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The CADMUS trial – Multi-parametric Ultrasound targeted biopsies compared to Multi-parametric MRI targeted biopsies in the diagnosis of clinically significant prostate cancer

Alistair Grey², Rebecca Scott², Susan Charman⁵, Jan van der Meulen⁵, Peter Frinking⁶, Peter Acher⁷, Sidath Liyanage⁸, Sanjeev Madaan⁹, Gabriel Constantinescu¹⁰, Bina Shah¹¹, Chris Brew Graves¹¹, Alex Freeman³, Charles Jameson³, Navin Ramachandran⁴, Mark Emberton², Manit Arya²,¹², Hashim U. Ahmed¹,²

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Abstract

Objective: To compare the proportion of clinically significant prostate cancers (PCa) found in lesions detected by multiparametric MRI (mpMRI) with that found in lesions detected by multiparametric ultrasound (mpUSS), in men at risk.

Patients and Methods: CADMUS (Cancer Detection by Multiparametric Ultrasound of the prostate) is a prospective, multi-centre paired cohort diagnostic utility study with built-in randomisation of order of biopsies. The trial is registered ISRCTN38541912. All patients will undergo the index test under evaluation (mpUSS +/- biopsies), as well as the standard test (mpMRI +/- biopsies). Eligible men will be those at risk of harbouring prostate cancer usually recommended for prostate biopsy, either for the first time or as a repeat, who have not had any prior treatment for prostate cancer. Men in need of repeat biopsy will include those with prior negative results but ongoing suspicion, and those with an existing prostate cancer diagnosis but a need for accurate risk stratification. Both scans will be reported blind to the results of the other and the order in which the targeted biopsies derived from the two different imaging modalities are taken will be randomised. Comparison will be drawn between biopsy results of lesions detected by mpUSS with those lesions detected by mpMRI. Agreement over position between the two imaging modalities will be studied.

Discussion: CADMUS will provide level one evidence on the performance of mpUSS derived targeted biopsies in the identification of clinically significant prostate cancer in comparison to mpMRI targeted biopsies. Recruitment is underway and expected to complete in 2018.

Keywords: CADMUS, prostate cancer, multiparametric ultrasound, multiparametric MRI, targeted prostate biopsy, TRUS
Funding statement: Funding has been generously provided by Prostate Cancer UK and The Moulton Foundation (PG13-025) to conduct the trial. Equipment upgrades at no charge have been provided by Hitachi, BK Ultrasound and Esaote. Bracco have agreed to provide quantitative analysis of the contrast enhanced images on ultrasound free-of-charge through an academic agreement. None of the commercial entities had any input into trial design or conduct and will have no involvement in the analysis and write-up of the results. The trial is academically sponsored by University College London.
Introduction

The diagnostic pathway for prostate cancer is one that offers significant opportunities for improvement. The lack of an accurate biomarker[1] means that confirmation of disease is dependent upon a positive tissue diagnosis and the international standard remains an unguided systematic transrectal prostate biopsy[2]. Standard TRUS biopsy does not sample the prostate either systematically or reliably[3,4].

Multiparametric MRI offers a great deal in terms of potential improvements to this pathway. Recently published reports have estimated the negative predictive value of mpMRI to be 79% for prostate cancer containing any grade 4 disease with a maximum cancer core length of 4mm (UCL definition 2), and a NPV of 90-95% for dominant pattern grade 4 with any cancer core length greater than 6mm or both (UCL definition 1)[5]. Level 1 evidence has now been provided in the first report from the PROMIS trial[6] showing a sensitivity of 93% for MRI versus 48% for systematic TRUS in the detection of clinically significant disease. MRI targeted transperineal biopsies have been reported as showing equivalence to transperineal mapping biopsies but with a greatly reduced pathological burden and detection rate for clinically insignificant prostate cancer[7] as well as offering a rate of post biopsy septicaemia which approaches zero[8].

