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Individualised non-contrast MRI-based risk estimation and shared decision-making in men with a suspicion of prostate cancer: protocol for multicentre randomised controlled trial (multi-IMPROD V.2.0)

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ABSTRACT

Introduction European Association of Urology and UK National Institute for Health and Care Excellence guidelines recommend that all men with suspicions of prostate cancer should undergo prebiopsy contrast enhanced, that is, multiparametric prostate MRI. Subsequent prostate biopsies should also be performed if MRI is positive, that is, Prostate Imaging–Reporting and Data System (PI-RADS) scores 3–5. However, several retrospective post hoc analyses have shown that this approach still leads to many unnecessary biopsy procedures. For example, 88%–96% of men with PI-RADS, three findings are still diagnosed with clinically non-significant prostate cancer or no cancer at all.

Methods and analysis This is a prospective, randomised, controlled, multicentre trial, being conducted in Finland, to demonstrate non-inferiority in clinically significant cancer detection rates among men undergoing prostate biopsies post-MRI and men undergoing prostate biopsies post-MRI only after a shared decision based on individualised risk estimation. Men without previous diagnosis of prostate cancer and with abnormal digital rectal examination findings and/or prostate-specific antigen between 2.5 ug/L and 20.0 ug/L are included. We aim to recruit 830 men who are randomised at a 1:1 ratio into control (all undergo biopsies after MRI) and intervention arms (the decision to perform biopsies is based on risk estimation and shared decision-making). The primary outcome of the study is the proportion of men with clinically significant prostate cancer (Gleason 4+3 prostate cancer or higher). We will also compare the overall biopsy rate, benign biopsy rate and the detection of non-significant prostate cancer between the two study groups.

Ethics and dissemination The study (protocol V.2.0, 4 January 2021) was approved by the Ethics Committee of the Hospital District of Southwest Finland (IORG number: 0001744, IBR number: 00002216; trial number: 99/1801/2019). Participants are required to provide written informed consent. Full reports of this study will be submitted to peer-reviewed journals, mainly urology and radiology.

Trial registration number NCT04287088; the study is registered at ClinicalTrials.gov.

Strengths and limitations of this study

- A strength of the study is the use of well-established IMPROved prostate cancer Diagnosis (IMPROD) bi-parametric MRI protocol (http://mrc.utu.fi/protocols/prostate), which is a result of long-term research on diffusion-weighted imaging, data acquisition and postprocessing of MRI images.
- Another strength is that all data will be publicly available, like data from previous IMPROD-trials (IMPROD-study, http://petiv.utu.fi/improd/, multi-IMRPOD-study, http://petiv.utu.fi/multiimprod/).
- Although study participants are recruited from several centres, the vast majority of them are Caucasian in origin and, therefore, the generalisability of the results might be limited.
- The relatively low prevalence of opportunistic screening for prostate cancer in Finland will have an impact on the baseline characteristics of the study population; therefore, the generalisability of the results to nationalities with higher levels of screening might be limited.

INTRODUCTION

The incidence of prostate cancer continues to increase worldwide, mainly as a result of population ageing, better diagnostic methods and probably due to a real increase in incidence. Although most prostate cancers are currently being diagnosed at an early stage, 30% of prostate cancers

in Finland now are metastatic at diagnosis.[1] Prostate cancer also continues to be the second leading cause of cancer deaths in men calling, for better diagnostic methods.[2]

Traditionally, the diagnosis of prostate cancer is mostly based on the result of systematic transrectal ultrasonography (TRUS)-guided biopsies.[3] Recently, several prospective trials claimed that an alternative pathway using multiparametric magnetic resonance imaging (mpMRI) or biparametric MRI (bpMRI) as a triage test reduces unnecessary biopsies, decreases the detection of clinically non-significant prostate cancer and improves the detection of clinically significant prostate cancer.[4–11] Therefore, in addition to men with previous negative prostate biopsies, European Association of Urology, American Urological Association and UK National Institute for Health and Care Excellence guidelines also recommend that all men with a suspicion of prostate cancer should undergo prebiopsy MRI. Also, subsequent prostate biopsies should be performed if MRI is deemed positive, that is, PI-RADS scores 3–5.[3]

That said, it is not clear whether the results of these trials reflect a true change in relative detection of significant and non-significant or reflect upgrading associated with MRI.[12] Moreover, several retrospective post hoc analyses have shown that this approach still leads to many unnecessary biopsy procedures. For example, 88%–96% of men with PI-RADS 3 finding are still diagnosed with clinically non-significant prostate cancer or no cancer at all.[5 7 8] In our retrospective post hoc analyses, we have shown that prostate-specific antigen (PSA) density (PSA divided by prostate volume) combined with bpMRI is useful when determining the need to perform biopsies.[13] This finding is supported by retrospective analysis both in bpMRI[10] and mpMRI[14] settings.

