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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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Keywords:	Magnetic resonance imaging < RADIOLOGY & IMAGING, Urological tumours < UROLOGY, Prostate disease < UROLOGY



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4 1 Individualized non-contrast MRI-based risk estimation and  
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7 2 shared decision making in men with a suspicion of prostate  
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11 3 cancer – A multi-centre randomised controlled trial (multi-  
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14 4 IMPROD2.0) – a study protocol  
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27 **Abbreviations**

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

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## 35 **Introduction**

36 EAU and NICE guidelines recommend that all men with a suspicion of prostate cancer  
37 should undergo pre-biopsy contrast-enhanced i.e. multiparametric prostate magnetic  
38 resonance imaging (mpMRI). Also, subsequent prostate biopsies should be performed if MRI  
39 is deemed as positive i.e. Prostate Imaging–Reporting and Data System (PI-RADS) scores 3-  
40 5. However, several retrospective post-hoc analyses have shown that this approach still leads  
41 to a large number of unnecessary biopsy procedures. For example, 88-96% of men with PI-  
42 RADS 3 finding are still diagnosed with clinically non-significant prostate cancer or no  
43 cancer at all.

## 44 **Methods and analysis**

45 This is a prospective, randomised, controlled, multicentre trial to demonstrate non-inferiority  
46 in clinically significant cancer detection rate between men undergoing prostate biopsies post-  
47 MRI and men undergoing prostate biopsies post-MRI only after a shared decision based on  
48 individualized risk estimation. Men without previous diagnosis of prostate cancer and with  
49 abnormal digital rectal examination findings and/ or prostate specific antigen (PSA) between  
50 2.5ug/L and 20.0ug/L are included. We aim at recruiting 830 men who are randomised 1:1  
51 fashion into control (all undergo biopsies after MRI) and intervention arms (the decision to  
52 perform biopsies is based on risk estimation and shared decision making). The primary  
53 outcome of the study is the proportion of men with clinically significant prostate cancer  
54 (Gleason 4+3 prostate cancer or higher) in the control. We will also compare the overall  
55 biopsy rate, benign biopsy rate, and the detection of non-significant prostate cancer between  
56 the two study groups.

## 57 **Ethics and dissemination**

58 The study (protocol version 2.0, Jan 04, 2021) is approved by the Ethics Committee of the  
59 Hospital District of Southwest Finland (IORG number: 0001744, IBR number: 00002216),

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

## 62 **Registration**

63 The study is registered at [clinicaltrials.gov](http://clinicaltrials.gov), NCT04287088.

## 64 **Strengths and limitations of this study**

- 65 • **1** The biparametric MRI protocol used in the study is a result of systematic research  
66 on diffusion weighted imaging, data acquisition and post-processing of MRI imaging.
- 67 • **2** Public availability of all data from previous testing (IMPROD-study) and validation  
68 (multi-IMRPOD-study) studies (<http://petiv.utu.fi/improd/>, and  
69 <http://petiv.utu.fi/multiimprod/>) and the MRI protocol  
70 (<http://mrc.utu.fi/protocols/prostate>)
- 71 • **3** Although study participants are recruited from several centres, vast majority of them  
72 are Caucasian of origin and, therefore, in this respect, the generalization of the results  
73 might be limited
- 74 • **4** Also, the relatively low prevalence of opportunistic screening of prostate cancer in  
75 Finland has definitely an impact on the baseline characteristics of the study  
76 population, which may limit the generalization of the results to nationalities with  
77 higher levels of screening

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

80

## 81 Introduction

82 The incidence of prostate cancer continues to increase worldwide, mainly as a result of  
83 population aging, better diagnostic methods and potentially due to real increase in  
84 incidence. Although most of the prostate cancers are currently being diagnosed at early  
85 stage, at present 30% of prostate cancer in Finland are metastatic at diagnosis (1). In  
86 addition, prostate cancer continues to be the second leading cause of cancer death in men  
87 calling for better diagnostic methods (2).

