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Individualized non-contrast MRI-based risk estimation and shared decision making in men with a suspicion of prostate cancer – A multi-centre randomised controlled trial (multi-IMPROD2.0) – a study protocol

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Abbreviations

bpMRI	biparametric MRI
mpMRI	multiparametric MRI
PI-RADS	Prostate Imaging–Reporting and Data System
MRI	prostate magnetic resonance imaging
PSA	prostate specific antigen
TRUS	transrectal ultrasonography

Introduction

EAU and NICE guidelines recommend that all men with a suspicion of prostate cancer should undergo pre-biopsy contrast-enhanced i.e. multiparametric prostate magnetic resonance imaging (mpMRI). Also, subsequent prostate biopsies should be performed if MRI is deemed as positive i.e. 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 a large number of 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.

Methods and analysis

This is a prospective, randomised, 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 individualized risk estimation. Men without previous diagnosis of prostate cancer and with abnormal digital rectal examination findings and/ or prostate specific antigen (PSA) between 2.5ug/L and 20.0ug/L are included. We aim at recruiting 830 men who are randomised 1:1 fashion 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) in the control. 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 version 2.0, Jan 04, 2021) is approved by the Ethics Committee of the Hospital District of Southwest Finland (IORG number: 0001744, IBR number: 00002216),

(trial number: 99 /1801/2019). Full reports of this study will be submitted to peer-reviewed journals, mainly urology and radiology.

Registration

The study is registered at clinicaltrials.gov, NCT04287088.

Strengths and limitations of this study

- **1** The biparametric MRI protocol used in the study is a result of systematic research on diffusion weighted imaging, data acquisition and post-processing of MRI imaging.
- **2** Public availability of all data from previous testing (IMPROD-study) and validation (multi-IMRPOD-study) studies (http://petiv.utu.fi/improd/, and http://petiv.utu.fi/multiimprod/) and the MRI protocol (http://mrc.utu.fi/protocols/prostate)
- **3** Although study participants are recruited from several centres, vast majority of them are Caucasian of origin and, therefore, in this respect, the generalization of the results might be limited
- **4** Also, the relatively low prevalence of opportunistic screening of prostate cancer in Finland has definitely an impact on the baseline characteristics of the study population, which may limit the generalization of the results to nationalities with higher levels of screening

Keywords: clinically significant prostate cancer, prostate MRI, risk estimation, shared decision making

Introduction

The incidence of prostate cancer continues to increase worldwide, mainly as a result of population aging, better diagnostic methods and potentially due to real increase in incidence. Although most of the prostate cancers are currently being diagnosed at early stage, at present 30% of prostate cancer in Finland are metastatic at diagnosis (1). In addition, prostate cancer continues to be the second leading cause of cancer death 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 (mpMRI) and biparametric (bpMRI) magnetic resonance imaging 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). Based on these trials, EAU, AUA and NICE guidelines recommend that all men with a suspicion of prostate cancer should undergo pre-biopsy MRI. Also, subsequent prostate biopsies should be performed if MRI is deemed as positive i.e. 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 PCa or reflect upgrading associated with MRI (12). Moreover, several retrospective post-hoc analyses have shown that this approach still leads to a large number of 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 whether to perform biopsies or not is not just about MRI and PSA but a shared decision making accounting for patient characteristics, such as co-morbidities, life-expectancy, and expectations and values (15). Unfortunately, no risk tool applying a truly individualized approach for each man have been evaluated in prospective clinical trials. Therefore, the concept of this trial is to generate a risk calculator, based on MRI and clinical variables describing individual man's 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, multi-centre 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 if there is a difference compare the 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 individualized risk estimation.

Objectives

Primary objective

A non-inferiority between significant prostate cancer detection rate in men undergoing prostate biopsies after 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, and benign biopsies between arms.

To compare biopsy rates between arms.

To compare the detection rate of clinically significant prostate cancer during the five year of follow-up between arms

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

Outcomes

Primary outcome

The proportion of men with clinically significant prostate cancer (Gleason 4+3 prostate cancer or higher) in the control and intervention arms after primary diagnostic pathway

Secondary outcome

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

The proportion of men undergoing biopsies.

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

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

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 in 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 judgment of the responsible urologist
- uni- or bilateral hip prosthesis

Study procedures

Study flow is presented in Figure 1.

Pre-screening (visit 0) After a referral to participating centres, all subjects are evaluated for inclusion and exclusion criteria. If eligible, the subject will receive an information sheet of the study, the information sheet of shared decision-making process, and the 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. After consenting, subjects will complete baseline questionnaires, and baseline blood and urine samples are taken.

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

Randomisation is performed before the TRUS-visit. Subjects are randomised 1:1 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 predefined allocation table implemented by the study statistician (EL). The allocation table will be implemented in RedCap database and is in-accessible once uploaded, hence ensuring allocation concealment.

TRUS-visit (visit 3) The visit follows a protocol used in 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, in addition to systematic biopsies, 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 risk, benefits and harms of prostate biopsy and

patient values are discussed. A shared decision whether to perform biopsies is made. If biopsies are to be performed, in subjects with IMPROD bpMRI likert scores of 1-2, 12-core systematic TRUS guided biopsies are performed and in subjects with Likert 3-5 score lesions, in addition to systematic biopsies, 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 a telephone conference or a visit, subject is contacted to discuss the results of the biopsies and biopsy-related adverse events. If biopsies were 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 biopsies performed PSA is measured according to local guidelines in each centre but should be performed at least as follows:

Years 1-2: every six 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 treating physician. However, if no such suspicion, re-visit (discussion and consideration of MRI and/ or biopsies), should be performed at least as follows:

1. PSA increases over 20
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, up to 20 years in order to have a 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 Ltd) for bowel preparation. Details of the MRI protocol are described in http://mrc.utu.fi/protocols/prostate. In short, prostate MRI examinations prostate 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 axial and sagittal plane. Single-shot spin-echo echo-planar imaging will be used for DWI and performed in three separate acquisitions. The total scan time will be approximately 15-16min.

MRI will be interpreted using a IMPROD bpMRI Likert scoring system 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 Likert scoring system. An additional classification of MRI lesions is performed using a modified PI-RADS2.1 system (16).

All reports and data sets are uploaded to the central study server within seven days of the MRI scan. A standardised form to report the MRI is used (16). All MRI data sets are reported centrally by two designated central readers (IJ, JV). Also, MRI data sets are re-reported by a

local radiologist (at least one year of prostate MRI experience). The central readers are blinded to all clinical data such as PSA, age, and subject's past medical history.

