CLINICAL STUDY PROTOCOL

A randomized controlled trial comparing bp-MRI and mp-MRI on the screening accuracy for clinically significant prostate cancer before MRI-fusion targeted biopsy

VERSION NO.3

DATES (20240429)

INVESTIGATORS

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SITES

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1. Synopsis

Protocol Title：A randomized controlled trial comparing bp-MRI and mp-MRI on the screening accuracy for clinically significant prostate cancer before MRI-fusion targeted biopsy.

Study Objectives：We aim to address these questions for Taiwan males suspicious of csPCA, with PSA range of 4-20 ng/ml by conducting a RCT trial.

Investigational product(s)：Magnetic Resonance Imaging (MRI)

Development Phase：☐ I ☐II ■III ☐IV ☐其它_____ ☐不適用

Study Design：

1. ■ Experimental Group
   ☐ Control Group ： ☐ Placebo
   ☐ Study Drug (Name、Dose、Usage) _____
   ☐ Other _____
2. Blinding：■ Open ☐ Evaluator-blind ☐ Single-blind(patient) ☐ Double-blind(patient+PI)
   ☐ Double Dummy ☐ Other _____
3. Randomization: ■ Yes ☐ No
4. ☐ Parallel design ☐ Crossover design ☐ Other _____ ■ Not applicable
5. Treatment Period：_____(days/weeks/months/years) ■ Not applicable
6. Study Period: _____2_____years (or From 01/02/2024 to 31/01/2026)
6. Dose adjustment：☐ Mandatory ☐ Selectively ☐ No ■ Not applicable
7. Study location：■ Single ☐ Multi-center ☐ Global

Endpoints (Outcome measure)：

1. Primary endpoint:
   The proportion of men with clinically significant Prostate cancer(csPCa), defined as a diagnosis of ISUP (International Society of Urogenital Pathology) Grade group ≥2 prostate cancer, in at least one biopsy core.

2. Secondary endpoints:
   1. The proportion of men with a diagnosis of any PCa
   2. The proportion of men with a diagnosis of clinically insignificant PCa, defined as ISUP grade group 1 PCa (ISUP 1 PCa)
   3. The proportion of men with a diagnosis of csPCa
      Only in targeted biopsy
      Only in systematic biopsy
   4. The proportion of csPCa of all suspicious lesions from bp-MRI and mp-MRI.

3. Exploratory endpoints (if any):
   nil

Inclusion/Exclusion Criteria：

Inclusion criteria (All of the followings)

1. Men ≥50 years of age
2. Clinical suspicion of prostate cancer and indicated for prostate biopsy
3. Serum Prostate-specific antigen (PSA) between 4~20 ng/mL
4. Eligible for MRI study
5. Digital rectal examination ≤ cT2 (organ-confined cancer)
6. Able to provide written informed consent.

Exclusion criteria: (any of the followings)

1. Prior prostate biopsy in the 6 months before screening visit
2. Prior diagnosis of prostate cancer
3. Contraindicated to prostate biopsy: active urinary tract infection, failed insertion of transrectal ultrasound probe into rectum (abdominal perineal resection, anal stenosis), uncorrectable coagulopathy, antiplatelet or anticoagulant which cannot be stopped (continue low-dose aspirin before and after biopsy is permitted)
4. Contraindicated to MRI study: contrast medium allergy, claustrophobia, or other contraindications (e.g.: intra-abdominal metal foreign bodies).
5. Patients without histological results of prostate biopsies due to patient refusal for biopsy or loss of follow up before biopsy being done
6. Patients have prior treatments for prostate cancers or any kinds of hormone therapy, immunotherapy, chemotherapy, radiation therapy of the pelvic cavity.
7. Patients' withdrawal of informed consents of this study

Withdrawal criteria

1. Patients could not complete the scheduled MRI examinations
2. MRI images of insufficient quality to localized csPCA or to exclude the presence of csPCA

Study Procedures：

Feasibility in recruiting adequate patients for this trial

There are estimated 600+ patients diagnosed and treated as prostate cancer in our institute every year. We performed about 800+ prostate biopsies in our hospital per year. Assuming 40-50% of men agree recruitment to this study, about 200-250 men will be recruited per year, and the recruitment for the whole study should complete in 24 months, and the study to complete in 30 months.

