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PROMIS—ProstateMR imagingstudy: A paired validating cohort study evaluating the roleof multi-parametric MRI inmen with clinicalsuspicion of prostate cancer ☆

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abstract

Background:Transrectalultrasound-guidedprostate biopsies are proneto detection errors. Multi-parametricMRI (MP-MRI) may improve thediagnosticpathway.
Methods:PROMIS isa prospective validating paired-cohort study that meets criteria for level1 evidence indiagnostic test evaluation.PROMIS will investigate whether multi-parametric (MP)-MRI candiscriminate betweenmen with and without clinically-significantprostate cancer who are atrisk prior to first biopsy. Upto 714 men willhave MP-MRI (index), 10 –12 core TRUS-biopsy (standard) and 5 mmtransperineal template mapping(TPM) biopsies (reference).The conduct and reporting of each test will beblindedto the others.
Results: PROMIS will measure and compare sensitivity, specificity, and positive and negative predictivevalues of both MP-MRI and TRUS-biopsy against TPM biopsies. The MP-MRIresults will beused to determinetheproportion of men who could safely avoid biopsy without compromising detection of clinically-significantcancers. For the primary outcome,significant cancer on TPM is definedas Gleason grade ≥ 4 + 3 and/or maximum cancer core length of ≥ 6mm. PROMIS will also assessinter-observer variability among radiologists amongother secondary outcomes. Cost-effectiveness of MP-MRI prior to biopsy will also beevaluated.
Conclusions: PROMIS will determinewhether MP-MRI of the prostateprior to first biopsy improves thedetection accuracy of clinically-significant cancer.

1.Background & introduction

Pr os tate c ancer is the most c ommon male cancer , witha d ou b li ng in incide nce over the la st 15 ye ars in the UK. Curr ently over 40,000 ne w cases are di agnosed ev ery ye ar in the UK [1,2] and 223,307 new cases in th e USA [3].Many prost ate cancer s cur rently detected are cl inicall y insig nificant and do not have any cli nical impact on the individual duri ng his remaining life if left untre ated [4,5].Thisassertionhasreceivedconsider-able suppo rt from a numbe r of l arge randomised controll ed

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Table2
Patientinclusionandexclusioncriteria.

Patientinclusioncriteria
Menatleast18yearsoroveratriskofprostatecancerwhohavebeen advisedtohaveaprostatebiopsy
SerumPSA ≤ 15ng/mlwithintheprevious3months
Suspectedstage ≤ T2onrectalexamination(organcon fi ned)
Fitforgeneral/spinalanaesthesia
Fittoundergoallprotocolproceduresincludingatransrectalultrasound
Signedinformedconsent
Patientexclusioncriteria
Treatedusing5-alpha-reductaseinhibitorsattimeofregistrationor duringtheprior6months
Previoushistoryofprostatebiopsy,prostatesurgeryortreatmentfor prostatecancer(interventionsforbenignprostatichyperplasia/ bladderout fl owobstructionisacceptable)
Evidenceofaurinarytractinfectionorhistoryofacuteprostatitiswithin thelast3months
ContraindicationtoMRI(e.g.,claustrophobia,pacemaker,estimated GFR≤ 50)
Anyothermedicalconditionprecludingproceduresdescribedinthe protocol
Previoushistoryofhipreplacementsurgery,metallichipreplacementor extensivepelvicorthopaedicmetalwork.

Inordertomaintainthequalityof scansandensure uniformityacrossallcentres,optimizationoftheconductof scanswillbeappliedtoallcentresthrougharobustquality control process. This will beundertakenbyaseparate independentcommercialsub-contractor(IxicoLtd,UK)select-edthroughanopencompetitioncompliantwiththeEuropean Unionguidelinesonthetender process. Scansdeemedof insufficientqualitybythecommercialpartnerorthereporting radiologistwillberepeated.