88 Traditionally the diagnosis of prostate cancer is mostly based on the result of systematic  
89 transrectal ultrasonography (TRUS) guided biopsies (3). Recently, several prospective  
90 trials claimed that an alternative pathway using multiparametric (mpMRI) and biparametric  
91 (bpMRI) magnetic resonance imaging as a triage test reduces unnecessary biopsies,  
92 decreases the detection of clinically non-significant prostate cancer, and improves the  
93 detection of clinically significant prostate cancer (4-11). Based on these trials, EAU, AUA  
94 and NICE guidelines recommend that all men with a suspicion of prostate cancer should  
95 undergo pre-biopsy MRI. Also, subsequent prostate biopsies should be performed if MRI  
96 is deemed as positive i.e. PI-RADS scores 3-5 (3).

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



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3 106 The decision whether to perform biopsies or not is not just about MRI and PSA but a shared  
4  
5 107 decision making accounting for patient characteristics, such as co-morbidities, life-  
6  
7 108 expectancy, and expectations and values (15). Unfortunately, no risk tool applying a truly  
8  
9 109 individualized approach for each man have been evaluated in prospective clinical trials.  
10  
11 110 Therefore, the concept of this trial is to generate a risk calculator, based on MRI and clinical  
12  
13 111 variables describing individual man's risk of having clinically significant prostate cancer.  
14  
15 112 This risk-estimation is then used as a basis for discussion of the benefits and potential harms  
16  
17 113 of proceeding with the prostate biopsy.  
18  
19 114 The aim of this prospective, randomised, multi-centre controlled, trial is to demonstrate non-  
20  
21 115 inferiority in clinically significant cancer detection rate between men undergoing prostate  
22  
23 116 biopsies post-MRI and men undergoing prostate biopsies post-MRI only after a shared  
24  
25 117 decision based on risk estimation. The aim is also to compare if there is a difference compare  
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27 118 the overall biopsy rate, benign biopsy rate, and the detection of non-significant prostate  
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29 119 cancer between the two study groups.  
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3 121 **Methods and analysis**  
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6 122 ***Study design***  
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8 123 This is a prospective, randomised (allocation 1:1), controlled, multicentre trial to demonstrate  
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10 124 non-inferiority in clinically significant cancer detection rate between men undergoing  
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12 125 prostate biopsies post-MRI and men undergoing prostate biopsies post-MRI only after a  
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15 126 shared decision based on individualized risk estimation.  
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19 127 ***Objectives***

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21 128 ***Primary objective***  
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23 129 A non-inferiority between significant prostate cancer detection rate in men undergoing  
24  
25 130 prostate biopsies after post-MRI (control arm) and men undergoing prostate biopsies post-  
26  
27 131 MRI only after a shared decision based on individualised risk estimation (intervention arm)  
28  
29

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31 132 ***Secondary objectives***  
32

33 133 To compare the detection rate of clinically non-significant prostate cancer, and benign  
34  
35 134 biopsies between arms.  
36

37  
38 135 To compare biopsy rates between arms.  
39

40 136 To compare the detection rate of clinically significant prostate cancer during the five year of  
41  
42 137 follow-up between arms  
43

44  
45 138 To study and compare anxiety related to the prostate cancer between arms  
46  
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48 139 ***Outcomes***

49  
50 140 ***Primary outcome***  
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52  
53 141 The proportion of men with clinically significant prostate cancer (Gleason 4+3 prostate  
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55 142 cancer or higher) in the control and intervention arms after primary diagnostic pathway  
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3 143 *Secondary outcome*  
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5 144 The proportion of men with clinically non-significant prostate cancer (Gleason 3+3 and  
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8 145 Gleason 3+4) and benign biopsies in the control and intervention arms after primary  
9  
10 146 diagnostic pathway

11  
12 147 The proportion of men undergoing biopsies.