The decision on whether to or not perform biopsies is not just about MRI and PSA but a shared decision-making accounting for patient characteristics, such as comorbidities, life expectancy and expectations and values.[15] Unfortunately, no risk tool using prostate MRI and applying a truly individualised approach for each man has been evaluated in prospective clinical trials.[16 17] Therefore, the aim of this trial is to generate a risk calculator based on MRI and clinical variables describing an individual risk of having clinically significant prostate cancer. This risk estimation is then used as a basis for discussion of the benefits and potential harms of proceeding with the prostate biopsy.

The aim of this prospective, randomised, multicentre controlled, trial is to demonstrate non-inferiority in clinically significant cancer detection rate between men undergoing prostate biopsies post-MRI and men undergoing prostate biopsies post-MRI only after a shared decision based on risk estimation. The aim is also to compare whether there is a difference in overall biopsy rate, benign biopsy rate and the detection of non-significant prostate cancer between the two study groups.

METHODS AND ANALYSIS

Study design

This is a prospective, randomised (allocation 1:1), controlled, multicentre trial to demonstrate non-inferiority in clinically significant cancer detection rate between men undergoing prostate biopsies post-MRI and men undergoing prostate biopsies post-MRI only after a shared decision based on individualised risk estimation.

Objectives

Primary objective

A non-inferiority between significant prostate cancer detection rate in men undergoing prostate biopsies post-MRI (control arm) and men undergoing prostate biopsies post-MRI only after a shared decision based on individualised risk estimation (intervention arm).

Secondary objectives

To compare the detection rate of clinically non-significant prostate cancer, intermediate risk prostate cancer and benign biopsies between the arms.

To compare biopsy rates between the arms.

To compare biopsy-related complications between the arms.

To compare the detection rate of clinically significant prostate cancer during the 5 years of follow-up between the arms.

To study and compare anxiety related to prostate cancer between the arms.

To evaluate how biopsy rates in the experimental arm vary by predicted risk produced by the risk model.

To evaluate inter-reader variability between central and local radiologists.

Exploratory objectives

To evaluate the hypothetical results in the control group had biopsy been restricted to those meeting different biopsy criteria.

To calibrate the prediction model in the control arm.

To evaluate if biomarkers could improve the prediction model in the control group.

Outcomes

Primary outcome

The proportion of men with clinically significant prostate cancer (Gleason 4+3 (International Society of Urological pathology grade group, the GGG, 3)) prostate cancer or higher) in the control and intervention arms after primary diagnostic pathway.

Secondary outcomes

The proportion of men with clinically non-significant prostate cancer and intermediate risk prostate cancer (Gleason 3+3 (GGG 1) and Gleason 3+4 (GGG 2)) and benign biopsies in the control and intervention arms after primary diagnostic pathway

The proportion of men undergoing biopsies in the control and intervention arms

The proportion of men having biopsy-related complications in the control and intervention arms

The proportion of men with clinically significant prostate cancer (Gleason 4+3 (GGG 3), prostate cancer or higher) in the control and intervention arms during the 5 years of follow-up

Total score of Memorial Sloan Kettering Cancer Centre Anxiety questionnaire in the control and intervention arms at baseline, at 6 months and at 12 months.

The rate of biopsy in patients with low (<5%), intermediate (5%–20%) and high (≥20%) predicted risk of clinically significant prostate cancer

Kendall rank correlation coefficient between central and local reader reported PI-RADS scores.

Exploratory outcome measures

The number of biopsies and the number of clinically significant prostate cancers detected in patients with PI-RADS 3 or higher, PI-RADS 4 or higher, PI-RADS 3 or higher or PSA density higher than 0.2 ng/mL/mm^3.

Calibration of the model using both Likert and PI-RADS V.2.1 criteria.

Calibration of the model using future biomarkers aiming to improve prostate cancer diagnostics.

Sample selection

All men with clinical suspicion of prostate cancer living in the Hospital Districts of Southwest Finland, Satakunta, Keski-Suomi and Pirkanmaa are potentially eligible. The study will enrol 830 subjects allocated into two groups.

Inclusion criteria

- Age: 18 years or older.
- Language spoken: Finnish or Swedish.
- Clinical suspicion of prostate cancer, based on: serum level of PSA from 2.5 ng/mL to 20.0 ng/mL and/or abnormal digital rectal examination.
- Mental status: the subject must be able to understand the meaning of the study.
- Informed consent: the subject must sign the appropriate Ethics Committee (EC) approved informed consent documents in the presence of the designated staff

Exclusion criteria

- Previous diagnosis of prostate cancer.
- Any contraindications for MRI.
- Any other conditions that might compromise subject's safety, based on the clinical judgement of the responsible urologist.
- Unilateral or bilateral hip prosthesis.

Study procedures

The study flow is presented in figure 1.