Pre biopsy MRI scanning is latterly the recommendation of some guidelines[9] but its status as a second tier investigation, suggested only for men with a previous negative prostate biopsy, is likely a reflection of its significant disadvantages in cost and availability. MRI scans for suspected prostate cancer can cost £350-400, double the cost of mpUSS, in the UK system and many multiples of that elsewhere with US estimates of between USD1,000-3,000. Some of the published data relies upon 3 Tesla machines, largely unavailable outside of specialist units, and that require lengthy and cost intensive sequences. A small but significant number of patients are unsuited to MRI because of metal prostheses or claustrophobia.

Ultrasound has long been employed to guide prostate biopsies and is a technique familiar to most urologists. More recent developments in the technology include elastography where tissue response to compression, either by the operator or by use of a focussed ultrasound pulse in the shear wave variant, is displayed as a coloured overlay for the B-mode imaging. The increased tissue density of malignancy, a phenomenon widely accepted in clinical
examination, has been related in the lab to increased cell density and differing collagen
distribution.[10,11] Contrast enhanced ultrasound is another form of ultrasound whereby
injection of an agent such as sulphur hexafluoride microbubbles can highlight areas of
increased vascularity. Software for the quantitative interpretation of the resultant images is in
development. Substantial trials of these technologies remain scarce but encouraging results
have emerged from some recent, smaller series[12]. It seems that the combination of these
various parameters of ultrasound (B-mode, power Doppler, elastography and contrast-
enhanced) in a similar fashion to the way in which mpMRI incorporated T2-weighted,
diffusion and contrast enhancement to improve accuracy of cancer detection, might be the
key[13].

**Trial information**

CADMUS is a prospective, multi centre paired cohort study assessing diagnostic utility. It will
include independent blind reporting of each scanning technique and randomisation of biopsy
order. The UCL Surgical and Interventional Trials Unit is responsible for the maintenance of
good clinical practice within the trial. CADMUS was granted ethics committee approval by the
London (Brent) Health Research Authority Ref 15/LO/1331 and is registered with the ISRCTN
(ISRCTN38541912).
Figure 1. Doppler (fine flow CFI) showing suspicious signal in left peripheral zone (circled). Subsequent biopsies confirmed Gl 3+4 7mm in this area.

Study Objectives

Primary

To determine the overall agreement in identifying lesions to biopsy between multi-parametric ultrasound and multi-parametric MRI in men who are at risk and normally recommended for a prostate biopsy; to then compare the overall agreement in the proportions of men diagnosed with clinically significant prostate cancer on biopsy.

Clinically significant prostate cancer for the purpose of the primary objective will be defined by UCL/Ahmed definition 1 (Gleason ≥4+3 and/or maximum cancer core length ≥6mm).
Secondary

To compare the overall agreement in proportions of men diagnosed with other thresholds of clinically significant prostate cancer on biopsy, namely

- UCL/Ahmed definition 2: Gleason $\geq 3+4$ and/or maximum cancer core length $\geq 4$mm
- Gleason $\geq 3+4$ and/or MCCL $\geq 6$mm
- Any length of Gleason $\geq 3+4$
- Any length of Gleason $\geq 4+3$

To determine the detection of clinically significant cancer (using all of the pre-specified definitions based on histology) by using the combination of both mpUSS and mpMRI techniques versus either modality alone

To determine whether the order in which the targeted biopsies are carried out, either to the same target (present on both scans) or different targets impacts on detection of clinically significant cancer (using all of the pre-specified definitions based on histology)

To compare, in those men who go on to radical prostatectomy, the mpMRI, mpUSS and histology from targeted biopsy with the whole mount specimen obtained at surgery.

To determine rates of adverse events, resource utilization and impact of each test on health-related quality-of-life using the EQ-5D-5L questionnaire.

To create an inception cohort of men, consented for long-term follow-up and linkage, providing the potential for further translational and clinical studies.

Study Population

The study participants will be drawn from those men at risk referred to one of the study centres who are normally recommended to need a prostate biopsy, either as new presentations with an elevated PSA or who have previously undergone prostate biopsy with either a positive or negative result but require more accurate risk stratification. Table 1 shows inclusion and exclusion criteria.
Table 1. Eligibility criteria for the CADMUS trial.