4.3.1.1. Standardizationof MRI reporting. Inorder toavoid variationinmethodofinterpretation,astandardisedoperating procedureforMP-MRIreportinghasbeenadoptedinlinewith therecommendationsoftheEuropeanconsensusmeetingand theEuropeanSocietyofUro-RadiologyprostateMRIguidelines [68]. Allradiologistswillundergotrainingandstandardisation ofreportingbytheleadradiologistcentrallypriortoreporting withinthetrial.Theactualreportingwillrequireallradiologists beingprovidedwiththesameclinical detailsincludingPSA, DREfindingsandanyotherriskfactors.Imageswillbereported insequencesothatT2-weightedimageswillbereportedfirst, T2-weightedanddiffusion-weightedtogetherandthenathird report issuedforT2-weightedwithdiffusionanddynamic contrastenhancedscanstogether. Aseparatereportwill be producedfor eachcombinationof sequences inorder to secondarilyinvestigatewhetherbothdiffusion-weightedand DCEarebothrequired.AsDCErequirescontrastagent(withits needforintravenousaccess,medicalsupervisionandcontrast-relatedrisks)andanadditional10 −15minofscantimethereis considerablemerit indeterminingwhether thisadditional resourceandcostisnecessary(Fig.5).

A1to5Likertscoringsystem[67,68,71]will beusedto indicateprobabilityofcancer(1 —highlylikelytobebenign, 2—likelytobebenign,3 —equivocal,4 —likelytobemalignant and5 —highlylikelytobemalignant)withtheprostatedivided into12regionsofinterest(ROI)andeachregionscoredfrom1 to5.Further,eachlesionwillbeidentifiedandscoredonthe1 to5scaleseparatelyandthelongestaxial diameter, lesion volume,ADCvalueandcontrastenhancementcurvetypewill berecorded[72 −75]. Anoverall 1to5scoreof thewhole prostatewill berecordedfor eachlevel of cancer burden thattheradiologistthinksmightbepresent. Thiswillbe ‘all cancer’, ‘definition1clinicallysignificantcancer ’ and ‘definition 2clinicallysignificantcancer ’ (seebelow).

Withrespecttotheprimaryoutcome, anoverallscoreof 3ormorewill beusedtoindicatethepossiblepresenceof clinicallysignificantcancer(i.e.,apositiveMP-MRIscore).This reflectsthelevelatwhichfurthertests(e.g.,biopsy)wouldbe consideredifMP-MRIweretobeintroducedintothediagnostic pathwayinthefuture.

4.3.1.2.Assessingforinter-observervariabilityandqualitycontrol andassessment. Inordertoestablishif adiagnostictest can improveorchangethediagnosticpathwayinprostatecancer, it mustbeassessedforintra-andinter-observervariability.Thus,a subsetofscanswillbereportedbyanotherexperiencedcentral radiologist. Asubsetofscanswillalsobereportedbythesame reporteragainatadifferenttime-pointtoassessintra-observer variability.

InordertomakesurethattheresultoftheMP-MRIdoesnot influencetheconductofthebiopsy,theresultsoftheMP-MRI willnotberevealedtoeitherthemenhavingthebiopsiesor tothecliniciansundertakingthebiopsiesuntilaftertheresults oftheTRUS-biopsyandTPMbiopsiesareavailable(withthe exceptions for un-blindinggivenbelow). This blindingis necessarytopreventtheresultsof theMP-MRI influencing whethermenarebiopsiedandiftheyare,howthebiopsiesare conducted.

Forsafetypurposes, theresultsoftheMP-MRIcanbeun-blindedbytheradiologistiftheMP-MRIrevealsanenlarged

Table3
StandardoperatingprocedureforMRIparametersforallcentrestofollow.

