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Optimization of prostate biopsy - Micro-Ultrasound versus MRI (OPTIMUM): A 3-arm randomized controlled trial evaluating the role of 29 MHz micro-ultrasound in guiding prostate biopsy in men with clinical suspicion of prostate cancer

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ABSTRACT

Background: Micro-ultrasound (microUS) is a novel ultrasound-based imaging modality which has demonstrated the ability to visualize prostate cancer. Multiparametric MRI/ultrasound (mpMRI/US) fusion has recognized advantages for the performance of prostate biopsy, however, it encompasses additional cost, time and technical expertise to performing prostate biopsy in comparison to conventional trans-rectal ultrasound biopsy. MicroUS may simplify and optimize this pathway.

Methods: OPTIMUM is a 3-arm randomized controlled trial comparing microUS guided biopsy with MRI/US fusion and MRI/MicroUS "contour-less" fusion. This trial will investigate whether microUS alone, or in combination with mpMRI, provides effective guidance during prostate biopsy for the detection of clinically significant prostate cancer (csPCa) for biopsy naïve subjects. 1200 subjects will be randomized. The economic impact will be evaluated.

Results: The rate of csPCa (defined as Grade Group 2 and above) in each arm will be compared. The primary hypothesis is non-inferiority of csPCa rate between the MRI/US fusion arm and the microUS-only arm (including the blinded microUS-only portion of the MRI/MicroUS arm). As a secondary objective, the csPCa rate between MRI/MicroUS fusion and MRI/US fusion arms will also be compared. Other secondary objectives include the increase in rate of patients diagnosed with csPCa due to each type of sample (mpMRI targeted, microUS targeted, systematic), the negative predictive value of each imaging modality, and a health economic analysis of the procedures in each arm.

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Conclusions: OPTIMUM will determine whether microUS can be used as an alternative to MRI/US fusion biopsy. The trial will also evaluate the efficacy of the simplified "contour-less" MRI/MicroUS fusion procedure. The adoption of the microUS technique will increase the proportion of men who can benefit from modern imaging-centric diagnostic strategies, and may help reduce variability, complexity, waiting time and cost within the diagnostic pathway.

1. Background & introduction

The most common technique for diagnosis of prostate cancer involves screening based on prostate specific antigen (PSA), followed by systematically spacing biopsy samples throughout the gland in men at risk. Unfortunately, this systematic biopsy procedure has a sensitivity of only 48% to detect clinically significant prostate cancer (csPCa) compared to template mapping biopsy [1], and a 30% rate of underestimating the risk profile of the cancer when it is found [2]. Men undergoing this systematic biopsy pathway are at risk of underdiagnosis, resulting in a delay to appropriate treatment, increased risk of prostate cancer mortality, and an unnecessary exposure to the morbidity of repeat biopsy [3–5]. While various strategies including both advanced imaging and biomarkers are available to refine the population exposed to biopsy-related morbidity, improved biopsy guidance is necessary to ensure these men receive appropriate therapy matched to the true aggressiveness of their disease.

Multiparametric MRI (mpMRI) targeted biopsy has been extensively studied as a solution to this problem and represents a clear improvement over systematic biopsy [6–9]. According to a Cochrane review on the subject, the addition of mpMRI targeting improved detection of csPCa by 5% over systematic biopsy in biopsy naïve men [10]. A meta-analysis by Goldberg showed a greater impact with a 7–18% improvement [11]. Similar reductions in upgrading have also been demonstrated, lowering the upgrading rate on radical prostatectomy from 30% to 6.7% [2].

1.1. The mpMRI-informed diagnostic pathway

The American Urology Association, European Association of Urology, and National Comprehensive Cancer Network all recognize the use of mpMRI in order to improve the efficacy of the prostate biopsy procedure [18–20]. However, mpMRI targeted biopsy still misses small high grade cancers and up to 20% of GG2 cancers [1,6,8]. These groups agree that mpMRI targeted biopsy should be combined with systematic biopsy in order to optimize the procedure, and that systematic biopsy should still be performed in the event of negative mpMRI but persistent clinical suspicion of cancer.