**Inclusion Criteria**

<p>| | |</p>
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<thead>
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<tr>
<td>1</td>
<td>A potential need for prostate biopsy indicated by raised PSA or other clinical parameter, the final decision over which will be taken after imaging.</td>
</tr>
<tr>
<td>2</td>
<td>PSA $\leq 20$ng/ml measured within 6 months of screening visit</td>
</tr>
<tr>
<td>3</td>
<td>An understanding of the English language sufficient to understand written and verbal information about the trial and consent process</td>
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<tr>
<td>4</td>
<td>Estimated life expectancy of 5 years or more</td>
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<tr>
<td>5</td>
<td>Signed informed consent</td>
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**Exclusion Criteria**

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<tbody>
<tr>
<td>1</td>
<td>Any contraindication to the ultrasound contrast agent including right to left shunt, pulmonary hypertension and uncontrolled hypertension. Also patients with an acute coronary syndrome within the last 6 months or ischaemic heart disease that’s not well controlled by medication.</td>
</tr>
<tr>
<td>2</td>
<td>Any form of hormone manipulation or androgen deprivation therapy (except 5-alpha reductase inhibitors) within 6 months of screening visit</td>
</tr>
<tr>
<td>3</td>
<td>Irreversible coagulopathy predisposing to bleeding</td>
</tr>
<tr>
<td>4</td>
<td>Inability to undergo transrectal ultrasonography</td>
</tr>
<tr>
<td>5</td>
<td>Prostate volume, measured at the time of mp-USS if previously unknown, of $&gt;60$cc</td>
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</table>
6. Previous radiation therapy to the prostate

7. Previous HIFU, cryosurgery, thermal therapy, irreversible electroporation, photodynamic, photothermal therapy, microwave or injectable toxin therapy to the prostate.

8. Transurethral resection or vaporization of the prostate for benign prostatic hyperplasia using any energy modality within 6 months of screening visit

9. Nodal or metastatic prostate cancer on any form of imaging at any time-point

10. Not fit for general anaesthetic

11. Unable to give informed consent

This is a heterogenous group of men which aims to impart external validity to this study of diagnostic utility by better reflecting clinical practice than a narrower population. An upper prostate volume threshold of 60cc was chosen to maintain ultrasound image quality in the anterior gland in b-mode as well as to avoid a drop off in the utility of elastography anticipated in larger prostates.

Diagnostic imaging

All men recruited to CADMUS will receive both mpMRI and mpUSS scans. Suspicious lesions on either imaging type will be subjected to targeted biopsy.
Multiparametric MRI

Pre biopsy MRI is standard of care at the CADMUS study sites and comprises high resolution T2, diffusion weighted imaging (DWI) and gadolinium dynamic contrast enhanced sequences compliant with European Society of Uro-Radiology[14] and the British Society of Uro-Radiology[15]. DWI includes the generation of apparent diffusion coefficient (ADC) maps as well as images with a high b value of >1000. A variety of 1.5 and 3 Tesla machines are in use across the study sites, again allowing the trial population to reflect wider clinical practice. All MRIs will be reported by experienced Uro-Radiologists who are compliant with the standards laid down by the British Society of Uro-Radiology (BSUR). Lesions identified with a radiological score of 3, 4 or 5 would normally be subjected to targeted biopsy. Scores for both mpMRI and mpUSS reporting will be based on a Likert scale from 1 to 5, with 1 signifying a high likelihood of benign tissue and 5 a high likelihood of malignancy.

Multiparametric Ultrasound

The multiparametric ultrasound scan used in CADMUS has been developed to allow capture and image analysis that is in some respects analogous to that achieved with mp-MRI. Trial participants will first have prostate volume estimation from linear dimensions and those calculated at greater than 60cc, if the volume was previously unknown, will be excluded. The prostate is then examined using the 4 principal scanning modalities sequentially. All scans are recorded then exported as DICOM (mpeg) files for detailed later analysis and attention is paid to the slow capture of images along anatomical axes through the whole length of the prostate. This allows for frame-by-frame analysis in a manner analogous the slices produced by MRI and the side-by-side comparison of images produced by the various ultrasound technologies at the same anatomical position.