Study intervention

MRI prostate

Bi-parametric and multi-parametric MRI prostates can be performed using a 3.0 Tesla scanner with a pelvic phased array coil with or without contrast. MRI findings will be reported according to PI-RADS (Prostate Imaging-Reporting and Data Systems) v2.1 recommendations. (12) MRI will be reported by radiologists with experience in MRI prostate reporting. PI-RADS scores 3-5 will be regarded as suspicious, and targeted plus systematic biopsy will be performed.

Prostate biopsy

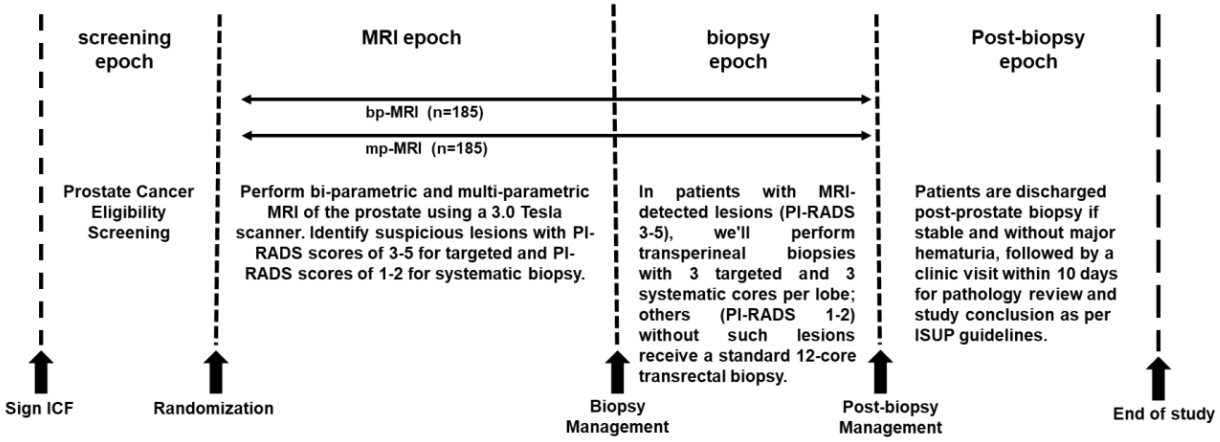
In patients with suspicious lesion found on MRI (identified as PI-RADS score 3-5 lesions on bp-MRI or mp-MRI), biopsies will be done via trans-perineal approach under general anesthesia with 3 cores of targeted biopsy from each lesion, alone with 3 cores of systemic biopsy from right and left

lobes respectively.
In those without identified suspicious lesions on MRI, a standard 12-core systematic biopsy will be performed via trans-rectal approach under local anesthesia.
All biopsies will be performed by Urologists experienced in both targeted and systemic prostate biopsy. Targeted biopsies will be done by software-assisted MRI-USG fusion registration. Peri-biopsy antibiotics are given according to our clinical guidelines.

Post-biopsy management

Patients will be discharged after prostate biopsy when they can pass urine without significant gross hematuria, and clinically stable. They will be followed up in the clinic within 10 days after a biopsy to review pathology results and complications. All biopsies will be assessed by experienced Urogenital pathologists and reported according to the International Society of Urological Pathology (ISUP) consensus. (23) The study period ends after the first clinic follow-up.

Figure 1. Study design



Concomitant Treatments： ■不適用

1. Concomitant Therapy：

2. Prohibited Therapy：

Statistical Methods：

1. Main study Hypothesis：☐ Equality ☐ Superiority ■ Non-inferiority ☐ Equivalence ☐ Other _____

2. Estimated Sample Size：整個試驗預計納入人數 370 ，整個試驗可評估人數 370
本中心預計納入人數 370 ，本中心可評估人數 370

3. Efficacy assessment group： ☐ Intent-to-treat (ITT) ■ Per-Protocol (**PP)** ☐ Other _____

附註：意圖治療：Intent-to-treat (ITT)；依計畫書：Per-Protocol (**PP)**

4. Interim analysis： ☐ Yes ■ No

Statistical methods：

The primary objective of this study is to evaluate the csPCa detection in bp-MRI arm versus mp-MRI arm. We hypothesise that bp-MRI is non-inferior to mp-MRI in detecting

csPCa. The baseline characteristics of the two groups will be compared. Continuous variables will be evaluated using the student's t-test and the Mann-Whitney U test. In contrast, categorical variables will be analysed using the Chi-squared and Fisher's exact tests, as applicable. The effect size and 95% CI will be presented for secondary outcomes, and a 2-sided p-value less than 0.05 will be considered statistically significant. All statistical analyses will be performed using SPSS v.24.0 (IBM Corp., Armonk, NY, USA).