TRUS and prostate biopsies

The time 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, and the regimen used is recorded. If suspicious MRI-lesions are present, targeted biopsies are performed followed by systematic TRUS guided 12-core biopsies. Targeting is performed either with cognitive- 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 suspicions lesions are observed only two of most suspicious ones are targeted. Therefore, four targeted biopsies at maximum are performed. A post-hoc analysis on inter-operator variability will be performed.

The risk estimation

To estimate the risk of clinically significant prostate cancer a calculator is developed and implemented in 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 $\geq$ 4+3 prior to prostate biopsy, using information on subject age, prostate volume, total PSA, 5-ARI use, and PI-RADS score to make predictions.

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

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

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

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

Shared decision making

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

In 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 whether to perform biopsies is made.

In addition to the details of the protocol and execution of the trial, the concept of shared decision-making is discussed with all the investigators during the investigator meeting before

the start of the trial. Also, the concept of the calculator is discussed, and the use of calculator is demonstrated. Anchors used to guide the shared decision making are presented in Table 1.

Laboratory evaluation

As a part of a 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 (min. 10 ml) are collected to investigate previously characterised biomarkers for prostate cancer detection such as the four kallikrein panel and potential new biomarkers. The blood and urine are drawn before the TRUS-visit. Subjects give their written consent to the sampling.

Histopathologic evaluation of tissue samples

All histopathological biopsies were reported separately (core length, cancer length, Gleason grade) at each centre by expert pathologists, each with at least five years of experience in genitourinary pathology at the beginning of the trial, using the 2014 International Society of Urological Pathology Modified Gleason Grading System (17). The biopsy specimen is analysed so that pathologists are aware that 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 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 (MAX-PC) (18). The questionnaire will be collected at baseline, at six, and 12 months.

Adverse events

Since anatomical MRI and DWI are not based on ionizing 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 of 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 the severity of the adverse events will be defined during the MRI-visit by using the CTCAE4.0 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 the severity of the complication are defined and recorded. The severity will be defined by using the Clavien-Dindo classification (19).

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. Given the fact that TRUS guided biopsies are

potentially harmful to the subject, subjects in the intervention arm may even have less adverse events than subjects in the control arm. Also, leaving a fraction of clinically significant prostate cancer un-diagnosed 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 subject retention rate is low, since all subjects have a suspicion of prostate cancer and they want to be involved in diagnostic pathway. For the same reason, no protocol deviations are expected. If subject decides to retain from the study or a study deviation occurs, subjects are included in the final analysis if he has undergone prostate MRI and TRUS-visits.

Sample size calculation

A two-stage sample size calculation was performed: 1, an initial calculation before the start of the trial; 2, a predetermined blinded re-estimation after the recruitment of first 300 subjects.

1. The estimation of 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 will be needed.
2. The re-estimation of sample size was based on observation that clinically significant prostate cancer was present in 20% of the first 300 subjects. Also, regarding the potential difference in clinically significant cancer rates between the arms, the sample size was 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 were the following:

a. with a rate of 20.0% in both arms, 624 participants will be needed
b. with rates of 20.5% (control arm) and 19.5% (intervention arm), 814 subjects will be needed
c. with rates of 21.0% (control arm) and 19.0% (intervention arm), 1104 subjects will be needed

It was decided that the final sample size will be calculated according to scenario b. Using a dropout rate of 2%, 830 subjects will be recruited.

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 University of Turku (20, 21). Every participating centre holds a pseudoanomisation key in their own server.

Qualitative analysis of MRI data

Prostate cancer in the peripheral zone appears as round or ill-defined, low-signal-intensity foci on T2-weighted images while central gland tumors appear as homogeneous low signal intensity lesions with irregular margins and without a capsule. Invasion of the pseudocapsule with lenticular extension into the urethra or anterior fibromuscular zone is commonly seen on T2-weighted images of central gland tumors (22). The central zone prostate cancers tend to have higher Gleason scores compared with cancers located in peripheral zone (23). Moreover, the central zone prostate cancers were shown to have higher pathological stage (higher rate of extracapsular extension and seminal vesicle invasion) as well higher Gleason score (23).

Quantitative analysis of DWI

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

Monoexponential calculation of apparent diffusion coefficient (ADC) 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 $SI(b_0)$ denotes 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 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 randomization strata as covariate. The odds ratio and confidence interval between groups will be applied to the risk in the control group in order to calculate a risk difference and confidence interval. A one-sided 95% confidence interval 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 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 ANCOVA, with randomization strata as covariate. In this case, a two-sided 95% C.I. 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 randomization strata as covariate.

As a descriptive analysis, we will evaluate how biopsy rates in the intervention arm vary by 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 biopsying all men. The results of these analyses will be standardized per 1000 men presenting with elevated PSA. In the second exploratory analysis, we will report the calibration of the prediction model in the control group.

Ethics and dissemination

Ethics

The study will be conducted in compliance with the current revision of Declaration of Helsinki guiding physicians and medical research involving human subjects (64th World Medical Association General Assembly, Fortaleza, Brazil 2013). The study (protocol version 2.0, Jan 04, 2021) is approved by the Ethics Committee of the Hospital District of Southwest Finland (IORG number: 0001744, IBR number: 00002216), (trial number: 99 /1801/2019) and registered (NCT04287088). The amended study protocol (version 2.1) including the recalculated sample size will be send for ethical reading Jun 15, 2021. Any important modifications and amendments to trial protocol will be approved by the Ethics committee and all parties participating the study will be informed.

Patient and Public Involvement

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

Data monitoring

A risk-based data monitoring will be performed according to monitoring plan, Supplement 1.

Insurance

The study subjectsts 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 trail, free public access to all data will be provided similar to our previous single- (IMPROD, NCT01864135) and multi-center (Multi-IMRPOD, NCT02241122) trials available at http://petiv.utu.fi/improd/ and http://petiv.utu.fi/multiimprod/, respectively.

Study schedule

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

Study centres

A detailed description of all study centres is provided in https://clinicaltrials.gov/ct2/show/NCT04287088.

Central Finland Central Hospital, Jyväskylä, Finland, 40620

Satakunta Central Hospital, Pori, Finland, 28500

Tampere University Hospital, Tampere, Finland, 33520

Turku University Hospital, Turku, Finland, 20521

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Authors´ contributions

OE was involved in drafting this protocol and participated in the conception, study design, assessments, data interpretation, writing and submission of the manuscript. PB, HA, IJ, DS, and AV contributed to the study design, assessments, data interpretation. MS, AK, HS, KS took part in management, analysis and data interpretation. All authors read and approved the final manuscript. OE takes the responsibility for the integrity of the work as a whole and have access to the final trial dataset.