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14  
15 148 The proportion of men with clinically significant prostate cancer (Gleason 4+3 prostate  
16  
17 149 cancer or higher) in the control and intervention arms during the five years of follow-up

18  
19 150 Total score of Memorial Sloan Kettering Cancer Centre Anxiety questionnaire in the control  
20  
21 151 and intervention arms at baseline, at six and 12 months  
22  
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25 152 ***Sample selection***

26  
27 153 All men with clinical suspicion of prostate cancer living in the Hospital Districts of  
28  
29 154 Southwest Finland, Satakunta, Keski-Suomi, and Pirkanmaa are potentially eligible. The  
30  
31 155 study will enrol 830 subjects allocated in two groups.  
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35 156 *Inclusion criteria*

36  
37 157 - Age: 18 years or older

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39 158 - Language spoken: Finnish or Swedish

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42 159 - Clinical suspicion of prostate cancer, based on: serum level of PSA from 2.5 ng/ml to  
43  
44 160 20.0 ng/ml and/or abnormal digital rectal examination

45  
46 161 - Mental status: The subject must be able to understand the meaning of the study

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49 162 - Informed consent: The subject must sign the appropriate Ethics Committee (EC)  
50  
51 163 approved informed consent documents in the presence of the designated staff  
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54 164 *Exclusion criteria*

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56  
57 165 - previous diagnosis of prostate cancer

58  
59 166 - any contraindications for MRI  
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3 167 - any other conditions that might compromise subject's safety, based on the clinical  
4  
5 168 judgment of the responsible urologist  
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8 169 - uni- or bilateral hip prosthesis  
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11 170 ***Study procedures***  
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13 171 Study flow is presented in Figure 1.  
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3 172 *Pre-screening (visit 0)* After a referral to participating centres, all subjects are evaluated for  
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5 173 inclusion and exclusion criteria. If eligible, the subject will receive an information sheet of  
6  
7 174 the study, the information sheet of shared decision-making process, and the time for the  
8  
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10 175 screening visit.

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13 176 *Screening visit (visit 1)* During the screening visit at the urology out-patient clinic the study  
14  
15 177 design is discussed in detail with the local investigator (urologist). If willing to participate,  
16  
17 178 the subject will sign the informed consent. After consenting, subjects will complete baseline  
18  
19 179 questionnaires, and baseline blood and urine samples are taken.

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23 180 *MRI scan (visit 2)* MRI scan is performed according to the guidelines in each centre.  
24  
25 181 However, for study related requirements please refer to chapter “Study instruments”.

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28  
29 182 *Randomisation* is performed before the TRUS-visit. Subjects are randomised 1:1 into two  
30  
31 183 arms: the control arm, and the intervention arm. Randomisation will be stratified by  
32  
33 184 categorised baseline PSA:  $<4$  ng / mL, 4-9.9 ng / mL,  $\geq 10$  ng / mL. Randomisation will be  
34  
35 185 performed using predefined allocation table implemented by the study statistician (EL). The  
36  
37 186 allocation table will be implemented in RedCap database and is in-accessible once uploaded,  
38  
39 187 hence ensuring allocation concealment.

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44 188 *TRUS-visit (visit 3)* The visit follows a protocol used in normal outpatient clinic. MRI results  
45  
46 189 are discussed with the subject.

47  
48 190 *The control arm:* All subjects undergo TRUS guided biopsies. In subjects with Likert  
49  
50 191 scores of 1-2, 12-core systematic TRUS guided systematic biopsies are performed. In  
51  
52 192 subjects with Likert 3-5 score lesions, in addition to systematic biopsies, two targeted biopsy  
53  
54 193 cores are taken from each lesion (up to two lesions).

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57 194 *The intervention arm:* The probability of clinically significant prostate cancer is  
58  
59 195 estimated using the risk calculator. The risk, benefits and harms of prostate biopsy and

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3 196 patient values are discussed. A shared decision whether to perform biopsies is made. If  
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5 197 biopsies are to be performed, in subjects with IMPROD bpMRI likert scores of 1-2, 12-core  
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7 198 systematic TRUS guided biopsies are performed and in subjects with Likert 3-5 score lesions,  
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10 199 in addition to systematic biopsies, two targeted biopsy cores are taken from each lesion (up to  
11  
12 200 two lesions). If biopsies are not performed, subjects are referred for a PSA follow-up.

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15 201 *Biopsy results (visit 4)* According to clinical guidelines in each centre, either a telephone  
16  
17 202 conference or a visit, subject is contacted to discuss the results of the biopsies and biopsy-  
18  
19 203 related adverse events. If biopsies were not taken, subjects are informed about follow-up  
20  
21 204 procedures.