The inclusion of mpMRI has altered the diagnostic pathway by requiring a cohort of expert radiologists specializing in prostate MRI to meet the demand. The care pathway has also required changes to include referral to radiology after (and, in some settings, before) initial consultation with the urologist.

1.2. mpMRI adds complexity to the diagnostic pathway and limits access

These changes to the patient care pathway have introduced new sources of error and delayed diagnosis in many places. In the UK for example, the median time to diagnosis is 55.5 days [21]. At one prostate diagnostic clinic, the time-to-diagnosis was significantly lower in patients who did not receive mpMRI compared to those that did (15 vs. 22 days) [21]. This discrepancy is greater in centers which have pre-existing resource constraints.

Variability in care has been exacerbated by the reliance on mpMRI due to significant and wide-spread inter-reader variability. Pickersgill et al. found poor agreement and poor accuracy among blinded radiologists for PI-RADS score and prediction of csPCa [22]. Similarly, Westphalen et al. found a large 27%–44% variability in the targeted detection rate (positive predictive value) of MRI-targeted biopsy across 24 imaging centers [23]. This increase in variability reduces confidence in the diagnostic process and may contribute to suboptimal results as mpMRI adoption increases. In the same way, the inclusion of MRI-derived data, along with the transfer of imaging data in pre-specified proprietary formats for fusion biopsy, adds complexity to the diagnostic pathway. This represents a source of error. The magnitude of this error has yet not been well quantified, but is likely to be substantial outside recognized centers of excellence.

Further, mpMRI cannot be used in all men. Among the contraindications are several conditions that are prevalent within the population at risk, including implanted devices such as pacemakers and hip replacements (hip prostheses alone represent up to 4% [24]), impaired kidney function (12% [25]), and claustrophobia (3–5% [26]). These men are not candidates for the mpMRI diagnostic pathway.

2. Micro-ultrasound imaging

Micro-ultrasound (microUS) is a recently developed, real-time ultrasound-based modality operating at 29 MHz compared to Conventional trans-rectal ultrasound systems at 6-9 MHz. Thus microUS results in a significantly higher resolution, 70 μm, which allows the underlying tissue structure to be visualized [27–29]. At a resolution of 70 μm, alterations in ductal anatomy associated with higher grade cancer can be visualized, based on the same principle as restricted diffusion with MRI.

Images are interpreted according to the PRI-MUS protocol (Fig. 1). This evidence-based risk scale was initially validated [30] in 2016, and a larger scale, prospective validation study [31] confirmed these results in 2019. The PRI-MUS protocol has similar risk stratification to the PI-RADS system for MRI [32].

Training on microUS is provided through a complimentary program run by Exact Imaging, which manufactures the ExactVu micro-ultrasound system. This 4-stage program provides detailed feedback to the user on their first 90 cases in order to ensure consistent interpretation of the images and reliable outcomes. While the initial learning curve for microUS appears to be short [33], this study is not intended to measure learning curve effects. Therefore all investigators performing microUS biopsy in this trial will be required to have completed at least stage 3 of 4 in this training program. Completion of the standardized training program may also provide improved inter-reader variability, which was initially found to be "fair to moderate" [30]. However examining the effect of this program on inter-reader variability is not a focus of this study.

2.1. How micro-ultrasound can improve mpMRI fusion biopsy

Due to the challenges of performing biopsy within the MRI gantry, MRI/US fusion biopsy is the more popular approach to sample targets identified by mpMRI. However, aligning the mpMRI data which is often taken on a different day and with the patient in a different position to the real-time ultrasound is not trivial and may be complicated by pressure from the ultrasound transducer on the prostate causing deformation. This procedure relies heavily on two factors to achieve accurate sampling: reliable position tracking and correction for soft tissue deformation.