Competing interest statement.

PT reports representation as a member on the Data Management Committee in the ProScreen trial. AV is named as a co-inventor on US patent #: 9,672,329 for a statistical method to predict the result of prostate biopsy. Patent has been commercialized 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 declared.

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This work is supported by academic grant from Finnish Cancer Society. The funding organisation will not have any authority over study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

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 to 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.

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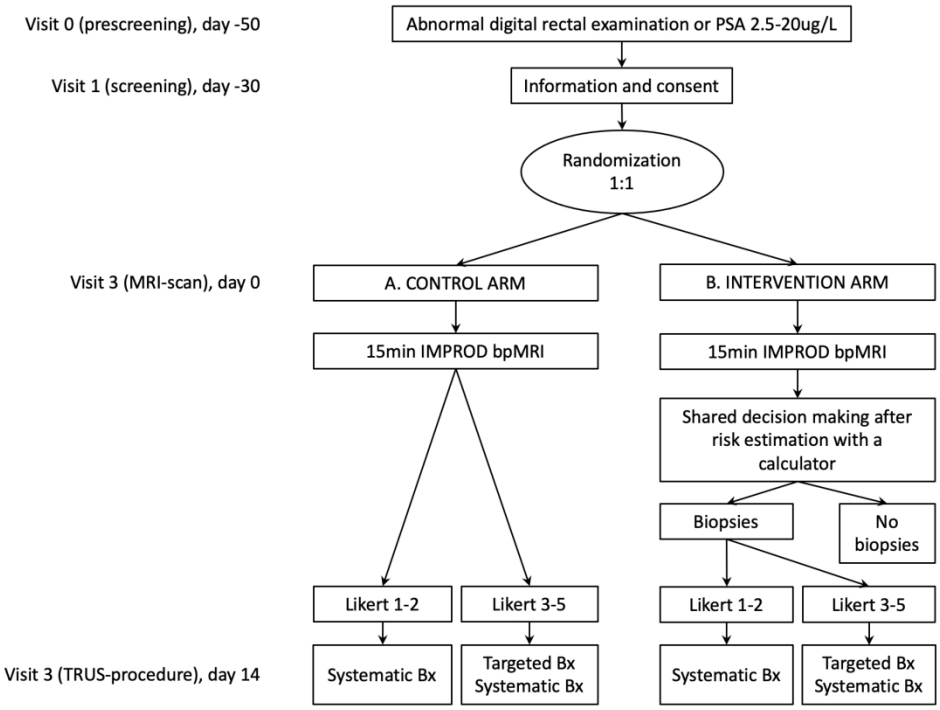

Figure 1. Study flow chart.

340x244mm (144 x 144 DPI)

MONITORING PLAN

1(1)

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

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym *Rows 1-4*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry *Rows 58-60 and Rows 424-430*
	2b	All items from the World Health Organization Trial Registration Data Set *Registered in clinicaltrials.gov, NCT03876912*
Protocol version	3	Date and version identifier *Row 58-60 and Rows 424-430*
Funding	4	Sources and types of financial, material, and other support *Row 558-562*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors *Rows 5-16 and rows 544-550*
	5b	Name and contact information for the trial sponsor *Rows 17-21*
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities *Rows 558-563*
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) *Not applicable. However, a risk-based monitoring will be performed. Please see Item 21a and Supplemental document 1.*

Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention *Research questions: rows 114-119* *Justification and relevant studies: rows 82-113* *Benefits and harms: rows 334-343*
	6b	Explanation for choice of comparators *Rows 106-113*
Objectives	7	Specific objectives or hypotheses *Rows 127-138*
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) *Rows 122-126*
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained *Rows 457-463*
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) *Rows 156-169*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered *Rows 188-200*
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) *No criteria for discontinuation due to harms or disease worsening exists, since the intervention is performed only once, and it is expected that no serious harms are related to it. However, in the control arm TRUS-guided biopsies should be performed to all patients. If a patient requests that biopsies are not be performed, the experimental nature of the shared decision making is discussed. Also, the importance of adhering to the study protocol is discussed. If the patient still refuses to undergo TRUS-guided biopsies, this is permitted. The patient is included to the final analysis normally.*

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) *Not applicable. The one-time intervention is performed in controlled circumstances i.e. in the urological out-patient clinic.*
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial *Rows 205-207*
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseRow, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended *Rows 139-151*
Participant timeRow	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) *Figure 1*
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations *Rows 350-370*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size *Rows 172-179*
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions *Rows 182-187*
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned *Rows 182-187*

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions *Rows 182-187*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how *Open label study. No blinding.*
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial *Open label study. No blinding.*
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol *Rows 372-375*
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols *We expect the frequency of participant non-adherence to be very low due to the nature of the intervention. Also, the follow-up protocol has been made as simple as possible and the follow-up will be performed during normal clinical practice or pre-planned measurements of serum PSA, and automated surveys sent by the REDCap data capture system.* *If non-adherence occurs, the participant will be contacted by the study nurse or study investigator who will motivate the participant to continue the study by the protocol.*
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol *Rows 372-375*
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol *Rows 393-421*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) *Rows 393-421*

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) *We expect the frequency of protocol non-adherence to be very low due to the nature of the intervention. All patients randomised are included to the final analysis even if they never undergo the intervention.*
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed *The study does not expose patients to additional harms or (serious) adverse events regarding the intervention. None of the participants undergo additional procedures compared to normal clinical practice. Therefore, data monitoring committee is not needed. However, to ensure scientific validity, a blinded recalculation of sample size was performed. The analysis was performed by an external statistician not involved in the study. Also, a risk-based monitoring of all main parameters in case report form is performed by an external monitor not involved in the study. See Supplement document 1.*
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial *Rows 351-370*
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct *Not applicable. Adverse events are collected and recorded after the TRUS-guided biopsies. However, no other procedures are performed during the study, spontaneous, study-related adverse events are not expected.*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor *No pre-planned audits.*
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval *Rows 424-432*

