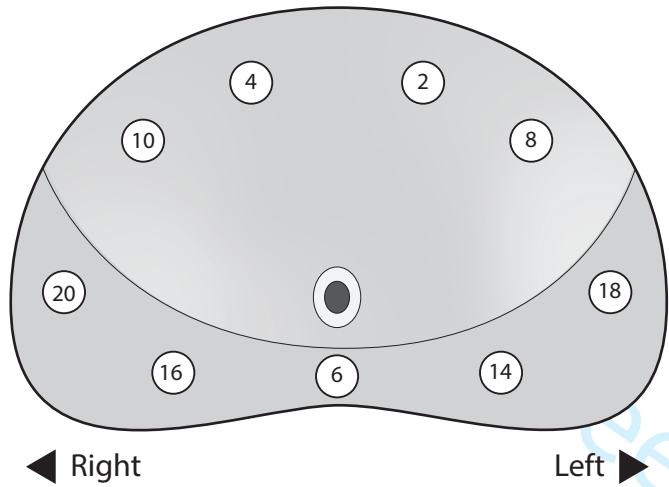
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