Micro-ultrasound has been hypothesized to improve the accuracy of mpMRI fusion biopsy by reducing the operator's reliance on the position tracking and deformation calculations of their fusion platform. Since micro-ultrasound is able to observe the majority of these suspicious

areas natively, the operator is able to sample under direct real-time visual guidance rather than relying on the accuracy of the fused MRI images, or any pre-defined contouring. This has been investigated by several groups (see Tables 1, 2), with Cornud et al. demonstrating that microUS was able to visualize 79% of all MRI targets natively and 100% of targets positive for csPCa [34]. Perhaps because of this, Claros et al. reported a 15% improvement in MRI-directed biopsy yield when comparing a robotic fusion platform with a microUS platform [35].

Micro-ultrasound may also find additional suspicious regions within the prostate, and these targets may further improve biopsy yields when added to the mpMRI fusion biopsy strategy. This has been demonstrated by several groups, showing additional detection of csPCa in the 1–17% range (Table 2).

Improving the accuracy of mpMRI-target sampling, removing contouring requirements, and finding additional targets that may have been missed on mpMRI would mitigate the complexity and variability in the mpMRI pathway.

2.2. Can micro-ultrasound avoid mpMRI fusion biopsy?

In order to simplify the diagnostic pathway further, it would be desirable to replace mpMRI with a real-time modality of equal clinical utility. This change would improve time to diagnosis, as well as access, by combining the imaging and biopsy steps. In order for such a pathway to be acceptable it should maintain the accuracy of the mpMRI pathway for the detection of csPCa.

Data available (see Table 3) on this topic include a large 11-center, 1040-subject registry study performing a direct comparison to mpMRI which concluded that the two techniques provided similar sensitivity and negative predictive value [38]. Various other single-center studies and meta-analyses have demonstrated similar rates of csPCa detection between mpMRI-guided and microUS-guided biopsy protocols

Table 1
Efficacy of additional mpMRI-directed samples over Systematic biopsy alone. Improvement in csPca detection ranges from 5% to 18% while overall detection rate ranges from 30%–61%.

Study	MRI + Sys csPCa	Sys csPCa	Difference	Limitations
Cochrane meta-analysis [10]	53%	48%	5%	
Goldberg et al. meta-analysis [11]	N/A	N/A	7–18% (11% in RCTs)	
Valerio et al. meta-analysis [12]	36%	26%	9%	Variability in csPCa definition and inclusion of prior neg biopsy
Kasivisvanathan et al. meta-analysis [13]	40%	27%	12%	Variability in csPCa definition and inclusion of prior neg biopsy
PRECISE [14]	35%	30%	5%	Targeted biopsy only on MRI
MRI-FIRST [6]	37%	30%	7%	
PAIREDCAP [15]	61%	52%	9%	
PRECISION [16]	38%	26%	12%	No systematic samples in MRI group
PROMIS [1]	37%	22%	15%	No MRI targeted biopsy
4M[9]	30%	23%	7%	In-bore MRI sampling rather than MRI/US fusion
ASIST [17]	33%	27%	6%	Active Surveillance population