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25 205 *Treatment* If diagnosed with prostate cancer, the subject and the treating physician, as part of  
26  
27 206 the multi-disciplinary team, will decide the treatment modality according to local, national  
28  
29 207 and international guidelines.

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33 208 *Follow-up* In subjects with benign biopsies or in subjects with no biopsies performed PSA is  
34  
35 209 measured according to local guidelines in each centre but should be performed at least as  
36  
37 210 follows:

38  
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40 211 Years 1-2: every six months

41  
42 212 Years 3-5: every 12 months

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44  
45 213 Thereafter, follow-up is performed according to clinical guidelines in every centre. If  
46  
47 214 suspicion of prostate cancer persists after initial benign biopsies or in subjects with no  
48  
49 215 biopsies taken, the decision to perform biopsies and/or MRI is according to local guidelines  
50  
51 216 in each centre and/ or treating physician. However, if no such suspicion, re-visit (discussion  
52  
53 217 and consideration of MRI and/ or biopsies), should be performed at least as follows:

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55  
56 218 1. PSA increases over 20

57  
58 219 2. PSA doubles during the follow-up  
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3 220 A long-term follow-up of all subjects will be performed from medical charts, Finnish national  
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5 221 registries and if needed, contacting the subject, up to 20 years in order to have a  
6  
7 222 comprehensive data concerning incident prostate cancer in subjects without a diagnosis of  
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9 223 prostate cancer and clinical end points (biochemical relapse, metastasis, death) in subjects  
10  
11 224 with diagnosed prostate cancer.  
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### 15 225 ***Study instruments***

#### 16 226 *Prostate MRI*

17  
18 227 Subjects scheduled for the MRI examination will receive sodium picosulfate drops  
19  
20 228 (Laxoberon, Boehringer Ingelheim GmbH) and a Bisacodyl enema (Toilax, Orion Pharma  
21  
22 229 Ltd) for bowel preparation. Details of the MRI protocol are described in  
23  
24 230 <http://mrc.utu.fi/protocols/prostate>. In short, prostate MRI examinations prostate will be  
25  
26 231 performed using a 1.5T or 3T MR scanner. Body array coils will be used for image data  
27  
28 232 acquisition. No endorectal coil will be used. T2-weighted anatomic imaging will be  
29  
30 233 performed in axial and sagittal plane. Single-shot spin-echo echo-planar imaging will be used  
31  
32 234 for DWI and performed in three separate acquisitions. The total scan time will be  
33  
34 235 approximately 15-16min.  
35  
36 236 MRI will be interpreted using a IMPROD bpMRI Likert scoring system follows: 1,  
37  
38 237 significant cancer is highly unlikely to be present; 2, significant cancer is unlikely to be  
39  
40 238 present; 3, significant cancer is equivocal; 4, significant cancer is likely to be present; 5,  
41  
42 239 significant cancer is highly likely to be present (7, 8). The calculator and clinical judgement  
43  
44 240 are based on Likert scoring system. An additional classification of MRI lesions is performed  
45  
46 241 using a modified PI-RADS2.1 system (16).  
47  
48 242 All reports and data sets are uploaded to the central study server within seven days of the  
49  
50 243 MRI scan. A standardised form to report the MRI is used (16). All MRI data sets are reported  
51  
52 244 centrally by two designated central readers (IJ, JV). Also, MRI data sets are re-reported by a  
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3 245 local radiologist (at least one year of prostate MRI experience). The central readers are  
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5 246 blinded to all clinical data such as PSA, age, and subject's past medical history.  
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8  
9 247 *TRUS and prostate biopsies*