B-mode images are captured in both oblique axial and saggital planes and the other ultrasound modes predominantly in the axial plane to avoid excessive scanning times. Both colour and high frequency or fine flow Doppler images are captured separately.

Real time elastography is employed to gather information about tissue response to slight compression by the probe with stiffer tissue displayed in blue and less stiff in red (Figure 2). Scanning is carried out stepwise through the prostate in an oblique axial plane with pauses.
every few mm to allow the elastogram to stabilise.

Figure 2. Decreased tissue elasticity in the right posteriolateral prostate which at biopsy revealed 3mm GI 3+4

Finally contrast enhanced ultrasound is employed in two stages. First, the area of the prostate so far considered most suspicious is brought into view in the axial plane and after video recording begins a bolus of SonoVue® microbubble contrast is injected through an intravenous cannula in response to a countdown triggered on screen (figure 3). Once the prostate is fully perfused with contrast and an examination time of more than 45 seconds is reached the first video is saved. A second recording is made using flashes of high powered ultrasound energy to burst the bubbles in the immediate field, allowing for reperfusion with the image focused on a new part of the prostate. In this way, some contrast perfusion information can be obtained for the whole prostate despite the limitation of our TRUS probes to the capture of 2 dimensional images. The authors consider these reperfusion sequences to
be less valuable than the first for the identification of early contrast enhancement as the wash in phase is less pronounced.

Figure 3. A large area of pronounced early contrast enhancement in the left anterior prostate. Biopsy revealed 15mm of Gl 4+3 adenocarcinoma.

Quantitative analysis of the CEUS videos is carried out remotely after the scan. This relies on a recently developed technique by Bracco Suisse SA (Geneva, Switzerland) which is based on a statistical analysis of parametric maps of Wash-in Rate (WiR), a perfusion parameter reflecting the rate of contrast enhancement. The parametric maps are generated by analysing time-intensity curves (TIC) representing the echo-power as a function of time, on a pixel-by-pixel basis.

The characteristics of each pixel on the parametric map are determined by an analysis of the WiR histograms from it and immediately surrounding pixels, incorporating statistical parameters such as mode and standard deviation (SD). The resulting map uses colour coding to display the probability of PCa occurrence. The classification criteria are derived from
analysis of 42 regions of interest containing PCa on whole mount prostatectomy histopathology[16].

Lesions identified on mpUSS will have a Likert type score generated for each of the above ultrasound technologies and an overall score for each lesion. As with mpMRI, scores of 3 or more will be targeted at biopsy. The reporting proforma allows lesions to be localised to one of 12 sectors produced by dividing the prostate into apical, midgland and basal segments and then each of these into left/right and anterior/posterior quadrants.

**Trial Biopsy**

The cognitively targeted transperineal prostate biopsy employed by the CADMUS trial is an adaption of the standard of care biopsy at the authors’ institutions. Performed in an operating theatre or procedure room under local anaesthetic with or without intravenous sedation, or general anaesthetic, the patient is placed in the lithotomy position and 3 targeted biopsies are taken using a brachytherapy template grid. Block randomisation is be used to determine whether mpUSS or mpMRI derived targets will be sampled first. This step aims to avoid any skewing of the results that might be caused by a fixed biopsy order, where specimens taken later in the procedure may be subject to increased targeting error caused by swelling or haemorrhage stemming from the earlier biopsies. This phenomenon, if present, will also be identifiable in our results.