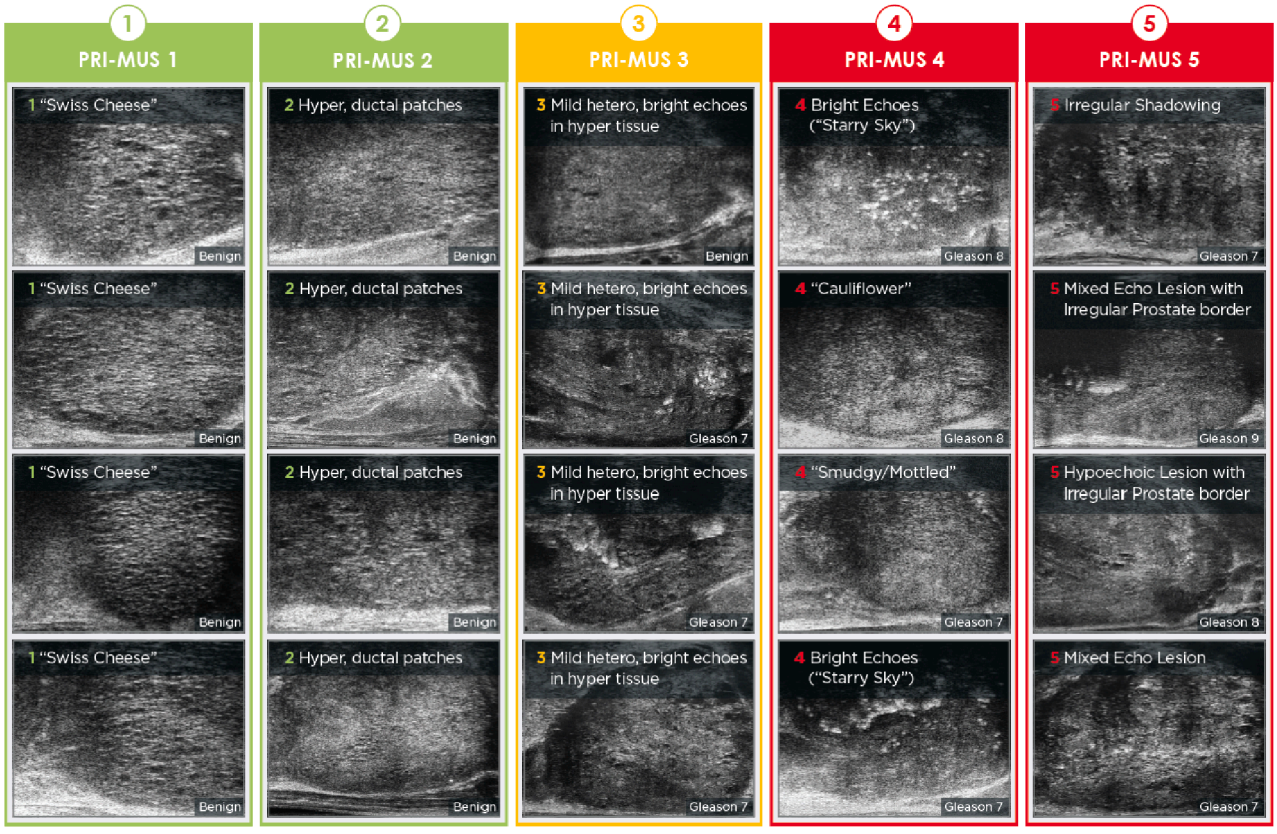

Fig. 1. Example images demonstrating the various imaging features of the PRI-MUS protocol. This risk-stratification protocol grades images based on tissue patterns seen in micro-ultrasound from 1 (very low risk fo significant cancer) to 5 (very high risk of significant cancer).

Table 2
Recent studies adding microUS to mpMRI protocols.

Study	Improvement
Cornud et al. [34]	79% of all mpMRI targets visualized, including 100% of csPCa targets.
Claros et al. [35]	15% improvement in MRI-targeted biopsy csPCa rate
Wiemer et al. [36]	17% added csPCa due to microUS targeted samples
Lughezzani et al. [32]	1% added csPCa due to microUS targeted samples
Socarrás et al. [37]	6% added csPCa due to microUS targeted samples

Table 3
Recent studies comparing microUS and mpMRI.

Study	Metric	MRI	MicroUS
Klotz et al. [38]	Sensitivity	90%	94%
Wiemer et al. [36]	csPCa detection	38%	44%
Lughezzani et al. [32]	csPCa detection	35%	35%
Socarrás et al. [39]	csPCa detection	28%	24%
Abouassaly et al. [40]	Increase in csPCa detection	N/A	12%

[28,32,36,39–41].

3. Design and methods

The OPTIMUM study is designed to determine whether both the microUS-only and MRI/MicroUS fusion procedures are acceptable alternatives to MRI/US fusion. This study will also compare the health economic benefits of each procedure. These data will support evidence-based decision-making on health care costs and ensure optimal quality of care and access to care for men at risk for prostate cancer. The overall schema for this study is presented in Fig. 2. The overall design of the trial and in particular outcome measures and non-inferiority thresholds were decided through an expert consensus panel approach based on the RAND procedure.