	TR	TE	Flipangle/ degrees	Plane	Slicethickness (gap)	Matrixsize	Fieldof view/mm	Timeforscan
T2TSE	5170	92	180	Axial,coronal, sagittal	3mm(10%gap)	256×256	180×180	3min54s(ax)
VIBEatmultiple fl ipanglesfor T1calculation(optional)								Willbeincludedinthe Phoenix fi le
VIBEfatsat	5.61	2.52	15	Axial	3mm	192×192	260×260	Continueforatleast5min 30saftercontrast
Diffusion(bvalues:0,150, 500,1000)	2200	Min(b98)		Axial	5mm	172×172	260×260	5min44s(16averages)
Diffusion(b=1400)	2200	Min(b98)		Axial	5mm	172×172	320×320	3min39s(32averages)

Table4
Combinedprostatebiopsyproceduresideeffectpro fileasstatedinthepatientinformationsheetandconsentdocumentation.

Sideeffect	Procedure	
	TRUSalone(standardcare)	Combinedbiopsy:TPM+TRUS(inthePROMISstudy)
Pain/discomfort	Almostallmenexperiencetemporarydiscomfort intherectum	Almostallmenexperiencetemporarydiscomfortin therectum
Burningwhenpassingurine	Almostallmen	Almostallmen
Bloodyurine	1in2men(self-resolving,2 −3days)	Almostallmen(self-resolving,2 −3days)
Bloodysperm	3in10men(2 −3monthstoresolve)	Almostallmen(lastingupto3months)
Poorerections	3in10men(self-resolvingafter6 −8weeks).Rarely, tabletsmaybeneededtohelptheerectionsimprove.	Almostallmen(self-resolvingafter6 −8weeks).Rarely, tabletsmaybeneededtohelptheerectionsimprove.
Infectionofskinorurine	1−8in100men	1−8in100men
Infectionofskinorurinerequiringadmission andintravenousantibiotics	Between1 −4in100men	Between1 −4in100men
Dif fi cultypassingurine	1in100men	1−3in20men
Bruisingofskin	None	Almostallmen
Bruisingspreadtoscrotum	None	Between1in20to1in10men

4.9.5.MP-MRIversusTRUS-biopsy

WehaveassumedthatTRUS-biopsydetects48%ofclinically significantprostatecancer[28,90]andMP-MRIwilldetectat least70%(conservativeestimates). UsingMcNemar'stestfor pairedbinaryobservations[91], inordertoshowanabsolute increaseintheproportionof clinicallysignificant cancers detectedofatleast22%(from48%to70%)withapowerof 90%anda2-sidedalphaof5%,atotalof107casesarerequired. Thisisequivalenttoatotalstudypopulationof714menfor UCLdefinitiononeand428menforUCLdefinitiontwo.

4.9.6.Costeffectivenessanalyses

Amodel will bepopulatedfromthestudyaswell asa reviewof secondarysourcesof epidemiological, clinical and economicevidencetogetherwithappropriatelyelicitedexpert opinion[92].Theuseofprobabilisticsensitivityanalysis,value ofinformationmethodsandscenarioanalysis[93]willquantify theuncertaintyassociatedwithidentifyingthemost cost-effectivediagnosticstrategy, thecostsofthatuncertainty(in healthandresourceterms)andthekeyuncertaintiestoresolve withfurtherresearch.Thiswillinformtheinputsintothemain economicmodel. Thiscost-effectivenessmodel will seekto quantifythelong-termimplicationofchangestothediagnostic classificationofprostatecancerthatresultfromadoptionof alternativediagnosticpathwayswithintheNHS. Theimplica-tionswill relatetothehealtheffects(intermsof quality adjustedlifeexpectancy)andNHScostsofagivendiagnostic pathwayplacingpatientsintoeachofthefourgroups:1. MRI testpositive,clinicallysignificantdisease;2.MRItestnegative, clinicallysignificant disease; 3. MRI test positive, clinically insignificant disease; and4. MRI test negative, clinically insignificantdisease.Byalteringthelikelihoodofamanfalling intoanyoneof thesegroups, thevalueof MP-MRI will be assessedbythechangesinaverageoutcomesexperiencedby menandthecoststhatresult.Themodelwillalsoincludethe implicationsofapositiveresultintheindextestconcurrent withanegativeresult inthecurrent standardaswell as accountingforthesideeffectprofileof differentdiagnostic pathways. Structurally, themodelwillconsistofadiagnostic elementthatwill model theprobabilitiesof agivenpatient fallingintoeachof thediagnostic groups above, anda prognosticelementthatwillestimatethelongtermimplica-tions for healthandcosts. Thespecific details of model structurewill beinformedbyareviewof existingprostate cancermodelsincludingthoserelatingtoscreening,diagnosis andtreatment. Ingeneraltermsthemodellingwilladhereto themethodsadvocatedtoinformguidancebytheUKNational InstituteforHealthandClinicalExcellence[94].