Pre-screening (visit 0): after a referral to participating centres, all subjects are evaluated for inclusion and

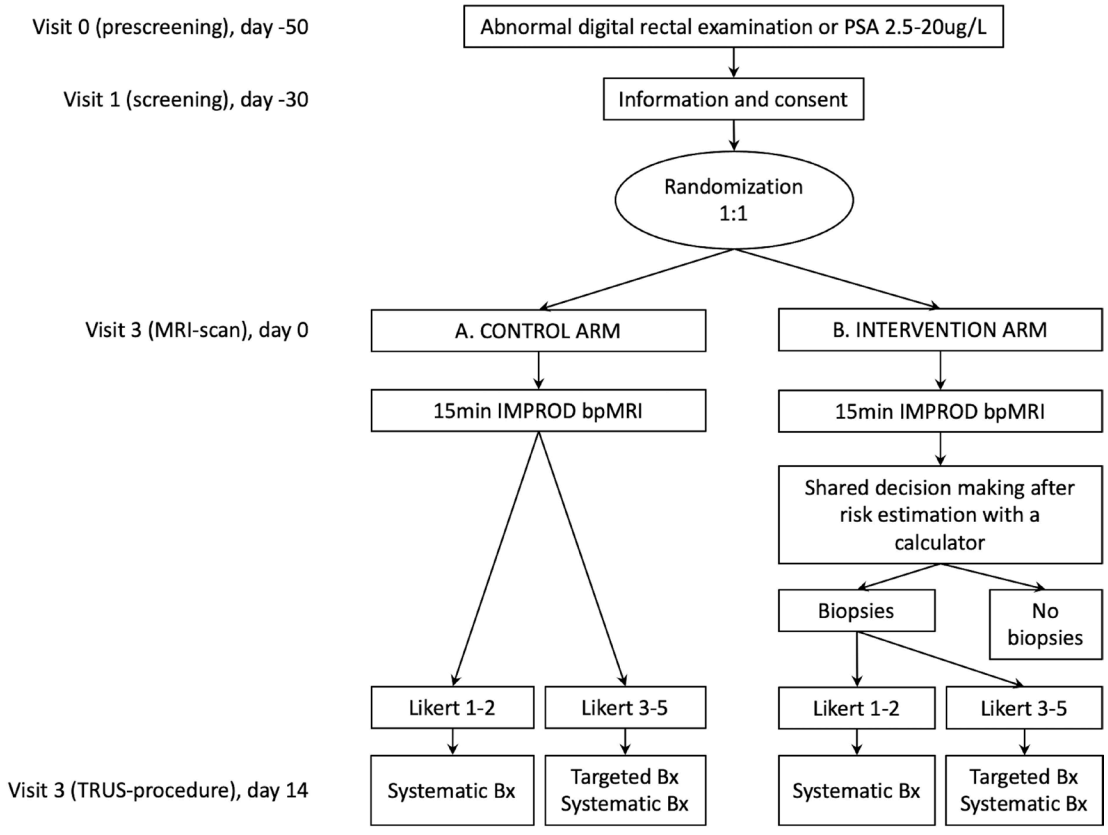

Figure 1 Study flow chart. Bx, prostate biopsies; IMPROD bpMRI, bi-parametric magnetic resonance imaging of prostate performed according to IMPROD MRI protocol (http://mrc.utu.fi/protocols/prostate); PSA, prostate specific antigen; TRUS, transrectal ultrasound of prostate.

exclusion criteria. If eligible, the subject will receive a study information sheet, an information sheet of the shared decision-making process and a time for the screening visit.

Screening visit (visit 1): during the screening visit at the urology out patient clinic, the study design is discussed in detail with the local investigator (urologist). If willing to participate, the subject will sign the informed consent form (online supplemental file 1). Thereafter, subjects will complete baseline questionnaires and baseline blood and urine samples are taken.

MRI scan (visit 2) is performed according to the guidelines in each centre. However, for study-related requirements, please refer to the chapter on study instruments.

Randomisation is performed before the TRUS visit. Subjects are randomised in a 1:1 ratio into two arms: the control arm and the intervention arm. Randomisation will be stratified by categorised baseline PSA: <4 ng / mL, 4–9.9 ng/mL, ≥10 ng/mL. Randomisation will be performed using a predefined allocation table implemented by the study statistician (EL). The allocation table will be implemented in the Research Electronic Data Capture (REDCap) database and is inaccessible once uploaded, hence ensuring allocation concealment.

TRUS visit (visit 3): the visit follows a protocol used in a normal outpatient clinic. MRI results are discussed with the subject.

The control arm: all subjects undergo TRUS-guided biopsies. In subjects with Likert scores of 1–2, 12-core systematic TRUS-guided systematic biopsies are performed. In subjects with Likert 3–5 score lesions, systematic biopsies and two targeted biopsy cores are taken from each lesion (up to two lesions).

The intervention arm: the probability of clinically significant prostate cancer is estimated using the risk calculator. The risks and benefits of prostate biopsy and patient values are discussed. A shared decision regarding whether to perform biopsies is made. If biopsies are to be performed, in subjects with Likert scores of 1–2, 12-core systematic TRUS-guided biopsies are performed and in subjects with Likert 3–5 score lesions systematic biopsies and two targeted biopsy cores are taken from each lesion (up to two lesions). If biopsies are not performed, subjects are referred for a PSA follow-up.

Biopsy results (visit 4): according to clinical guidelines in each centre, either by telephone conference or a visit, the subject is contacted to discuss the results of the biopsies and biopsy-related adverse events. If biopsies are not taken, subjects are informed about follow-up procedures.