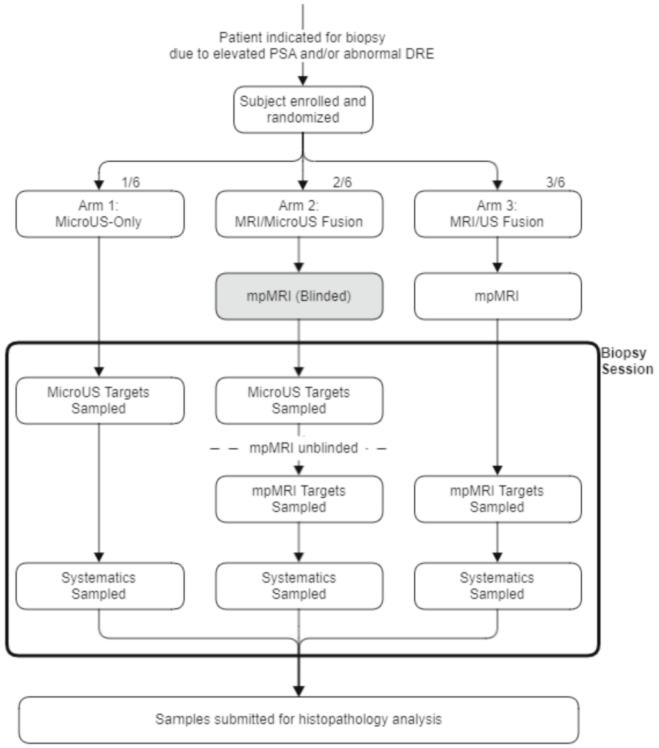

Fig. 2. Study schema.

3.1. Patient population

This protocol aims to study men undergoing biopsy for suspicion of prostate cancer. The inclusion criteria are broad to allow for some individual variation among centers and clinical judgement on the need for biopsy as shown in Table 4. Note that MRI results are not included in the justification for biopsy. This is consistent with EUA, AUA, and NCCN guidelines which recommend systematic TRUS in the event of negative mpMRI. Sub-population analyses will be performed at the conclusion of the study to examine the effects of negative MRI, variation in PSA thresholds, etc.

It is the intention of this study design that all patients receive MRI only after study enrollment and randomization (depending on the arm to which they are randomized). However, we believe that adding a criterion to exclude men who have already received mpMRI prior to first consultation would add a significant and unacceptable bias to the population as this practice has become common in some areas. Thus, men presenting with prior MRI will be eligible to enroll. Should these men be randomized to the microUS-only arm, the physician performing the biopsy will be blinded to the MRI report until after the microUS samples have been acquired. Any additional samples taken based on the MRI will not be included in the study outcomes.

3.2. Study interventions

3.2.1. MicroUS-only biopsy

MicroUS biopsy will be performed on subjects who have not received mpMRI. The biopsy will include targeted sampling based on the PRI-MUS protocol [30], with lesions of PRI-MUS 3–5 receiving 3 targeted samples each. As well, 12 systematic samples will be taken spread evenly throughout the gland. Videos will be saved to document the initial appearance of the gland and the locations of each biopsy sample. If more than 2 targets are documented, the number of systematic samples may be reduced at physician discretion to avoid oversampling certain regions of the prostate and keep the total number of samples equal to that in men with only 1 or 2 targets (i.e. up to 18 samples).

3.2.2. MRI/MicroUS fusion biopsy

MRI/MicroUS biopsy will be performed using the FusionVu feature of the ExactVu micro-ultrasound platform. This is a “contour-less” approach to fusion which does not require contouring or segmentation of the prostate capsule on either the MRI or ultrasound images. At the beginning of the procedure the operator will be blinded to the mpMRI report and images, with fusion annotations made by a co-investigator or colleague. MicroUS targeted samples will be taken first based on real-time analysis of the imaging. After the operator has confirmed that all microUS targets have been sampled, the mpMRI will be unblinded and fused. mpMRI targeted samples and systematic samples will then be taken. The biopsy will include targeted sampling based on the mpMRI targets as well as additional microUS findings (PRI-MUS 3–5). 3 samples will be taken from each target. As well, 12 systematic samples will be taken spread evenly throughout the gland. Videos will be saved to document the initial appearance of the gland and the locations of each biopsy sample. If more than 2 targets are documented, the number of systematic samples may be reduced at physician discretion to avoid

Table 4
Inclusion Criteria.