Wewill alsocollect dataonthecostsof testsandthe managementofadverseevents,andthehealth-relatedquality oflife(HRQL)implicationsofanyadverseeventsexperienced withtests. Thelatter will beassessedusingtheEQ-5D

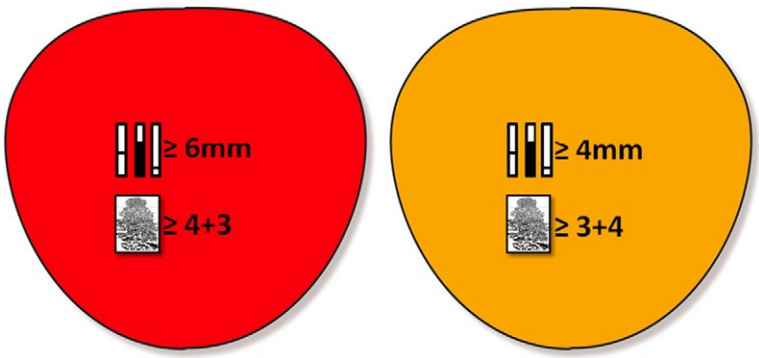

Fig.7.DefinitionsofclinicalsignificanceonTTPM-biopsy.RedsignifiesUCLdefinition1againstwhichtheprimaryoutcomewillbevalidated. YellowsignifiesUCL definition2andisasecondaryoutcome.
FromAhmedHUetal.,JUrol,2011;186(2):458-64.

Table5
PrimaryandsecondaryoutcomesforthePROMIStrial.

Primaryoutcomes:
Proportionofmenwhocouldsafelyavoidabiopsyasdeterminedby specificityandnegativepredictivevalues(NPV),basedonde finition oneofclinicalsigni ficanceasassessedbyTPM.
Proportionofmencorrectlyidenti fiedbyMP-MRItohaveclinically signi ficantprostatecancerasdeterminedbysensitivityandpositive predictivevalue,basedonde finitiononeofclinicalsigni ficanceas assessedbyTPM.
Secondaryoutcomes:
Theproportionofmenwhocouldsafelyavoidbiopsy,giventhattheydo nothavede finitiontwoprostatecancerasassessedbyTPM.
TheproportionofmentestingpositiveonMP-MRIoutofthosewith DEFINITIONTWOprostatecancerassessedbyTPM.
PerformancecharacteristicsofTRUSversusTPM(sensitivity,speci ficity, NPV,PPV)accordingtode finitionsoneandtwo
Evaluationoftheoptimalcombinationof MP-MRIfunctionalparameters (T2,DW,DCE)todetectorrule-outclinicallysigni ficantprostate cancer.
Intra-observervariabilityinthereportingofMP-MRI.
Inter-observervariabilityinthereportingofMP-MRI.
Evaluationofsocio-demographic,clinical,imagingandradiological variablesinrelationtothedetectionofclinicallysigni ficantprostate cancer.
Patients'health-relatedqualityoflifeusingtheEQ-5Dinstrument.
Resourceuseandcostsforfurthereconomicevaluation(seesectionon Cost-effectivenessanalyses).

instrumentaspartofthemainclinicalstudy. Thisisawidely usedgenericmeasureofHRQLwhichcanbeusedtoderive qualityadjustedlifeyears(QALYs)[95]. Ultimately, thiswork willprovideanassessmentoftheimplicationsofanychange that theuseof MP-MRI hasonunder-detectionandover-detection. Theseimplicationswill beintermsof expected qualityadjustedsurvivaldurationandlong-termhealthservice costs. ThiswillallowthevalueformoneyofMP-MRIinthis contexttobeassessedusingthesamemetricsemployedto evaluatetherapeutictechnologiesbyorganisationssuchas NICE.