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) *Rows 430-432*
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) *Rows 176-177*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable *Biological specimens (blood and urine) are collected. This is included in the consent.*
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial *Rows 370-375*
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site *No financial or other competing interest*
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators *Rows 549-550*
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation *No compensation.* *Insurance: rows 439-441*
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions *Rows 443-451*
	31b	Authorship eligibility guideRows and any intended use of professional writers *Eligibility for authorship in the primary report of the study includes a status of principal or local investigator, a status of study radiologist or at least two of the following: study design, obtaining funding, data collection, data analysis, a key role in management of the study* *No professional writers will be involved.*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code *All images, datasets and statistical codes will be open access.*

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Individualized 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-IMPROD2.0)

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Diagnostics, Patient-centred medicine, Oncology
Keywords:	Magnetic resonance imaging < RADIOLOGY & IMAGING, Urological tumours < UROLOGY, Prostate disease < UROLOGY, Urological tumours

	< ONCOLOGY

Individualized 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-IMPROD2.0)

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References: 25
Tables: 1
Figures: 1
Supplementary documents: 3

Abbreviations

bpMRI	biparametric MRI
GGG	ISUP gleason grade group
mpMRI	multiparametric MRI
PI-RADS	Prostate Imaging–Reporting and Data System
MRI	prostate magnetic resonance imaging
PSA	prostate specific antigen
TRUS	transrectal ultrasonography

Introduction

EAU and NICE guidelines recommend that all men with a suspicion of prostate cancer should undergo pre-biopsy contrast-enhanced i.e. multiparametric prostate magnetic resonance imaging (mpMRI). Also, subsequent prostate biopsies should be performed if MRI is deemed as positive i.e. 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 a large number of 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.

Methods and analysis

This is a prospective, randomised, 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 individualized risk estimation. Men without previous diagnosis of prostate cancer and with abnormal digital rectal examination findings and/ or prostate specific antigen (PSA) between 2.5ug/L and 20.0ug/L are included. We aim at recruiting 830 men who are randomised 1:1 fashion 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) in the control. 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 version 2.0, Jan 04, 2021) is approved by the Ethics Committee of the Hospital District of Southwest Finland (IORG number: 0001744, IBR number: 00002216),

(trial number: 99 /1801/2019). Full reports of this study will be submitted to peer-reviewed journals, mainly urology and radiology.

Registration

The study is registered at clinicaltrials.gov, NCT04287088.

Strengths and limitations of this study

- The biparametric MRI protocol used in this study is a result of profound research on diffusion weighted imaging, data acquisition and post-processing of MRI images.
- All data from previous IMPROD-trials and the MRI protocol are publicly available: development of IMPROD-MRI-protocol (IMPROD-study, http://petiv.utu.fi/improd/) validation of IMPROD-MRI-protocol (multi-IMRPOD-study, http://petiv.utu.fi/multiimprod/) and the MRI protocol (http://mrc.utu.fi/protocols/prostate)
- Although study participants are recruited from several centres, vast majority of them are Caucasian of origin and, therefore, in this respect, the generalization of the results might be limited
- Also, the relatively low prevalence of opportunistic screening of prostate cancer in Finland has definitely an impact on the baseline characteristics of the study population, which may limit the generalization of the results to nationalities with higher levels of screening

Keywords: clinically significant prostate cancer, prostate MRI, risk estimation, shared decision making

Introduction

The incidence of prostate cancer continues to increase worldwide, mainly as a result of population aging, better diagnostic methods and potentially due to real increase in incidence. Although most of the prostate cancers are currently being diagnosed at early stage, at present 30% of prostate cancer in Finland are metastatic at diagnosis (1). In addition, prostate cancer continues to be the second leading cause of cancer death 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 (mpMRI) or biparametric (bpMRI) magnetic resonance imaging 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, EAU, AUA and NICE guidelines also recommend that all men with a suspicion of prostate cancer should undergo pre-biopsy MRI. Also, subsequent prostate biopsies should be performed if MRI is deemed as positive i.e. 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 PCa or reflect upgrading associated with MRI (12). Moreover, several retrospective post-hoc analyses have shown that this approach still leads to a large number of 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 whether to perform biopsies or not is not just about MRI and PSA but a shared decision making accounting for patient characteristics, such as co-morbidities, life-expectancy, and expectations and values (15). Unfortunately, no risk tool utilising prostate MRI and applying a truly individualized approach for each man have been evaluated in prospective clinical trials (16, 17). Therefore, the concept of this trial is to generate a risk calculator, based on MRI and clinical variables describing individual man's 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, multi-centre 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 if 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 individualized 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 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 five years of follow-up between arms

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

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

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 [ISUP 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 five years of follow-up

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

The probability of performing biopsy in experimental arm

Exploratory outcome measures

The number of biopsies and the number of clinically significant prostate cancer detected for each biopsy criteria

Calibration of the model using both Likert and PI-RADS2.1 criteria

Calibration of the model using biomarkers such as the four kallikrein panel

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 in 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 judgment of the responsible urologist
- uni- or bilateral hip prosthesis

Study procedures

Study flow is presented in Figure 1.

Pre-screening (visit 0) After a referral to participating centres, all subjects are evaluated for inclusion and exclusion criteria. If eligible, the subject will receive an information sheet of the study, the information sheet of shared decision-making process, and the 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. After consenting, subjects will complete baseline questionnaires, and baseline blood and urine samples are taken.

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

Randomisation is performed before the TRUS-visit. Subjects are randomised 1:1 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 predefined allocation table implemented by the study statistician (EL). The allocation table will be implemented in REDCap database and is in-accessible once uploaded, hence ensuring allocation concealment.

TRUS-visit (visit 3) The visit follows a protocol used in 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, in addition to systematic biopsies, 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 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, in addition to systematic biopsies, 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 a telephone conference or a visit, 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 biopsies performed, PSA is measured according to local guidelines in each centre but should be performed at least as follows:

Years 1-2: every six 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 treating physician. However, if no such suspicion, re-visit (discussion and consideration of MRI and/ or biopsies), should be performed at least as follows:

1. PSA increases over 20
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, up to 20 years in order to have a 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 Ltd) for bowel preparation. Details of the MRI protocol are described in http://mrc.utu.fi/protocols/prostate. In short, prostate MRI examinations prostate 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 axial and sagittal plane. Single-shot spin-echo echo-planar imaging will be used for DWI and performed in three separate acquisitions using b-values of 500, 1500 and 2000. The total scan time will be approximately 15-16min.

MRI will be interpreted using a IMPROD bpMRI Likert scoring system 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 Likert scoring system. An additional classification of MRI lesions is performed using a modified PI-RADS2.1 system (18).