5. Handling of Missing Data：

Analysis would be carried on for available data after exclusion of the missing data.

2. Introduction and Rationale

Prostate cancer (PCa) is the second most commonly diagnosed cancer and the fifth leading cause of cancer death in males worldwide [1]. It is traditionally less prevalent in Asia but the incidence has increased in the past decades [2-4]. According to the data released by Taiwan Health Promotion Administration, Ministry of Health and Welfare Cancer Statistics, Prostate cancer is now the fifth most common male cancer in Taiwan [5].

Prostate-specific antigen (PSA) is a widely used test for prostate cancer detection. However, PSA is highly sensitive but not very specific [6]. Elevated PSA levels typically lead to referrals to urologists for further evaluation, including magnetic resonance imaging (MRI) and potentially a prostate biopsy. Biopsies carry a risk of complications, with infections at the biopsy site being a major concern, leading to sepsis in 2–5% of cases [7]. Concerns about missing clinically significant cancer, unnecessary biopsies, and overtreatment of low-risk disease have driven the search for improved biopsy methods that are both more accurate in detecting cancer and safer for patients.

The application of Magnetic Resonance Imaging (MRI) in identifying potentially cancerous lesions within the prostate gland dates back to the 1980s [8, 9]. A significant leap forward occurred in the 1990s with the introduction of dynamic contrast-enhanced (DCE) and diffusion-weighted imaging (DWI) MRI protocols [10, 11]. With the introduction of MRI of the prostate and the improvement in PCa detection and localization, an alternative procedure, known as MRI-targeted biopsy (MRI-TB), has been shown to have comparable or even higher detection rates of csPCa compared to TRUS-system biopsy (SB). Targeted prostate biopsies from MRI-suspicious lesions have improved the cancer detection rate (CDR) of csPCa compared with systematic TRUS-guided biopsies. The implementation of pre-biopsy multiparametric MRI has effectively reduced the risk of both underdiagnosis of clinically significant disease and overdiagnosis of clinically insignificant disease, which were previously associated with random prostate sampling. (19)

Two types of MRIs have emerged for diagnosing PCa: Bi-parametric MRI (bpMRI), which combines T2-weighted images with DWI, and multi-parametric MRI (mpMRI), which incorporates DCE with or without spectroscopy, into its imaging protocol [12]. The determination of PCa utilizing mpMRI relies on the Prostate Imaging Reporting and Data System (PI-RADS) score based on PI-RADS versions 2.1 recommendation; however, if DCE is of insufficient quality or not available, an alternative PIRADS scores based on mp MRI could be evaluated using modified score rules provided by PRIRADS v 2.1 as well [13].

In 2015, Rais-Bahrami et al. employed mpMRI with the exclusion of DCE results to analyze

biopsy outcomes of individuals. Their research explored the application of bpMRI in diagnosing PCa. They found the bpMRI with PCa detection overall accuracy of 80% [14]. Bass et. al. conducted a meta-analysis across 44 cohort studies, revealing that the sensitivity, specificity, and AUC of bpMRI for csPCa were 87%, 72%, and 87%, respectively [15]. Furthermore, several studies have demonstrated that both bpMRI and mpMRI exhibit comparable diagnostic effectiveness in detecting PCa and csPCa. The overall sensitivity and specificity for mpMRI were 76% and 89%, while bpMRI achieved 74% sensitivity and 90% specificity [16]. For patients with varying total prostate-specific antigen (tPSA) levels, both mpMRI and bpMRI exhibit identical accuracy in detecting PCa or csPCa. However, Pan et al. found that mpMRI detected more cases of PCa and csPCa in the tPSA range of 10–20 ng/ml. In contrast, for other tPSA ranges (tPSA < 4 ng/ml, 4–10 ng/ml, 20–100 ng/ml), the detection rates of PCa and csPCa were similar between bpMRI and mpMRI [17]. Collectively, bpMRI proves to be an effective tool for PCa screening and diagnosis, with comparable diagnostic accuracy to mpMRI. Additionally, when omitting the DCE protocol from the MRI, patients experience reduced costs and shorter imaging times, while healthcare providers can offer more tests to their patient population.