Treatment: if diagnosed with prostate cancer, the subject and the treating physician, as part of the multi-disciplinary team, will decide the treatment modality according to local, national and international guidelines.

Follow-up: in subjects with benign biopsies or in subjects with no performed biopsies, PSA is measured according to local guidelines in each centre but should be performed at least as follows:

Years 1–2: every 6 months.

Years 3–5: every 12 months.

Thereafter, follow-up is performed according to clinical guidelines in every centre. If suspicion of prostate cancer persists after initial benign biopsies or in subjects with no biopsies taken, the decision to perform biopsies and/or MRI is according to local guidelines in each centre and/or the treating physician. However, if there is no such suspicion, a revisit (discussion and consideration of MRI and/or biopsies) should be performed at least as follows:

1. PSA increases over 20 ng/mL
2. PSA doubles during the follow-up.

A long-term follow-up of all subjects will be performed from medical charts, Finnish national registries and if needed, contacting the subject, for up to 20 years to have comprehensive data concerning incident prostate cancer in subjects without a diagnosis of prostate cancer and clinical end points (biochemical relapse, metastasis, death) in subjects with diagnosed prostate cancer.

Study instruments

Prostate MRI

Subjects scheduled for the MRI examination will receive sodium picosulfate drops (Laxoberon, Boehringer Ingelheim GmbH) and a Bisacodyl enema (Toilax, Orion Pharma) for bowel preparation. Details of the MRI protocol are described in http://mrcutufi/protocols/prostate. In short, prostate MRI examinations will be performed using a 1.5T or 3T MR scanner. Body array coils will be used for image data acquisition. No endorectal coil will be used. T2-weighted anatomic imaging will be performed in the axial and sagittal planes. Single-shot spin-echo echo-planar imaging will be used for diffusion-weighted imaging (DWI) and performed in three separate acquisitions using b-values of 0 s/mm^2, 100 s/mm^2, 200 s/mm^2, 350 s/mm^2, 500 s/mm^2; 0 s/mm^2, 1500 s/mm^2 and 0 s/mm^2, 2000 s/mm^2. Apparent diffusion coefficient (ADC) maps are calculated from each acquisition, but the one calculated from the acquisition with low b-values (0–500 s/mm^2) is considered to be the most reliable. The total scan time will be approximately 15–16 min.

MRI will be interpreted using an IMPROved prostate cancer Diagnosis (IMPROD) bpMRI Likert scoring system as follows: (1) significant cancer is highly unlikely to be present; (2) significant cancer is unlikely to be present; (3) significant cancer is equivocal; (4) significant cancer is likely to be present; (5) significant cancer is highly likely to be present.[7 8] The calculator and clinical judgement are based on a Likert scoring system. An additional classification of MRI lesions is performed using a modified PI-RADS V.2.1 system.[18]

All reports and data sets are uploaded to the central study server within 7 days of the MRI scan. A standardised form to report the MRI is used.[18] All MRI data sets are reported centrally by a designated central reader (IJ). The reported PI-RADS score of central reading is used for the risk calculator and for the MRI-guided biopsies. To assess inter-reader variability, MRI data sets are also

rereported retrospectively by a local radiologist in each centre (at least 1 year of prostate MRI experience). The readers are *all* blinded to all clinical data such as PSA, age and the subject's previous medical history.

TRUS and prostate biopsies

The period between the MRI examination and TRUS guided biopsy will be a maximum of 4 weeks. Prophylactic antibiotic treatment is given according to institutional guidelines. If suspicious MRI lesions are present, targeted biopsies followed by systematic TRUS-guided 12-core biopsies are performed. Targeting is performed either with cognitive-fusion or MRI-fusion according to clinical guidelines in each centre. A maximum of two cores will be taken from each MRI suspicious lesion. If more than two suspicious lesions are observed only two of most suspicious ones are targeted. Therefore, a maximum of four targeted biopsies are performed.

The risk estimation

To estimate the risk of clinically significant prostate cancer, a calculator is developed and implemented in eletronic case report form (eCRF), the RedCap. The calculator is based on our previous prospective MRI studies (the IMPROD trial, NCT01864135 and the multi-IMPROD trial NCT02241122) and it predicts the presence of biopsy Gleason ≥4+3 (GGG 3) prior to prostate biopsy, using information on subject age, prostate volume, total PSA, 5-ARI use and Likert score.