All reports and data sets are uploaded to the central study server within seven 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). Also, MRI data sets are re-reported by a local

radiologist (at least one year of prostate MRI experience). The readers are *all* blinded to all clinical data such as PSA, age, and subject's past medical history.

TRUS and prostate biopsies

The time 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- 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, four targeted biopsies at maximum are performed.

The risk estimation

To estimate the risk of clinically significant prostate cancer a calculator is developed and implemented in 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 PI-RADS 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

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

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

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

Shared decision making

All consented subjects will be provided an information sheet about 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 subject's values of life, especially related to risk of prostate cancer, its treatment, and treatment related side effects.

In 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 whether to perform biopsies is made.

In addition to the details of the protocol and execution of the trial, the concept of shared decision-making is discussed with all the investigators during the investigator meeting before the start of the trial. Also, the concept of the calculator is discussed, and the use of calculator is demonstrated. Anchors used to guide the shared decision making are presented in Table 1.

Laboratory evaluation

As a part of a 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 (min. 10 ml) are collected to investigate previously characterised biomarkers for prostate cancer detection such as the four kallikrein panel and potential new biomarkers. The blood and urine are 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 five years of experience in genitourinary pathology at the beginning of the trial, using the 2014 International Society of Urological Pathology Modified Gleason Grading System (19). The biopsy specimen is analysed so that pathologists are aware that 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 (MAX-PC) (20). The questionnaire will be collected at baseline, at six, and 12 months.

Adverse events

Since anatomical MRI and DWI are not based on ionizing 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 of 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 the severity of the adverse events will be defined during the MRI-visit by using the CTCAE4.0 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 the 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. Given the fact that TRUS guided biopsies are

potentially harmful to the subject, subjects in the intervention arm may even have less adverse events than subjects in the control arm. Also, leaving a fraction of clinically significant prostate cancer un-diagnosed 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 subject retention rate is low, since all subjects have a suspicion of prostate cancer, and they want to be involved in diagnostic pathway. For the same reason, no protocol deviations are expected. If subject decides to retain from the study or a study deviation occurs, subjects are included in the final analysis if he has undergone prostate MRI and TRUS-visits.

Sample size calculation

The concept of sample size re-calculation was brought up in protocol version 2.0 (Jan 04, 2021). A two-stage sample size calculation was performed: 1, an initial calculation before the start of the trial; 2, a predetermined blinded re-estimation after the recruitment of first 300 subjects.

1. The estimation of 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 will be needed.
2. The re-estimation of sample size is based on 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 the following:

a. with a rate of 20.0% in both arms, 624 participants will be needed
b. with rates of 20.5% (control arm) and 19.5% (intervention arm), 814 subjects will be needed
c. 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 re-calculated sample size was implemented in latest protocol amendment (version 2.1, Sep 21, 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 University of Turku (22, 23). Every participating centre holds a pseudoanomisation key in their own server.

Quantitative analysis of DWI

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

Monoexponential calculation of apparent diffusion coefficient (ADC) 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 $SI(b_0)$ denotes 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 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 randomization strata as covariate. The odds ratio and confidence interval between groups will be applied to the risk in the control group in order to calculate a risk difference and confidence interval. A one-sided 95% confidence interval 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 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 ANCOVA, with randomization strata as covariate. In this case, a two-sided 95% C.I. 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 randomization strata as covariate.

As a descriptive analysis, we will evaluate how biopsy rates in the intervention arm vary by 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 biopsying all men. The results of these analyses will be standardized per 1000 men presenting with elevated PSA. 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-RADS2.1 scores, and also incorporating biomarkers such as the four kallikrein panel.

Patient and Public Involvement

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

Ethics and dissemination

Ethics

The study will be conducted in compliance with the current revision of 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 version 1.0, Sep 17, 2019; latest protocol version 2.1, Sep 21, 2021) is approved by the Ethics Committee of the Hospital District of Southwest Finland (IORG number: 0001744, IBR number: 00002216), (trial number: 99 /1801/2019) and registered (NCT04287088). The amended study protocol (version 2.1) including the recalculated sample size will be send for ethical reading Jun 15, 2021. Any important modifications and amendments to trial protocol will be approved by the Ethics committee and all parties participating the study will be informed.

Data monitoring

A risk-based data monitoring will be performed according to monitoring plan, Supplement 1.

Insurance

The study subjectsts 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 trail, free public access to all data will be provided similar to our previous single- (IMPROD, NCT01864135) and multi-center (Multi-IMRPOD, NCT02241122) trials available at http://petiv.utu.fi/improd/ and http://petiv.utu.fi/multiimprod/, respectively.

Study schedule

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

Study centres

A detailed description of all study centres is provided in https://clinicaltrials.gov/ct2/show/NCT04287088.

Central Finland Central Hospital, Jyväskylä, Finland, 40620

Satakunta Central Hospital, Pori, Finland, 28500

Tampere University Hospital, Tampere, Finland, 33520

Turku University Hospital, Turku, Finland, 20521

Discussion

The trial is designed to show that as a triage test an individualized 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 exists, the study is extremely timely and relevant by establishing a contemporary risk score with data from prostate MRI, and, more importantly, utilising the score in a scenario of shared decision making.

There are some issues to discuss. 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 of course an issue for a debate. 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. Doing 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 grade. The approach is also supported by two recent prostate MRI trials, the PROMIS and the National Cancer Institute (NCI) MRI-trial, which both utilised GGG 3 as a definition of clinically significant prostate cancer (4, 24). Therefore, we consider the approach as justified.

Second, the usage of non-inferiority margin of -8% needs to be addressed. We acknowledge that other prostate MRI trials utilising the non-inferiority setting have used a margin of -5% (5, 25). However, it should be noted that the study designs are not comparable to our study. In the PRECISION and the trial by Klotz et al., novel technology i.e. MRI-guided biopsies was compared to traditional technology the TRUS-guided biopsies and the outcome from the technology dictated patient interventions. In that setting it is crucial that outcome after interventional diagnostics is very similar or even superior to compared to traditional one. In our trial patient characteristics and preferences, and clinicians' recommendation are taken into account, and, therefore we feel that more liberal non-ineriority margin can be accepted. As in the end of the day the patient makes the decision.

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Authors´ contributions

OE was involved in drafting this protocol and participated in the conception, study design, assessments, data interpretation, writing and submission of the manuscript. PB, HA, IJ, DS, and AV contributed to the study design, assessments, data interpretation. MS, AK, HS, KS took part in management, analysis and data interpretation. All authors read and approved the final manuscript. OE takes the responsibility for the integrity of the work as a whole and have access to the final trial dataset.