Although these retrospective studies and some meta-analysis shows similar sensitivity and specificity for detecting csPCA in Europe and US patients, there is still a lack of randomized control trials validating the non-inferiority of bpMRI as compared with mpMRI for detecting and guiding targeted biopsies of csPCA in patients of PSA 4-20 ng/ml in the world and Taiwan. Thus, we aim to address this questions for Taiwan males suspicious of csPCA, with PSA range of 4-20 ng/ml by conducting a RCT trial.

2.1 Investigational product(s)

Not Applicable

2.2 Animal and preclinical study data

Not Applicable

2.3 Clinical data

Not Applicable

2.4 Risks / benefits Assessment

MRI (Magnetic Resonance Imaging) is a commonly used medical imaging technology, primarily for detailed observation of internal body structures and functions. Its risks are relatively low, but there are still some considerations, while its potential benefits are quite significant.

Risks:

- For patients with cardiac pacemakers, metal implants, or certain types of metal fragments, MRI can pose risks.
- The high-intensity magnetic field may affect or move metal objects inside the body.
- In very rare cases, the use of contrast agents may cause mild to severe allergic reactions.

Potential Benefits:

- MRI does not use ionizing radiation, resulting in less exposure to radiation for patients compared to X-rays or CT scans.
- It provides extremely detailed images of soft tissues, which helps in diagnosing various diseases such as brain and spinal cord lesions, musculoskeletal injuries, heart diseases, and cancer.

- MRI is very useful for long-term tracking and assessing the progression of certain medical conditions.

2.5 Regulatory

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB as soon as possible.

Subject data confidentiality is maintained through the use of identification numbers to protect the privacy of participants. It ensures that no information about the participants' involvement in the study or their personal information is disclosed. Regarding the results and diagnoses from participant interviews, the research leader will maintain a confidential stance, carefully safeguarding their privacy.

3. Objectives and Endpoints

3.1 Study Objectives:

3.1.1 Primary objective:

We aim to address these questions for Taiwan males suspicious of csPCA, with PSA range of 4-20 ng/ml by conducting a RCT trial.

3.2 Study endpoints:

3.2.1 Primary endpoint:

The proportion of men with clinically significant Prostate cancer(csPCa), defined as a diagnosis of ISUP (International Society of Urogenital Pathology) Grade group ≥2 prostate cancer, in at least one biopsy core.

3.2.2 Secondary endpoints:

1. The proportion of men with a diagnosis of any PCa
2. The proportion of men with a diagnosis of clinically insignificant PCa, defined as ISUP grade group 1 PCa (ISUP 1 PCa)
3. The proportion of men with a diagnosis of csPCa
4. Only in targeted biopsy
5. Only in systematic biopsy
6. The proportion of csPCa of all suspicious lesions from bp-MRI and mp-MRI.

4. Study Design

We propose to conduct a phase III randomised controlled trial to evaluate the detection of clinically significant prostate cancer (csPCa) by bp-MRI versus mp-MRI before MRI-fusion targeted biopsy. Clinically significant prostate cancer (csPCa) is defined as ISUP (International Society of Urogenital Pathology) Grade group ≥ 2 prostate cancer.

Patients who are suspicious of prostate cancers with abnormal digital examination, or abnormal ultrasound and having a pre-MRI and were scheduled to receive prostate biopsy will be enrolled in this study. Patients will be randomized in a 1:1 manner to bp-MRI and mp-MRI. Patients with clinical suspicion of prostate cancer on MRI with PI-RADS (Prostate Imaging-Reporting and Data System, version 2.1) [18] score 3-5 will be arranged to receive MRI-Ultrasound fusion biopsy for targeted and systemic biopsy. Patients who have no suspicious lesions found on MRI will receive standard

systemic biopsy only instead. The study flowchart is provided in Figure 1. The detection rates of csPCa will be compared between arms. The study hypothesis is that bp-MRI has similar detection rate for csPCa comparing to mp-MRI.

To formulate the randomization codes and distribution process, we first plan to recruit a total of 370 participants. Then, we choose a block size of 4 to maintain balance between groups while reducing the predictability of the assignment sequence. Utilizing the block randomization method, we generate random codes for each block to ensure an equal number of participants in each treatment group. Subsequently, a complete table of random codes is created using a random number generator, serving as the basis for participant assignment.