1. If the subject uses 5-ARI, modifications are needed to the subject's PSA and prostate volume.
   - Multiple PSA by 2.
   - Divide prostate volume by 0.7.
2. Calculate cubic spline terms for PSA.
   - The knot locations are t = (3.80, 6.60, 9.40, 18.47), where t_1=3.80, t_2=6.60. etc.

$$PSASpline_{j+1} = max(PSA - t_j, 0)^3 - max(PSA - t_3, 0)^3 * \frac{t_4 - t_j}{t_4 - t_3} + max(PSA - t_4, 0)^3 * \frac{t_4 - t_j}{t_4 - t_3} \; for j = 1, 2$$

3. Calculate the regression model linear predictor

$$X\beta = -6.97314184 + 0.064172722 * \{Age\} + -0.008141264 * \{ProstateVolume\} + -0.182694534 * \{PSA\} + 0.006136442 * \{PSASpline2\} + -0.013049396 * \{PSASpline3\} + 1.37637197 \{Likert == 3\} + 2.50939431 * \{Likert == 4\} + 4.07331563 * \{Likert == 5\}$$

4. Convert linear predictor to the risk of Gleason≥3 on biopsy (will be a probability between 0 and 1)

$$\text{Risk} = \frac{e^{X\beta}}{1+e^{X\beta}}$$

Shared decision-making

All consented subjects will be provided an information sheet on the concept of shared decision. The sheet will describe the biopsy pathway, the risks and benefits related to the biopsies and the application of the risk calculator. At the end of the sheet, there will be questions related to the subject's values of life, especially related to the risk of prostate cancer, its treatment and treatment-related side effects.

In the TRUS visit (visit 3), the information sheet is used to aid the discussion with subjects randomised to the intervention arm. The risk of clinically significant cancer is calculated and a shared decision regarding whether to perform biopsies is made.

The details of the protocol and execution of the trial and the concept of shared decision-making are discussed with all investigators during the investigator meeting before the start of the trial. The concept of the calculator is also discussed and its use is demonstrated. The anchor guides to the shared decision-making are presented in table 1.

Laboratory evaluation

As a part of routine clinical practice blood tests including serum PSA, free-to-total PSA ratio, standard and differential blood counts, serum alkaline phosphatase and serum testosterone are collected.

Serum and urine biomarkers

Anticoagulated EDTA plasma (10 mL) and urine (a minimum of 10 mL) are collected to investigate previously characterised biomarkers for prostate cancer

Table 1 The anchors used to guide the share decision making.

Risk category	Actual risk	Recommendation
Low risk	≤5%	It is recommended that biopsy is avoided
Favourable intermediate risk	5.1%–7.5%	It is recommended that biopsy is avoided. However, consider performing the biopsies if the patient is young, he has a strong family history of prostate cancer or he is very anxious about cancer.
Intermediate risk	7.6%–14.9%	Shared decision-making with the patient about biopsy, taking into account the patient's age and health and their preferences about avoiding an invasive procedure compared with concerns about cancer
In-favourable intermediate risk	15.0%–19.9%	It is recommended to that biopsy is performed. Consider avoiding biopsy in patients with significant comorbidities or if the patient is particularly anxious about the biopsy procedure.
High risk	≥20.0%	It is recommended that biopsy is performed.

detection such as the four kallikrein panel and potential new biomarkers. The blood and urine are samples drawn before the TRUS visit. Subjects give their written consent to the sampling.

Histopathologic evaluation of tissue samples

All histopathological biopsies are reported separately (core length, cancer length, Gleason grade) at each centre by expert pathologists, each with at least 5 years of experience in genitourinary pathology at the beginning of the trial. Reports are made using the 2014 International Society of Urological Pathology Modified Gleason Grading System.[19] The biopsy specimen is analysed, so that pathologists are aware that the subjects are part of the study. However, they are not aware of the exact details of the study protocol and they are blinded to the sequence of individual biopsy cores.

Definition of overall Gleason grade and clinically significant prostate cancer

Clinically significant prostate cancer is defined as Gleason 4+3 (GGG 3) or higher in overall Gleason grade which is defined for each subject as the combination of the most frequent Gleason grade and the highest Gleason grade.

Questionnaire

Prostate cancer-related anxiety is measured with Memorial Anxiety Score for Prostate Cancer anxiety score.[20] The questionnaire will be collected at baseline, at 6 months and at 12 months.

Adverse events

Since anatomical MRI and DWI are not based on ionising radiation, the risk for adverse events in properly selected subjects is considered minimal, if any. Claustrofobic subjects will be excluded from the study. Commonly, no side effects or only mild side effects are associated with taking sodium picosulfat drops (Laxoberon, Boehringer Ingelheim GmbH) or Bisacodyl enema (Toilax, Orion Pharma Ltd) for bowel preparation, but it is recommended for subjects to maintain their water balance with increased water intake. No MRI contrast agents will be given to the subjects. The type and severity of the adverse events will be defined during the MRI visit by using the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 classification.

TRUS-guided biopsies are associated with risk of complications, the most important being serious infections (0.5%) and bleeding (4%) complications. Adverse events related to TRUS and prostate biopsies are recorded for 14 days after the biopsies. The type and severity of the complication are defined and recorded. The severity will be defined by using the Clavien-Dindo classification.[21]

Potential benefits and harms

Potential harms include adverse events related to TRUS-guided biopsies and the fact that a fraction of clinically significant prostate cancer is left undiagnosed in subjects not undergoing TRUS-guided biopsies in the intervention arm. However, the study does not expose subjects to any extra procedures since in normal clinical practice all included subjects would undergo bpMRI and subsequent TRUS-guided biopsies. TRUS-guided biopsies are potentially harmful to the subject, however, subjects in the intervention arm may have even fewer adverse events than subjects in the control arm. Furthermore, leaving a fraction of clinically significant prostate cancer undiagnosed in the intervention arm does not harm the subjects since a robust follow-up after the initial diagnostic procedure is included in the study design.