Competing interest statement.

PT reports representation as a member on the Data Management Committee in the ProScreen trial. AV is named as a co-inventor on US patent #: 9,672,329 for a statistical method to predict the result of prostate biopsy. Patent has been commercialized 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 declared.

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Figure legends

Figure 1. Study flow chart.

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 to 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.

613

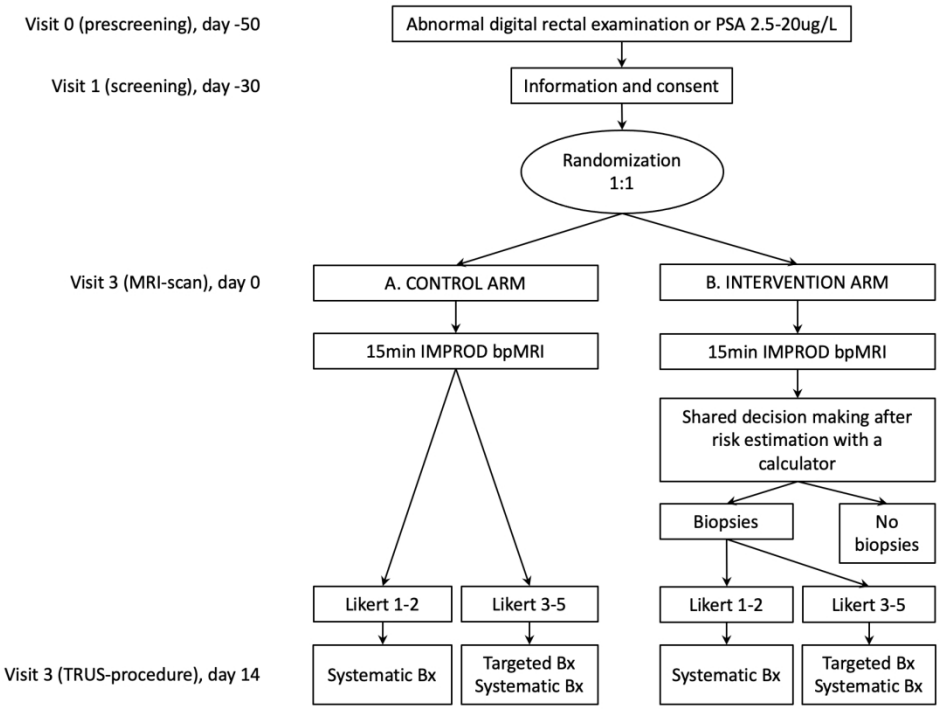

Figure 1. Study flow chart.

340x244mm (144 x 144 DPI)

MONITORING PLAN

1(1)

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

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym *Rows 1-4*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry *Rows 58-60 and Rows 424-430*
	2b	All items from the World Health Organization Trial Registration Data Set *Registered in clinicaltrials.gov, ~~NCT03876912~~ NCT04287088*
Protocol version	3	Date and version identifier *Row 58-60 and Rows 424-430*
Funding	4	Sources and types of financial, material, and other support *Row 558-562*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors *Rows 5-16 and rows 544-550*
	5b	Name and contact information for the trial sponsor *Rows 17-21*
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities *Rows 558-563*
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) *Not applicable. However, a risk-based monitoring will be performed. Please see Item 21a and Supplemental document 1.*

Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention *Research questions: rows 114-119* *Justification and relevant studies: rows 82-113* *Benefits and harms: rows 334-343*
	6b	Explanation for choice of comparators *Rows 106-113*
Objectives	7	Specific objectives or hypotheses *Rows 127-138*
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) *Rows 122-126*
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained *Rows 457-463*
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) *Rows 156-169*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered *Rows 188-200*
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) *No criteria for discontinuation due to harms or disease worsening exists, since the intervention is performed only once, and it is expected that no serious harms are related to it. However, in the control arm TRUS-guided biopsies should be performed to all patients. If a patient requests that biopsies are not be performed, the experimental nature of the shared decision making is discussed. Also, the importance of adhering to the study protocol is discussed. If the patient still refuses to undergo TRUS-guided biopsies, this is permitted. The patient is included to the final analysis normally.*

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) *Not applicable. The one-time intervention is performed in controlled circumstances i.e. in the urological out-patient clinic.*
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial *Rows 205-207*
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseRow, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended *Rows 139-151*
Participant timeRow	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) *Figure 1*
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations *Rows 350-370*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size *Rows 172-179*
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions *Rows 182-187*
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned *Rows 182-187*

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions *Rows 182-187*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how *Open label study. No blinding.*
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial *Open label study. No blinding.*
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol *Rows 372-375*
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols *We expect the frequency of participant non-adherence to be very low due to the nature of the intervention. Also, the follow-up protocol has been made as simple as possible and the follow-up will be performed during normal clinical practice or pre-planned measurements of serum PSA, and automated surveys sent by the REDCap data capture system.* *If non-adherence occurs, the participant will be contacted by the study nurse or study investigator who will motivate the participant to continue the study by the protocol.*
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol *Rows 372-375*
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol *Rows 393-421*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) *Rows 393-421*

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) *We expect the frequency of protocol non-adherence to be very low due to the nature of the intervention. All patients randomised are included to the final analysis even if they never undergo the intervention.*
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed *The study does not expose patients to additional harms or (serious) adverse events regarding the intervention. None of the participants undergo additional procedures compared to normal clinical practice. Therefore, data monitoring committee is not needed. However, to ensure scientific validity, a blinded recalculation of sample size was performed. The analysis was performed by an external statistician not involved in the study. Also, a risk-based monitoring of all main parameters in case report form is performed by an external monitor not involved in the study. See Supplement document 1.*
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial *Rows 351-370*
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct *Not applicable. Adverse events are collected and recorded after the TRUS-guided biopsies. However, no other procedures are performed during the study, spontaneous, study-related adverse events are not expected.*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor *No pre-planned audits.*
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval *Rows 424-432*

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) *Rows 430-432*
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) *Rows 176-177*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable *Biological specimens (blood and urine) are collected. This is included in the consent.*
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial *Rows 370-375*
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site *No financial or other competing interest*
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators *Rows 549-550*
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation *No compensation.* *Insurance: rows 439-441*
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions *Rows 443-451*
	31b	Authorship eligibility guideRows and any intended use of professional writers *Eligibility for authorship in the primary report of the study includes a status of principal or local investigator, a status of study radiologist or at least two of the following: study design, obtaining funding, data collection, data analysis, a key role in management of the study* *No professional writers will be involved.*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code *All images, datasets and statistical codes will be open access.*