Inclusion Criteria
- Men indicated for prostate biopsy due to elevated PSA and/or abnormal DRE
- No history of prior prostate biopsy
- No history of genitourinary cancer, including prostate cancer
- ≥18 years of age
- No contraindications to biopsy
- No contraindications to mpMRI

oversampling certain regions of the prostate and keep the total number of samples equal to that in men with only 1 or 2 targets.

3.2.3. MRI/US fusion biopsy

MRI/US fusion biopsy will be performed using whichever fusion platform on operator is most familiar with, so long as true software or robotic fusion is performed and not solely cognitive fusion. As in the other arms of the study, the biopsy will include targeted sampling based on the mpMRI targets (PI-RADS >2) with 3 samples taken from each target. 12 systematic samples will be taken as well, and also as described above this number may be reduced if the number of targets is high to keep the total number of samples equal to that in men with only 1 or 2 targets.

3.2.4. Biopsy route

Both transperineal and transrectal approaches will be permitted. Whichever approach is selected should be consistent across arms for a given site. For example, if a site performs transperineal biopsy they must do so regardless of which arm the subject is randomized to. It will not be permitted to perform transperineal for the microUS arm and transrectal biopsy for the MRI/US fusion arm.

3.3. Outcomes

3.3.1. Primary

The primary outcome will be the difference in detection rate of csPCa found using microUS-only biopsy vs. MRI/US fusion biopsy. For the purposes of this outcome measure the microUS-only portion of the MRI/MicroUS arm (i.e. prior to unblinding the MRI) will be combined with the microUS-only arm to increase the study power. A non-inferiority hypothesis will be tested, with csPCa defined as Gleason Grade Group >1 disease.

3.3.2. Secondary: Fusion comparison (powered)

The difference in detection rate of csPCa with MRI/MicroUS fusion biopsy vs. MRI/US fusion biopsy. A non-inferiority hypothesis will be tested, with csPCa defined as Gleason Grade Group >1 disease. The study will be powered to meet this endpoint along with the Primary end point.

3.3.3. Secondary: Added value of each biopsy technique

In each arm a variety of biopsy strategies will be employed. These are summarized in Table 5. While not all of these combinations are blinded, they allow an estimate of the additional csPCa detection afforded by each strategy. For example, the study will demonstrate how many csPCa cases would be missed if systematic samples were avoided. This will be reported as the decrease in overall csPCa rate for each combination.

3.3.4. Secondary: Efficacy for screening

The most important metric for the decision of whether to biopsy a given patient is the negative predictive value. This will be assessed based on the overall risk score (PI-RADS and/or PRI-MUS depending on arm of study) for each patient and the biopsy outcome. Sensitivity, specificity, positive predictive value, and number able to avoid biopsy will also be determined.

3.3.5. Secondary: Health economic analysis

The overall cost of the biopsy procedure (with or without mpMRI) is composed of several parts which are expected to vary between arms of the study. The following will be recorded so as to judge the economic impact of the procedures under evaluation:

- Procedure time from introduction of the transducer to removal of the transducer
- Cost of MRI scan
- MRI magnet time
- Radiologist time
- Complications and associated treatment costs
- Patient reported outcomes and satisfaction

3.4. Statistical considerations

3.4.1. Primary – MRI vs. MicroUS

Overall number of patients diagnosed with csPCa in the MRI/US fusion arm will be compared to number of patients diagnosed with csPCa using microUS targeted and systematic biopsy samples in the MicroUS-only and MRI/MicroUS arms (i.e. discounting the MRI targeted samples taken after blinding in the MRI/MicroUS arm). A non-inferiority threshold of 10% will be used. Assuming a csPCa detection rate of 43% in each group, with 2-sided alpha of 5%,1082 subjects are needed for 90% power.