As participants enter the study, they will be assigned to the respective groups according to the sequence of the random code table, namely the bp-MRI group or the mp-MRI group. This process not only ensures the randomness of the assignments but also helps maintain the fairness and transparency of the research. After each assignment, we record the detailed information of the participants and the group they are assigned to, ensuring the traceability and transparency of the entire process.

4.1 Overall Design

Study intervention

MRI prostate

Bi-parametric and multi-parametric MRI prostates can be performed using a 3.0 Tesla scanner with a pelvic phased array coil with or without contrast. MRI findings will be reported according to PI-RADS (Prostate Imaging-Reporting and Data Systems) v2.1 recommendations. (12) MRI will be reported by radiologists with experience in MRI prostate reporting. PI-RADS scores 3-5 will be regarded as suspicious, and targeted plus systematic biopsy will be performed.

Prostate biopsy

In patients with suspicious lesion found on MRI (identified as PI-RADS score 3-5 lesions on bp-MRI or mp-MRI), biopsies will be done via trans-perineal approach under general anesthesia with 3 cores of targeted biopsy from each lesion, alone with 3 cores of systemic biopsy from right and left lobes respectively.

In those without identified suspicious lesions on MRI, a standard 12-core systematic biopsy will be performed via trans-rectal approach under local anesthesia.

All biopsies will be performed by Urologists experienced in both targeted and systemic prostate biopsy. Targeted biopsies will be done by software-assisted MRI-USG fusion registration. Peri-biopsy antibiotics are given according to our clinical guidelines.

Post-biopsy management

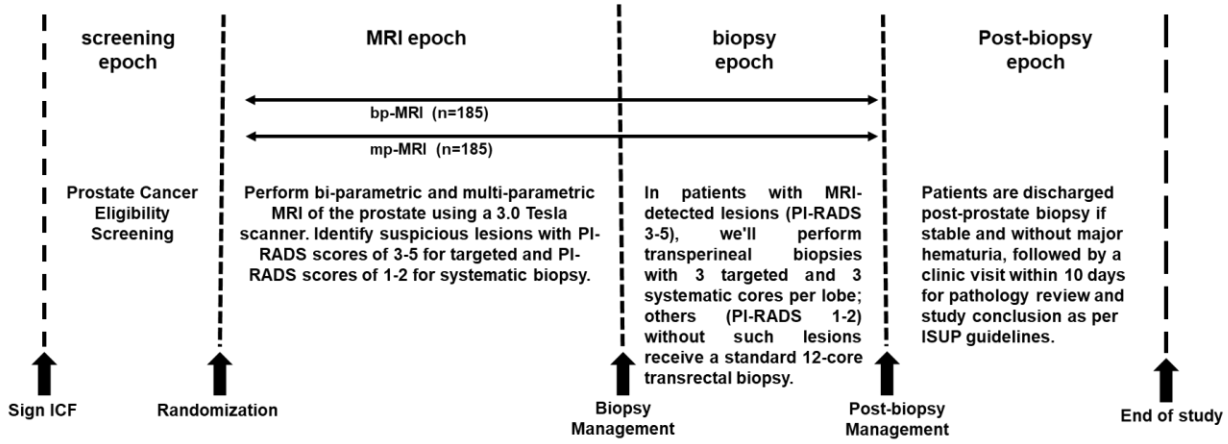
Patients will be discharged after prostate biopsy when they can pass urine without significant gross hematuria, and clinically stable. They will be followed up in the clinic within 10 days after a biopsy to review pathology results and complications. All biopsies will be assessed by experienced Urogenital pathologists and reported according to the International Society of Urological Pathology (ISUP) consensus. (23) The study period ends after the first clinic follow-up.

In our medical research, we prioritize protecting participant privacy and confidentiality. We use unique research codes to anonymize personal details like names and IDs. The principal investigator keeps consultation results and diagnoses confidential, even in published research. Participants consent to have their records reviewed by authorized parties for legal and ethical compliance, with a promise of maintaining their anonymity. For safety, we may inform

participants' other doctors about their trial involvement to manage treatment interactions. Overall, these steps ensure participant privacy and safety throughout the research.