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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-IMPROD2.0)

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Diagnostics, Patient-centred medicine, Oncology
Keywords:	Magnetic resonance imaging < RADIOLOGY & IMAGING, Urological tumours < UROLOGY, Prostate disease < UROLOGY, Urological tumours

	< ONCOLOGY

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-IMPROD2.0)

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Word count: 4622 (article), 293 (abstract)
References: 25
Tables: 1
Figures: 1
Supplementary documents: 3

Abbreviations

bpMRI	biparametric MRI
GGG	ISUP gleason grade group
mpMRI	multiparametric MRI
PI-RADS	Prostate Imaging–Reporting and Data System
MRI	prostate magnetic resonance imaging
PSA	prostate specific antigen
TRUS	transrectal ultrasonography

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 pre-biopsy contrast-enhanced, i.e., multiparametric prostate magnetic resonance imaging (mpMRI). Subsequent prostate biopsies should also be performed if MRI is positive i.e., 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 3 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 (PSA) between 2.5 - 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 version 2.0, January 04, 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.

Registration

The study is registered at ClinicalTrials.gov, NCT04287088.

Strengths and limitations of this study

- A strength of the study is the use of well-established IMPROD biparametric MRI protocol (http://mrc.utu.fi/protocols/prostate), which is a result of long-term research on diffusion weighted imaging, data acquisition and post-processing 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.

Keywords: clinically significant prostate cancer, prostate MRI, risk estimation, shared decision making

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 cancer**s** in Finland now are metastatic at diagnosis (1). Prostate cancer also continues to be the second leading cause of cancer death**s** 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 magnetic resonance imaging (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 pre-biopsy MRI. Also, subsequent prostate biopsies should be performed if MRI is deemed positive, i.e. 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 co-morbidities, life-expectancy and expectations and values (15). Unfortunately, no risk tool utilising 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, multi-centre 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 five 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 five years of follow-up

Total score of Memorial Sloan Kettering Cancer Centre Anxiety questionnaire in the control and intervention arms at baseline, at six 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/mm3

Calibration of the model using both Likert and PI-RADS2.1 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 -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 judgment of the responsible urologist
- Uni- 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 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 (Supplement 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 in-accessible 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 six 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 re-visit (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 a 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 Ltd) for bowel preparation. Details of the MRI protocol are described in http://mrc.utu.fi/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, 100, 200, 350, 500 s/mm2; 0, 1500 s/mm2; and 0, 2000 s/mm2. Apparent diffusion coefficient (ADC) maps are calculated from each acquisition, but the one calculated from the acquisition with low b-values (0-500 s/mm2) is considered to be the most reliable. The total scan time will be approximately 15-16 minutes.

MRI will be interpreted using an 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-RADS2.1 system (18).

All reports and data sets are uploaded to the central study server within seven 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 re-reported retrospectively by a local radiologist in each centre (at least one year of prostate MRI experience). The readers are *all* blinded to all clinical data such as PSA, age and the subject's past 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- 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 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 PI-RADS 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

$$\begin{aligned} X\beta = {} & -6.97314184 + 0.064172722 * \{Age\} + -0.008141264 * \{Prostate\ Volume\} \\ & + -0.182694534 * \{PSA\} + 0.006136442 * \{PSASpline2\} + \\ & -0.013049396 * \{PSASpline3\} + 1.37637197 * \{Likert == 3\} \\ & + 2.50939431 * \{Likert == 4\} + 4.07331563 * \{Likert == 5\} \end{aligned}$$

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

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

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 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 five 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 (MAX-PC) (20). The questionnaire will be collected at baseline, at six months and at 12 months.

Adverse events

Since anatomical MRI and DWI are not based on ionizing 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 CTCAE4.0 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 un-diagnosed 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 re-calculation was brought up in protocol version 2.0 (January 04, 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:
    a. with a rate of 20.0% in both arms, 624 participants will be needed
    b. with rates of 20.5% (control arm) and 19.5% (intervention arm), 814 subjects will be needed
    c. 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 re-calculated sample size was implemented in the latest protocol amendment (version 2.1, September 21, 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 (ADC) 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 $SI(b_0)$ denotes 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% confidence interval (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 odds ratio and confidence interval between groups will be applied to the risk in the control group to calculate a risk difference and confidence interval. A one-sided 95% confidence interval 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 ANCOVA, with randomisation strata as covariate. In this case, a two-sided 95% C.I. 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-RADS2.1 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 version 1.0, September 17, 2019; latest protocol version 2.1, September 21, 2021) is approved by the Ethics Committee of the Hospital District of Southwest Finland (IORG number: 0001744, IBR number: 00002216), (trial number: 99 /1801/2019) and registered (NCT04287088). Any important modifications and amendments to trial protocol will be approved by the Ethics Committee and all parties participating in the study will be informed.

Data monitoring

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

Insurance

The study subjects~~ts~~ 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://clinicaltrials.gov/ct2/show/NCT04287088.

Central Finland Central Hospital, Jyväskylä, Finland, 40620

Satakunta Central Hospital, Pori, Finland, 28500

Tampere University Hospital, Tampere, Finland, 33520

Turku University Hospital, Turku, Finland, 20521

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, utilising 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 (NCI) MRI-trial, which both utilised 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 utilising the non-inferiority setting have adopted a margin of -5% (5, 25). However, the study designs are not comparable to our study. In the PRECISION and the trial by Klotz et al., novel technology, i.e. MRI-guided biopsies, was compared to 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 to 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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Authors´ contributions

Otto Ettala, Ivan Jambor, Ileana Montoya Perez, Kari Syvänen, Pekka Taimen, Jani Saunavaara, Daniel D. Sjöberg, Andrew Vickers, Hannu Aronen, Peter J. Boström contributed to the planning of the study. Otto Ettala, Ivan Jambor, Marjo Seppänen, Antti Kaipia, Heikki Seikkula, Kari Syvänen, Pekka Taimen, Janne Verho, Aida Steiner, Ekaterina Saukko, Peter J. Boström participated in the conduction of the study. All authors contributed to the reporting of the study.

Competing interest statement.

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 #: 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.

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Figure legends

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.

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 to 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.