4.10.Ethicalconsiderations

Thestudyabidesbytheprinciplesof theDeclarationof HelsinkiandtheUKResearchGovernanceFrameworkversion 2andreceivedUKResearchEthicsCommitteeapproval on 16thMarch2011bytheNRESCommitteeLondon—Hampstead. PROMISispublishedonclinicaltrials.gov[96]

5.Discussionandlimitations

ThePROMISprotocol hassomepotential limitations. First, thethresholdswehaveusedforclinicallysignificantdiseaseare opentodebateasnouniversallyacceptedde finitionexists. Itis widelyacceptedthatsomeprostatecancerlesionsareclinically significant andothersarenot [97,99]. Volumethresholdsof 0.5ml and1.3ml forlowgradeGleason6lesionshavebeen supportedbyrecentdatafromtheEuropeanProstateCancer Screeningtrial[98].Thereareevensomecallsforsuchlesionsto bere-designatedassomethingotherthanmalignant, suchis theirindolentbehaviour[97,99,100]. However, werecognize that thereis legitimateprofessional disagreement onwhat constitutesclinicallysignificantprostatecancer, sowedecided toreflectthisbyusingotherdiseaseburdenthresholdstodefine thetargetconditiononthereferencetestforthepurposeof validatingmpMRI.

Second, TPMbiopsiesmaynotbeasaccurateaswhole-mountprostatectomy, butanumberof studiespointtoits accuracybeingsufficientlyhightouseasareferencetestforthe specificpopulationwewill recruit. Indeed, formenwithno

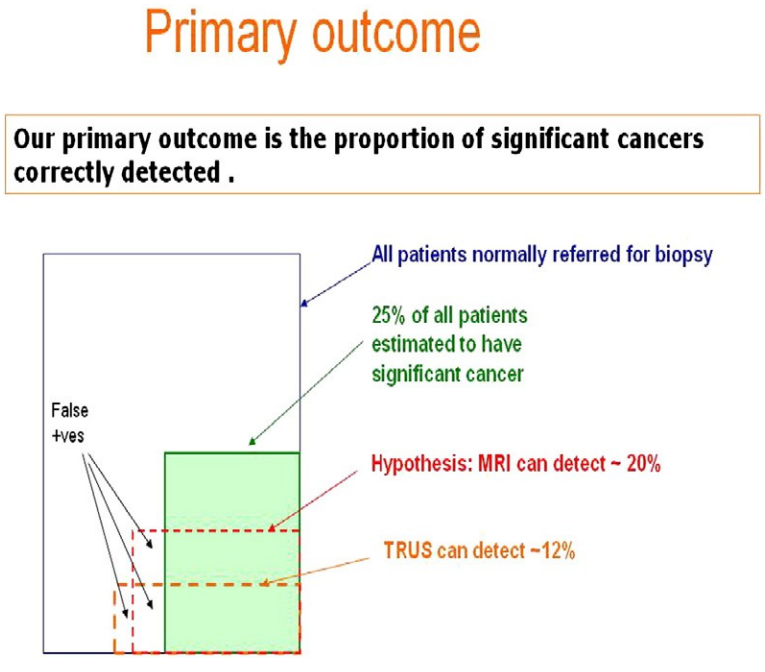

Fig.8.Illustrationsummarizingsomeoftheassumptionsmadeindeterminingsamplesizecalculationsfortheprimaryoutcome.