Flow Chart (試驗流程圖)：

Figure 1. Study design



4.1 Number of Patients

evaluable number

The sample sizes of 148 in the **bp-MRI group** and 148 in the **mp-MRI group** achieve 80.145% power to detect a non-inferiority margin difference between the group proportions of -0.1000. The **mp-MRI group proportion** is 0.280. Under the null hypothesis of inferiority, the **bp-MRI proportion** is assumed to be 0.180. The power was computed for the case where the actual treatment group proportion is 0.280. The test statistic used is the one-sided Z test (unpooled), and the significance level of the test is 0.025. We have set the dropout rate at 20%, thus the bp-MRI group and mp-MRI group each consist of 185 individuals, resulting in a total enrolled number of 370 people. **We have set the dropout rate at 20%, thus the mp-MRI group and bp-MRI group each consist of 185 individuals, resulting in a total enrolled number of 370 people.**

enrolled number

We have set the dropout rate at 20%, thus the mp-MRI group and bp-MRI group each consist of 185 individuals, resulting in a total enrolled number of 370 people.

4.2 Schedule of Activities

Time-Event scheme(評估時程表):

	Screening	Imaging	Verification	Post-biopsy management
Category	Registration	MRI	Prostate biopsy	
Time frame	Day 1-14	Day 15-28	DAY 29-58	Day 59-68
Assessment				

Inform consent	✓			
History taking	✓			
PSA level	✓			
Digital Rectal Examination	✓			
Abnormal Ultrasound	✓			
Staging bp-MRI or mp-MRI		✓		
Biopsy			✓	
Hematuria				✓
Pathology report				✓

5. Study Population

5.1 Inclusion Criteria

Inclusion criteria:

1. Men ≥50 years of age
2. Clinical suspicion of prostate cancer and indicated for prostate biopsy
3. Serum Prostate-specific antigen (PSA) between 4~20 ng/mL
4. Eligible for MRI study
5. Digital rectal examination ≤ cT2 (organ-confined cancer)
6. Able to provide written informed consent.

5.2 Exclusion Criteria

Exclusion criteria:

1. Prior prostate biopsy in the 6 months before screening visit
2. Prior diagnosis of prostate cancer
3. Contraindicated to prostate biopsy: active urinary tract infection, failed insertion of transrectal ultrasound probe into rectum (abdominal perineal resection, anal stenosis), uncorrectable coagulopathy, antiplatelet or anticoagulant which cannot be stopped (continue low-dose aspirin before and after biopsy is permitted)
4. Contraindicated to MRI study: contrast medium allergy, claustrophobia, or other contraindications (e.g.: intra-abdominal metal foreign bodies).
5. Patients without histological results of prostate biopsies due to patient refusal for biopsy or loss of follow up before biopsy being done
6. Patients have prior treatments for prostate cancers or any kinds of hormone therapy, immunotherapy, chemotherapy, radiation therapy of the pelvic cavity.
7. Patients' withdrawal of informed consents of this study

5.3 Withdrawal criteria

1. Patients could not complete the scheduled MRI examinations
2. MRI images of insufficient quality to localized csPCA or to exclude the presence of csPCA

6. Treatments

Not Applicable

6.1.Treatment Administration

Not Applicable

6.2. Concomitant Therapy

Not Applicable

7. Efficacy Assessments

Not Applicable

8. Safety Assessments

Allergic Reactions: Some individuals may have allergic reactions to MRI contrast agents (usually containing gadolinium). Before administering the contrast agent, medical staff will inquire about the patient's allergy history to determine the risk of an allergic reaction.

Renal Function: Contrast agents can affect renal function. Patients with renal impairment

require a renal function assessment before undergoing an MRI scan with gadolinium-based contrast agents.

9. Adverse event reporting

The PI Dr. See-Tong Pang will report SAEs to the IRB of Chang Gung Medical Foundation according to the Serious Adverse Event Reporting Procedures and Guidelines as posted in the Clinical Trials Resource on the website of Chang Gung Medical Foundation IRB. SAE reports to the IRB should include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- Protocol number
- Title of protocol
- Description of the SAE, including attribution to drug and expectedness

9.1 Definitions and reports of Adverse Events

All adverse events that occur after the informed consent is signed (including run-in) must be recorded on the adverse event CRF (paper and/or electronic) whether or not related to study agent. AE Data Elements including:

- AE reported date
- AE Verbatim Term
- CTCAE Term (v 5.0)
- Event onset date and event ended date
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a Serious Adverse Event (SAE)
- Action taken with the study agent
- Outcome of the event
- Comments

Identify the adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed.