**Statistical considerations**

Power calculations for CADMUS were generated using the following underlying assumptions. The rate of identification of men with a lesion to biopsy by mpMRI, based on data from the PICTURE16 study was 80%. A prevalence of 30% of men amongst the biopsy population with clinically significant disease (UCL/Ahmed definition 1) was considered likely. Assuming slightly lower rate of identification of lesions for biopsy by mpUSS (75%) and that 90% of those cases have the same lesion identified by mpMRI then one should expect to achieve a confidence level of 95% with 450 men recruited and 275 of those proceeding as
far as biopsy. Higher figures for cancer detection or agreement between the two imaging techniques will require a smaller number of recruits to achieve the same degree of confidence.

The primary outcome for the trial will be calculated by comparing proportions of men diagnosed with clinically significant prostate cancer by mpUSS or mpMRI using McNemar’s test. A full statistical analysis plan will be developed with the results of the pilot in hand.

**Outcome measures**

**Table 2. Outcome measures for the CADMUS trial**

<table>
<thead>
<tr>
<th>Primary</th>
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<tbody>
<tr>
<td>The proportion of men with a lesion detected using each diagnostic strategy and the proportion of men subsequently diagnosed with clinically significant prostate cancer as defined histologically as UCL/Ahmed definition 1 (Gleason 4+3 or greater and/or maximum cancer core length of 6mm or greater).</td>
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<table>
<thead>
<tr>
<th>Secondary</th>
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<tbody>
<tr>
<td>The proportion of men diagnosed with clinically significant prostate cancer by each diagnostic strategy as defined histologically using other thresholds for clinical significance, namely;</td>
</tr>
<tr>
<td>- UCL/Ahmed definition 2: Gleason ≥3+4 and/or maximum cancer core length ≥4mm</td>
</tr>
<tr>
<td>- Gleason ≥3+4 and/or MCCL ≥6mm</td>
</tr>
<tr>
<td>- Any length of Gleason ≥3+4</td>
</tr>
<tr>
<td>- Any length of Gleason ≥4+3</td>
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</table>

The proportion of men diagnosed with clinically significant cancer (using all of the prespecified definitions based on histology) by using the combination of these two imaging
techniques versus either modality alone.

<table>
<thead>
<tr>
<th>The proportion of men diagnosed with clinically significant prostate cancer (using all of the pre-specified definitions based on histology) when</th>
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<tbody>
<tr>
<td>- mp-USS targeted biopsies are carried out first compared to being carried out second</td>
</tr>
<tr>
<td>- mp-MRI targeted biopsies are carried out first compared to being carried out second.</td>
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</table>

| The proportion of men from the cohort who progress to radical prostatectomy, and have whole mount histology that matches the results of the mp-USS, mp-MRI and targeted biopsy. |

| Proportions of adverse events and health-related quality-of-life measures on the EQ-5D-5L questionnaire. |

| A cohort of men, consented for long-term follow-up and linkage, providing the potential for further translational and clinical studies. |

Table 2. Outcome measures for the CADMUS trial.

Trial outcomes for CADMUS may be seen in table 2 and tally with the objectives outlined. The question of clinical significance in prostate cancer remains one of controversy and is worthy of consideration. The contrast between reports from post mortem studies that some 50% of men will have detectable prostate cancer over the age of 50[17] and the population mortality from the disease of 3[18] makes it apparent that much of diagnosed prostate cancer may not threaten life. Level one evidence from the Prostate Cancer Intervention Versus Observation Trial (PIVOT)[19] demonstrated that men with lower risk prostate cancer did not benefit from treatment and the more recent ProtecT[20] trial, in which about three-quarters of men had low risk disease, showed no significant difference in mortality.
between men with prostate cancer randomised to either surgery, radiotherapy or active monitoring. The existence of at least some prostate cancer that is not clinically significant is now widely accepted.

Relative consensus on the need for a definition of clinical significance is of course no guarantee of agreement on what it should be. The debate is further coloured by the apparent improvement in the performance of imaging or targeted biopsy studies that stems from the use of a higher threshold of grade and stage for significance, versus the boost that a lower threshold will add to the apparent performance of systematic biopsy.