Subject retention and protocol deviation

It is expected that the subject retention rate is low, since all subjects have a suspicion of prostate cancer and they want to be involved in the diagnostic pathway. For the same reason, no protocol deviations are expected. Subjects who decide to refrain from the study are included in the final analysis, if they have undergone prostate MRI and TRUS visits.

Sample size calculation

The concept of sample size recalculation was brought up in protocol V.2.0 (4 January 2021). A two-stage sample size calculation was performed: first, an initial calculation before the start of the trial; second, a predetermined blinded re-estimation after the recruitment of the first 300 subjects.

1. The estimation of the clinically significant prostate cancer rate was based on data from our previous prospective trials (the IMPROD and the multi-IMPROD).[7 8] Using a clinically significant cancer rate of 25% in both arms, a non-inferiority margin of −8%, a beta level of 0.2 and an alpha level of 0.05, it was estimated that 600 subjects would be needed.
2. The re-estimation of sample size is based on the observation that clinically significant prostate cancer is present in 20% of the first 300 subjects. Also, regarding the potential difference in clinically significant cancer rates between the arms, the sample size is evaluated in three different scenarios. Using a non-inferiority margin of −8%, a beta level of 0.2 and an alpha level of 0.05, the scenarios are as follows:
   - with a rate of 20.0% in both arms, 624 participants will be needed.
   - With rates of 20.5% (control arm) and 19.5% (intervention arm), 814 subjects will be needed.
   - With rates of 21.0% (control arm) and 19.0% (intervention arm), 1104 subjects will be needed.

It is decided that the final sample size will be calculated according to scenario b. Using a dropout rate of 2%, 830 subjects will be recruited. The recalculated sample size was implemented in the latest protocol amendment (V.2.1, 21 September 2021).

Data handling

RedCap database

In addition to medical charts in each participating centre, study data are collected, managed and stored pseudoanonymised in REDCap electronic data capture tool hosted at the University of Turku.[22 23] Every participating centre holds a pseudonymisation key in its own server.

Quantitative analysis of DWI

The signal intensity of DWI will be fitted using monoexponetial fit.

Monoexponential calculation of apparent diffusion coefficient is described by the following equation (eq.1):

$$ADC = -\frac{1}{b2-b_1} ln \left[\frac{SI(b_1)}{SI(b_0)}\right]$$

where $SI(b_1)$ and $SI(b_0)$ denote the signal intensity at higher b value (b_1) and at b=0 mm^2/s (b_1).

Data analysis plan

The non-inferiority evaluation will be done based on one-sided 95% CI for the difference of proportions in the control arm and intervention arm. The primary analysis is the proportion of men with clinically significant cancer in each arm. Analysis will be done by logistic regression, with randomisation strata as covariate. The OR and CI between groups will be applied to the risk in the control group to calculate a risk difference and CI. A one-sided 95% CI will be used to place a bound on the maximum reduction in detection rates associated with the intervention arm. A similar approach will be used for the proportion of men with clinically non-significant prostate cancer, biopsy rate and biopsy-related complications. For the patient-reported outcome of biopsy-related anxiety, analysis will be by analysis of covariance (ANCOVA), with randomisation strata as covariate. In this case, a two-sided 95% CI will be calculated.

To evaluate the rate of clinically significant prostate cancer during follow-up, we will use time-to-event methods, with subjects censored at the time of their last biopsy or curative treatment (if received for clinically non-significant prostate cancer). Cox proportional hazards will be used to compare between groups, with randomisation strata as covariate.

As a descriptive analysis, we will evaluate how biopsy rates in the intervention arm vary by the predicted risk produced by the model. We will first divide subjects into low (<5%), intermediate (5%–20%) and high (≥20%) predicted risk of high-grade disease and report the rate of biopsy in each category. We will then calculate the probability of biopsy by the predicted risk of high-grade cancer using locally weighted scatterplot smoothing (lowess).

We will conduct two additional exploratory analyses. First, we will evaluate the hypothetical results in the control group had biopsy been restricted to those meeting different biopsy criteria—including PI-RADS 3 or higher; PI-RADS 4 or higher; PI-RADS 3 or higher or PSA density >0.2 ng/mL/mm^3—reporting the number of biopsies that would have been conducted and the number of clinically significant cancers found for each strategy in comparison to the observed strategy of taking biopsies from all men. The results of these analyses will be standardised per 1000 men presenting with elevated PSA. The inter-reader variability between central and local reader-reported PI-RADS scores will be analysed using the Kendall tau-b. In the second exploratory analysis, we will report the calibration of the prediction model in the control group. The calibration will be performed using two models: Likert and PI-RADS V.2.1 scores and by incorporating.

Patient and public involvement

Patients or the public were not involved in the design and will not be involved in the conduct, reporting or dissemination plans of our research.