635

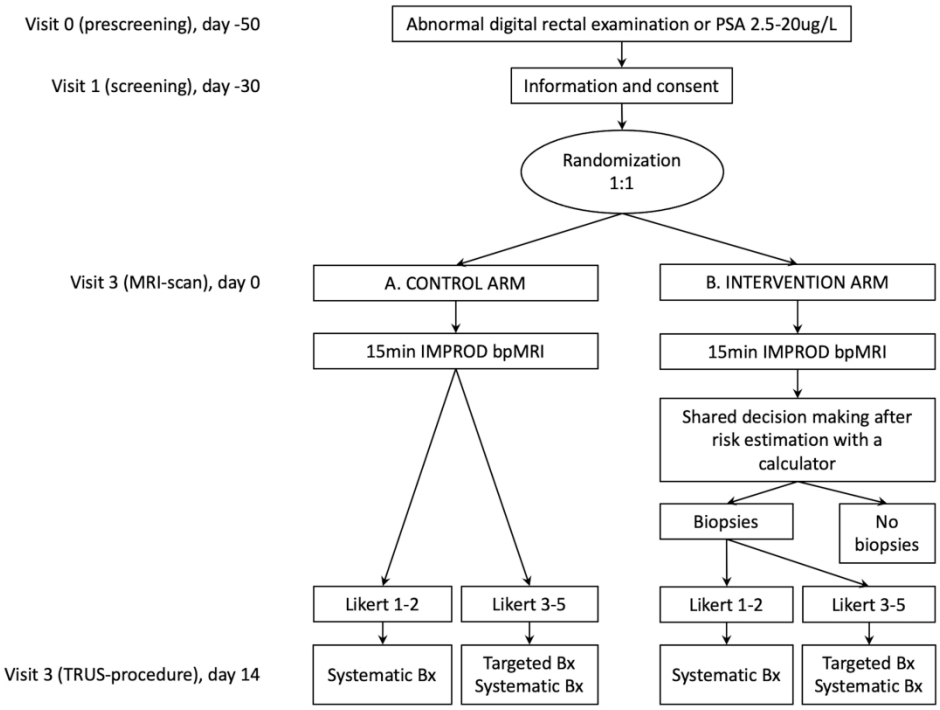

Figure 1. Study flow chart. Bx, prostate biopsies; IMPROD bpMRI, bi-parametric magnetic resonance imaging of prostate performed according to IMPROD MRI protocol (http://mrc.utu.fi/protocols/prostate); PSA, prostate specific antigen; TRUS, transrectal ultrasound of prostate.

340x244mm (300 x 300 DPI)

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

1(1)

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

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym *Rows 1-4*
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry *Rows 58-60 and Rows 424-430*
	2b	All items from the World Health Organization Trial Registration Data Set *Registered in clinicaltrials.gov, ~~NCT03876912~~ NCT04287088*
Protocol version	3	Date and version identifier *Row 58-60 and Rows 424-430*
Funding	4	Sources and types of financial, material, and other support *Row 558-562*
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors *Rows 5-16 and rows 544-550*
	5b	Name and contact information for the trial sponsor *Rows 17-21*
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities *Rows 558-563*
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) *Not applicable. However, a risk-based monitoring will be performed. Please see Item 21a and Supplemental document 1.*

Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention *Research questions: rows 114-119* *Justification and relevant studies: rows 82-113* *Benefits and harms: rows 334-343*
	6b	Explanation for choice of comparators *Rows 106-113*
Objectives	7	Specific objectives or hypotheses *Rows 127-138*
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) *Rows 122-126*
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained *Rows 457-463*
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) *Rows 156-169*
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered *Rows 188-200*
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) *No criteria for discontinuation due to harms or disease worsening exists, since the intervention is performed only once, and it is expected that no serious harms are related to it. However, in the control arm TRUS-guided biopsies should be performed to all patients. If a patient requests that biopsies are not be performed, the experimental nature of the shared decision making is discussed. Also, the importance of adhering to the study protocol is discussed. If the patient still refuses to undergo TRUS-guided biopsies, this is permitted. The patient is included to the final analysis normally.*

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) *Not applicable. The one-time intervention is performed in controlled circumstances i.e. in the urological out-patient clinic.*
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial *Rows 205-207*
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseRow, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended *Rows 139-151*
Participant timeRow	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) *Figure 1*
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations *Rows 350-370*
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size *Rows 172-179*
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions *Rows 182-187*
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned *Rows 182-187*

Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions *Rows 182-187*
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how *Open label study. No blinding.*
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial *Open label study. No blinding.*

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol *Rows 372-375*
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols *We expect the frequency of participant non-adherence to be very low due to the nature of the intervention. Also, the follow-up protocol has been made as simple as possible and the follow-up will be performed during normal clinical practice or pre-planned measurements of serum PSA, and automated surveys sent by the REDCap data capture system.* *If non-adherence occurs, the participant will be contacted by the study nurse or study investigator who will motivate the participant to continue the study by the protocol.*
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol *Rows 372-375*
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol *Rows 393-421*
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) *Rows 393-421*

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) *We expect the frequency of protocol non-adherence to be very low due to the nature of the intervention. All patients randomised are included to the final analysis even if they never undergo the intervention.*
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed *The study does not expose patients to additional harms or (serious) adverse events regarding the intervention. None of the participants undergo additional procedures compared to normal clinical practice. Therefore, data monitoring committee is not needed. However, to ensure scientific validity, a blinded recalculation of sample size was performed. The analysis was performed by an external statistician not involved in the study. Also, a risk-based monitoring of all main parameters in case report form is performed by an external monitor not involved in the study. See Supplement document 1.*
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial *Rows 351-370*
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct *Not applicable. Adverse events are collected and recorded after the TRUS-guided biopsies. However, no other procedures are performed during the study, spontaneous, study-related adverse events are not expected.*
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor *No pre-planned audits.*
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval *Rows 424-432*

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) *Rows 430-432*
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) *Rows 176-177*
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable *Biological specimens (blood and urine) are collected. This is included in the consent.*
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial *Rows 370-375*
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site *No financial or other competing interest*
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators *Rows 549-550*
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation *No compensation.* *Insurance: rows 439-441*
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions *Rows 443-451*
	31b	Authorship eligibility guideRows and any intended use of professional writers *Eligibility for authorship in the primary report of the study includes a status of principal or local investigator, a status of study radiologist or at least two of the following: study design, obtaining funding, data collection, data analysis, a key role in management of the study* *No professional writers will be involved.*
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code *All images, datasets and statistical codes will be open access.*

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.