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to their impact on the participant's ability to perform daily activities as follows:

Grade	Severity	Description
1	Mild	• Barely noticeable, does not influence functioning • Causing no limitations of usual activities

2	Moderate	• Makes participant uncomfortable, influences functioning • Causing some limitations of usual activities
3	Severe	• Severe discomfort, treatment needed • Severe and undesirable, causing inability to carry out usual activities
4	Life threatening	• Immediate risk of death • Life threatening or disabling
5	Fatal	• Causes death of the participant

The possibility that the adverse event is related to study drug will be classified as one of the following: not related, unlikely, possible, probable, definite.

DEFINITION of Serious Adverse Events: ICH Guideline E2A and GCP of Taiwan define serious adverse events as those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is life threatening (Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner.

9.2 Adverse event follow-up

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such. Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the IRB of Chang Gung Medical Foundation of SAE form in the appropriate format. Follow-up information should be sent to Chang Gung Medical Foundation IRB as soon as possible according to IRB's Serious Adverse Event Reporting Procedures and Guidelines.

10. Criteria for the termination of the trial

Following CGMH's Management of Study Termination guideline, the trail shall be terminated by the investigator or the CGMH IRB when deemed necessary after evaluation. Incidents that may cause the termination of the trail include the encounter of life-threatening AE, fatal AE, etc. The PI will send in an application via CGMH HRPMS system to file for the termination of the trial.

11. Statistical Considerations

11.1 Sample size Determination

The sample sizes of 148 in the **bp-MRI group** and 148 in the **mp-MRI group** achieve 80.145% power to detect a non-inferiority margin difference between the group proportions of -0.1000. The **mp-MRI group proportion** is 0.280. Under the null hypothesis of inferiority, the **bp-MRI proportion** is assumed to be 0.180. The power was computed for the case where the actual treatment group proportion is 0.280. The test statistic used is the one-sided Z test (unpooled), and the significance level of the test is 0.025. We have set the dropout rate at 20%,

thus the bp-MRI group and mp-MRI group each consist of 185 individuals, resulting in a total enrolled number of 370 people. **We have set the dropout rate at 20%, thus the mp-MRI group and bp-MRI group each consist of 185 individuals, resulting in a total enrolled number of 370 people.**

11.2 Planned Statistical methods of analysis

Statistical analysis

The primary objective of this study is to evaluate the csPCa detection in bp-MRI arm versus mp-MRI arm. We hypothesise that bp-MRI is non-inferior to mp-MRI in detecting csPCa. The baseline characteristics of the two groups will be compared. Continuous variables will be evaluated using the student's t-test and the Mann-Whitney U test. In contrast, categorical variables will be analysed using the Chi-squared and Fisher's exact tests, as applicable. The effect size and 95% CI will be presented for secondary outcomes, and a 2-sided p-value less than 0.05 will be considered statistically significant. All statistical analyses will be performed using SPSS v.24.0 (IBM Corp., Armonk, NY, USA).

11.2.1 Efficacy analysis

Not applicable

11.2.2 Safety analysis

Not applicable

11.2.3 Additional analysis

Not applicable

11.2.4 The level of significance

A p-value less than 0.05 was considered significant and was denoted by * and p-value less than 0.001 was denoted by **.

11.3 Analysis Population

Not applicable

11.4 Procedure for accounting for missing, unused and spurious data

The incomplete clinical data and sequencing data with poor quality will be excluded in the study.

11.5 Procedures for reporting any deviation(s) from the original statistical plan

If deviation(s) from the original statistical plan is identified, the investigator will follow the guideline of CGMH IRB to record and report such incident. The PI may login to the CGMH HRPMS system to report and IRB will proceed with further review.

12. Direct access to source data/documents

Investigators permit IRB to access to the source data of experiment for trial-related monitoring, audits and regulatory inspection.

13. Ethical considerations

This study will be conducted according to Taiwan and international standards of Good Clinical Practice for all studies. Applicable government regulations and Chang Gung Medical Foundation research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the Chang Gung Medical Foundation Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

14. Data handling and keeping

Clinical samples will be collected in Chang Gung Medical Foundation. The sequencing data will be stored in computers of laboratory with an electronic encryption. The clinical and source data can only be assessed by clinical doctors and investigators of the study.

15. Financing and Insurance

The Ministry of Health and Welfare will provide sufficient funding for this clinical study.

16. References

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