ETHICS AND DISSEMINATION

Ethics

The study will be conducted in compliance with the current revision of the Declaration of Helsinki guiding physicians and medical research involving human subjects (64th World Medical Association General Assembly, Fortaleza, Brazil, 2013). The study (initial approval, protocol V.1.0, 17 September 2019; latest protocol V.2.1, 21 September 2021) is approved by the EC of the Hospital District of Southwest Finland (IORG number: 0001744, IBR number: 00002216), (trial number: 99/1801/2019) and registered. Any important modifications and amendments to trial protocol will be approved by the EC and all parties participating in the study will be informed.

Data monitoring

Risk-based data monitoring will be performed according to the monitoring plan (online supplemental file 2).

Insurance

The study subjects are insured during the study by the 'Insurance against medicine-related injuries' (In Finnish: 'Lääkevahinkovakuutus') under regulations currently in effect in all participating centres.

Study report and publications

Any formal presentation or publication of data collected from this research protocol will be considered as a joint publication by the investigator(s) and other appropriate persons deemed to have a significant academic output in the implementation of the study. Full reports of this study will be submitted to peer-reviewed journals in concerned fields (mainly radiology and oncology).

Following completion of the trial, free public access to all data will be provided like to our previous single- (IMPROD, NCT01864135) and multi centre (Multi-IMRPOD, NCT02241122) trials available at http://petiv.utu.fi/improd/ and http://petiv.utu.fi/multiimprod/, respectively.

Study schedule

The study started in February 2020. All the subjects are expected to be recruited by May 2022. The prospective follow-up will stop in 2027. Long-term follow-up based on medical charts will stop in 2042.

Study centres

A detailed description of all study centres is provided in https://clinicaltrialsgov/ct2/show/.

Central Finland Central Hospital, Jyväskylä, Finland, 40 620

Satakunta Central Hospital, Pori, Finland, 28 500.

Tampere University Hospital, Tampere, Finland, 33 520.

Turku University Hospital, Turku, Finland, 20 521.

DISCUSSION

The trial is designed to show that as a triage test an individualised MRI-based risk estimation is non-inferior to MRI-targeted biopsies in men with suspicion of prostate cancer. Although one might argue that several risk scores for prostate cancer exist, the study is extremely timely and relevant by establishing a contemporary risk score with data from prostate MRI and, more importantly, using the score in a scenario of shared decision-making.

However, some issues should be discussed. First, the selection of GGG 3 or higher as a definition of clinically significant prostate cancer instead of using Gleason GGG2 as a cut-off is debatable. The overall Gleason score will be defined according to the most common Gleason pattern and the highest Gleason pattern based on the combination of Gleason patterns in targeted and systematic biopsies. This will eventually lead to saturation of the Gleason pattern of the targeted biopsies and most notably to a stage migration towards higher overall Gleason grades. The approach is also supported by two recent prostate MRI trials, the PROMIS and the National Cancer Institute MRI trial, which both used GGG 3 as a definition of clinically significant prostate cancer.[4 24] Therefore, we consider the approach justified.

Second, a non-inferiority margin of −8% needs to be addressed. We acknowledge that other prostate MRI trials using the non-inferiority setting have adopted a margin of −5%.[5 25] However, the study designs are not comparable to our study. In the Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not -trial (PRECISION) and the trial by Klotz *et al*, novel technology, that is, MRI-guided biopsies, was compared with traditional technology, the TRUS-guided biopsies and the outcome from the technology dictated patient interventions. In that setting, it is crucial that the outcome after interventional diagnostics is analogous or even superior compared with traditional ones. In our trial, patient characteristics and preferences and clinicians' recommendations are taken into account and, therefore, we are confident that a more liberal non-inferiority margin can be accepted. Ultimately, the patient makes the decision.

The cohort should also be addressed. It is purely of Caucasian origin and consists of Finnish men, a population presenting with a low level of opportunistic screening for prostate cancer. Therefore, the results may not be directly generalised to men of non-Caucasian origin or populations with higher rates of opportunistic prostate cancer screening.

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Competing interests PT reports representation as a member of the Data Management Committee in the ProScreen trial. AV is named as a co-inventor on US patent number: 9 672 329 for a statistical method to predict the result of prostate biopsy. Patent has been commercialised and will receive royalties from clinical use. AV is also a co-inventor of the 4kscore, a commercially available reflex test for predicting prostate biopsy. He may receive royalties from sales of the test. He owns stock options in Opko, which offers the test. Otherwise, no competing interest was declared.

Patient consent for publication Consent obtained directly from patient(s).

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Multi-IMPROD2.0

Sukunimi	Etunimi	Syntymäaika (ppkkvv)
		☐☐.☐☐.☐☐

Katuosoite	Postinumero	Postitoimipaikka	Puhelin

SUOSTUMUSASIAKIRJA INFORMED CONSENT FORM

SUOSTUMUS

Minua on pyydetty osallistumaan tutkimukseen, jossa selvitetään magneettikuvaksen ja minun ominaisuuksieni perusteella luodun riskiarvion soveltuvuutta arvioida eturauhasen koepalojen tarpeellisuutta.