For CADMUS the investigators aim to bypass much of this controversy by reporting at many thresholds including the detection of any prostate cancer and definitions independent either of Gleason grade or tumour volume (core length). A definition was needed for the primary outcome and UCL definition 1 (presence of any primary pattern 4 disease and/or maximum cancer core length of ≥6mm) was chosen. This has its basis in the proposal that cancers of 0.5cm$^3$ are likely to be significant[21] supported by more recent data from the European Prostate Cancer Screening trial[22]. This volume of tumour and a core length at biopsy of 6mm have been shown to correlate by computer modelling studies performed at this institution[23] and is the same as that used in the recently reported PROMIS and PICTURE trials[6,24].
Trial flow

CADMUS trial flow is shown in figure 4

1. Men with a potential need for prostate biopsy indicated by raised PSA or other clinical parameter.
2. Invitation to take part and information sheet sent to patient.
3. Telephone call by research team after 24hrs post invitation to discuss study.

**Visit 1 (During standard care visit day)**
- Screening & Consent
- If ICF signed: multi-parametric ultrasound scan
- Adverse events, EQ-5D-5L

**Visit 2 (Standard care)**
- Multi-parametric MRI scan (if not done within 6 months of consent)
- Adverse events, EQ-5D-5L

**Visit 3 (Standard care)**
- Targeted prostate biopsies under LA with optional sedation if those with suspicious imaging
- Adverse events, EQ-5D-5L

**Visit 4 (During standard care visit day)**
- Adverse events, EQ-5D-5L (results given by clinical team)
Discussion

CADMUS uses a multicentre paired cohort design with all patients undergoing both scans and the reporters of each scan blind to the results of the other, eliminating much potential bias. It will represent diagnostic level one evidence. The patient is also blind to the imaging origin of the lesion that triggered the biopsy procedure minimising work up bias and the potential attrition of recruits who had a negative MRI scan but a biopsy indicated on the grounds of the trial (mpUSS) scan alone.

The trial design has some potential limitations, the first of which is the comparison of only targeted biopsies between imaging modalities, rather than the employment of a template mapping biopsy as a reference standard. This has the disadvantage of precluding the analysis of true and false negatives generated by the scans which would be possible had patients undergone both targeted and systematic biopsies. CADMUS is designed as a clinical utility study to explore the potential for mpUSS to perform some or all of the role that mpMRI fills at this and other institutions. The authors’ unit having transitioned already to a policy of targeted only biopsies for most patients (cases with doubt over imaging or diagnosis will still undergo systematic biopsy), it was judged that the increase in pathological burden, operating time and biopsy complications that would come with a return to universal systematic biopsy would be unreasonable when considering negative predictive values of 90-95%. Added to the case for a targeted only study was evidence showing equivalence in diagnostic performance for the two techniques[7]

Another potential criticism might be directed at the use of cognitive (visually estimated) registration of imaging derived targets for biopsy, rather than the use of an image fusion system. The choice of cognitive registration, standard practice among biopsy surgeons at our units, was driven by the impracticalities of fusing mpUSS derived targets with the same precision as those from mpMRI and supported by reports on the performance of targeted only biopsy using cognitive registration[25]. The lack of a system to accurately fuse diagnostic mpUSS images with live ultrasound during biopsy had one further ramification, the removal of the planned blinding of the biopsy surgeon to the provenance of the lesion
to be biopsied. This would be impossible as cognitive registration relies upon review of the relevant images at the time of biopsy.

Conclusions

CADMUS is a multicentre diagnostic paired cohort study that will provide the first level one evidence on the clinical utility of multiparametric ultrasound in prostate cancer diagnosis, specifically in the context of targeted prostate biopsy, in comparison to mpMRI targeted biopsies. If mpUSS is demonstrated to have value in the diagnostic pathway it may have a role to play in spreading the use of imaging in the detection of prostate cancer and offsetting some of the significant economic barriers to the universal provision of a pathway based solely on MRI.

CADMUS is open to recruitment at centres in the UK and expected to complete recruitment in early 2018.
References