3.4.2. Secondary - fusion comparison (powered)

Overall number of patients diagnosed with csPCa will be compared between MRI/US fusion Arm and MRI/MicroUS Arm with a non-inferiority threshold of 10%. Assuming a csPCa detection rate of 42% in the MRI/US fusion Arm and 44% in the MRI/MicroUS Arm, with a 2-sided alpha of 5%, 358 subjects per group is required for 90% power.

3.4.3. Selection of non-inferiority thresholds

Non-inferiority thresholds were selected based on expert consensus taking into account clinically acceptable variations in detection rates.

3.4.4. Overall sample size and randomization

Each of the powered outcomes requires a differing number of subjects, and for the powered secondary outcome this number is split across two arms of the study. Table 6 shows the breakdown of the required subject enrollments, which are driven by the primary outcome. An equal number of men will receive biopsy on a standard MRI/US fusion system and biopsy on the ExactVu microUS system. Of the men biopsied using the microUS system, 2/3 will also receive mpMRI-guidance. This provides a sufficient sample size to assess both outcomes within the same overall cohort. These calculations include adjustment for a single interim analysis providing the opportunity to stop early for success on the primary objective.

3.4.5. Assay sensitivity

Non-inferiority trials must demonstrate that the similarity between the compared interventions is not due to both being equally ineffective. This will be done by comparing patient level csPCa rate and positive predictive value of targeted samples in the MRI/US fusion arm to the

Table 5
Combinations of biopsy strategies used in each arm of study. MicroUS targeted biopsy locations are sampled while blinded to mpMRI targeted biopsy locations in the MRI/MicroUS arm of the study, denoted with (B).

Arm	Systematic	MicroUS Targeted	mpMRI Targeted
MicroUS-Only	●	●	
MRI/MicroUS Fusion	●	● (B)	●
MRI/US Fusion	●		●

Table 6
Sample Size Calculation and Randomization Ratios. 1200 subjects will be enrolled with 3:1:2 randomization on informed consent.

Endpoints	MRI Arm	MicroUS Arm	FusionVu Arm	Total
Primary – MRI vs. MicroUS	541	541		1082
Secondary (powered) – Fusion	358	–	358	716
Final Sample Size	**600**	**200**	**400**	**1200**
Randomization Ratios	3	1	2	6

literature.

4. Discussion and limitations

The study has several potential limitations. The study defines significant disease as Grade Group >1. Some GG2 cancers are indolent, and this threshold is controversial. The choice of this threshold may impact the study results. Competing definitions of csPCa (such as those relating to tumor volume) will be applied post-hoc. Some men will have had an mpMRI prior to study enrollment, particularly in some areas where mpMRI is ordered by primary care physicians. In this case there will be a tendency to either avoid biopsy with a negative result (population bias) or review the MRI report (direct bias). Clinical guidelines recommend systematic biopsy in the event of negative mpMRI, unless other risk factors are sufficiently low. Therefore these men will be included. The operator performing the biopsy will be blinded to the MRI report and images. Post-hoc subpopulation analyses will be used to determine the extent of observer bias in these situations. Finally, since prior needle tracks are visible using microUS, complete blinding of the site of MRI/MicroUS fusions biopsies is not possible. Therefore, we have opted for a unidirectional blinding where microUS samples will be taken while blinded to the mpMRI but mpMRI samples will be taken with full knowledge of the microUS samples.

5. Conclusion

OPTIMUM will determine whether microUS alone is non-inferior to mpMRI with respect to the diagnosis of clinically significant PCa. The study will also investigate whether the “contour-less” micro-ultrasound/mpMRI fusion is an effective and more efficient alternative to MRI/US fusion biopsy. If demonstrated to be non-inferior, the adoption of the microUS technique may help reduce variability, complexity, waiting time and cost within the diagnostic pathway. It will also increase the proportion of men who can benefit from an imaging-first diagnostic strategy.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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