Olen lukenut ja ymmärtänyt saamani kirjallisen tutkimustiedotteen. Tiedotteesta olen saanut riittävän selvityksen tutkimuksesta ja sen yhteydessä suoritettavasta henkilötietojen keräämisestä, käsittelystä ja luovuttamisesta. Tiedotteen sisältö on kerrottu minulle myös suullisesti, minulla on ollut mahdollisuus esittää kysymyksiä ja olen saanut riittävän vastauksen kaikkiin tutkimusta koskeviin kysymyksiini.

Tiedot antoi _____ __/__201_.

Minulla on ollut riittävästi aikaa harkita osallistumistani tutkimukseen. Olen saanut riittävät tiedot oikeuksistani, tutkimuksen tarkoituksesta ja sen toteutuksesta sekä tutkimuksen hyödyistä ja riskeistä. Minua ei ole painostettu eikä houkuteltu osallistumaan tutkimukseen.

Tiedän, että tietojani käsitellään luottamuksellisesti eikä niitä luovuteta sivullisille. Kansainväliselle yhteistyökumppaneille tietoja ja näytteitä luovutetaan ainoastaan koodattuina niin, että heillä ei ole mahdollisuutta tunnistaa näistä yksittäisiä potilaita.

Ymmärrän, että osallistumiseni on vapaaehtoista. Olen selvillä siitä, että voin peruuttaa tämän suostumukseni koska tahansa syytä ilmoittamatta eikä peruutukseni vaikuta kohteluuni tai saamaani hoitoon millään tavalla.

Olen tietoinen siitä, että mikäli keskeytän tutkimuksen tai peruutan suostumuksen, minusta keskeyttämiseen ja suostumuksen peruuttamiseen mennessä kerättyjä tietoja ja näytteitä voidaan käyttää osana tutkimusaineistoa.

Allekirjoituksellani vahvistan osallistumiseni tähän tutkimukseen ja suostun vapaaehtoisesti tutkimushenkilöksi.

_____ ___/___201_ _____

paikka ja aika tutkimushenkilön allekirjoitus

Vakuutan, että olen antanut tutkittavalle ennen tämän asiakirjan allekirjoittamista riittävän selvityksen tutkittavan oikeuksista sekä tutkimukseen liittyvistä yksityiskohdista siten kuin lääketieteellisestä tutkimuksesta annetun lain 488/1999 6§:ssä edellytetään. Vakuutan, että kaikkea tutkimuksen aikana saatavaa tietoa käsitellään luottamuksellisesti ja että tutkimusryhmän ulkopuolisille annettavasta tiedosta (esim. julkaisut) tutkittavien henkilöllisyys ei ole tunnistettavissa. Tutkittavalla on oikeus milloin tahansa tutkimuksen kestäessä (myös syytä ilmoittamatta) peruuttaa suostumuksensa tutkimukseen, ilman että peruutus vaikuttaisi tutkittavan oikeuteen saada tarvitsemaansa hoitoa.

Turussa ___/___201_ _____

tutkijalääkärin allekirjoitus ja nimenselvennys

Versio 1.0 / 29.8.2019

Alkuperäinen suostumusasiakirja arkistoidaan tutkijan kansioon ja tutkittavalle annetaan kopio.
(Vaihtoehtoisesti täytetään ja allekirjoitetaan kaksi samansisältöistä kappaletta, joista toinen arkistoidaan tutkijan kansioon ja toinen annetaan tutkittavalle.)

MONITORING PLAN

Study name:	Multi-IMPROD2.0
Study code:	T326/2019
EurdraCT number:	Not applicable
Sponsor / Investigator:	Turku University Hospital
Name of study site:	Turku University Hospital
Duration of the study:	02/2020-02/2026
Planned No. of subjects:	600

EXTENT OF MONITORING

Minimum monitoring as specified by the organisation to implement the obligations of quality policy and good clinical practice.

ITEMS TO BE MONITORED (detailed description)

- **Study initiation visit**

- **1st monitoring in the beginning of the study:**

Items to be checked are:
Study documentation in investigator's trial file
Informed consents of screened and enrolled study subjects
CRFs completed by the date of monitoring visit of 1-2 first enrolled subjects.
Timing for the visit is Feb-2021.

- **2nd monitoring visit after the recruitment has been completed:**

Items to be checked are:
Informed consents of all screened and enrolled patients
Main parameters in CRFs of all study subjects:
Inclusion and exclusion criteria
Overall PI-RADS-score of the prostate
If TRUs-guided biopsies are performed, the overall histopathological gleason grade of the prostate
(Serious) Adverse events
Study documentation in investigator's study file.
Planned timing for the visit is Feb-2022.

- **3rd monitoring visit after last patient has completed the study:**

Items to be checked are:
study documentation of investigator's study file.
Planned timing for the visit is Feb-2026.

Estimated time used for monitoring

- *1st monitoring visit 10h*
- *2nd monitoring visit 40h*
- *3rd monitoring visit 10h*

The monitoring plan is valid until further notice and it can be updated by mutual consent.

Ilkka Nikulainen		
Name of Monitor	Date	Signature
Peter Boström		
Name of Sponsor/Investigator	Date	Signature

Version 1.0. 03-Jan-2021