10  
11 248 The time period between the MRI examination and TRUS guided biopsy will be a maximum  
12  
13 249 of 4 weeks. Prophylactic antibiotic treatment is given according to institutional guidelines,  
14  
15 250 and the regimen used is recorded. If suspicious MRI-lesions are present, targeted biopsies are  
16  
17 251 performed followed by systematic TRUS guided 12-core biopsies. Targeting is performed  
18  
19 252 either with cognitive- or MRI-fusion according to clinical guidelines in each centre. A  
20  
21 253 maximum of two cores will be taken from each MRI suspicious lesion. If more than two  
22  
23 254 suspicious lesions are observed only two of most suspicious ones are targeted. Therefore,  
24  
25 255 four targeted biopsies at maximum are performed. A post-hoc analysis on inter-operator  
26  
27 256 variability will be performed.  
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33 257 *The risk estimation*

34  
35 258 To estimate the risk of clinically significant prostate cancer a calculator is developed and  
36  
37 259 implemented in eCRF, the RedCap. The calculator is based on our previous prospective MRI  
38  
39 260 studies (the IMPROD trial, NCT01864135 and the multi-IMPROD trial NCT02241122) and  
40  
41 261 it predicts the presence of biopsy Gleason  $\geq 4+3$  prior to prostate biopsy, using information  
42  
43 262 on subject age, prostate volume, total PSA, 5-ARI use, and PI-RADS score to make  
44  
45 263 predictions.  
46  
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- 49 264 1. If the subject uses 5-ARI, modifications are needed to the subject's PSA and prostate  
50  
51 265 volume.  
52  
53  
54 266     ○ Multiple PSA by 2  
55  
56 267     ○ Divide Prostate Volume by 0.7  
57  
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59  
60 268 2. Calculate cubic spline terms for PSA.



- 269 ○ The knot locations are  $t = (3.80, 6.60, 9.40, 18.47)$ , where  $t_1 = 3.80$ ,  $t_2 = 6.60$ . etc.

$$270 \quad PSASpline_{j+1} = \max(PSA - t_j, 0)^3 - \max(PSA - t_3, 0)^3 * \frac{t_4 - t_j}{t_4 - t_3} + \max(PSA - t_4, 0)^3$$

$$* \frac{t_4 - t_j}{t_4 - t_3} \text{ for } j = 1, 2$$

- 271 3. Calculate the regression model linear predictor

$$272 \quad X\beta = -6.97314184 + 0.064172722 * \{Age\} + -0.008141264 * \{Prostate\ Volume\}$$

$$+ -0.182694534 * \{PSA\} + 0.006136442 * \{PSASpline2\} +$$

$$-0.013049396 * \{PSASpline3\} + 1.37637197 * \{Likert == 3\}$$

$$+ 2.50939431 * \{Likert == 4\} + 4.07331563 * \{Likert == 5\}$$

- 273 4. Convert linear predictor to risk of Gleason  $\geq 3$  on biopsy (will be a probability  
274 between 0 and 1)

$$275 \quad Risk = \frac{e^{X\beta}}{1 + e^{X\beta}}$$

### 276 *Shared decision making*

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

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

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

1  
2  
3 287 the start of the trial. Also, the concept of the calculator is discussed, and the use of calculator  
4  
5 288 is demonstrated. Anchors used to guide the shared decision making are presented in Table 1.  
6  
7

8 289

9  
10  
11 290 *Laboratory evaluation*

12  
13 291 As a part of a routine clinical practice blood tests including serum PSA, free-to-total PSA  
14  
15 292 ratio, standard and differential blood counts, serum alkaline phosphatase, and serum  
16  
17 293 testosterone are collected.  
18  
19

20  
21 294 *Serum and urine biomarkers*

22  
23 295 Anticoagulated EDTA plasma (10 ml) and urine (min. 10 ml) are collected to investigate  
24  
25 296 previously characterised biomarkers for prostate cancer detection such as the four kallikrein  
26  
27 297 panel and potential new biomarkers. The blood and urine are drawn before the TRUS-visit.  
28  
29 298 Subjects give their written consent to the sampling.  
30  
31

32  
33  
34 299 *Histopathologic evaluation of tissue samples*

35  
36 300 All histopathological biopsies were reported separately (core length, cancer length, Gleason  
37  
38 301 grade) at each centre by expert pathologists, each with at least five years of experience in  
39  
40 302 genitourinary pathology at the beginning of the trial, using the 2014 International Society of  
41  
42 303 Urological Pathology Modified Gleason Grading System (17). The biopsy specimen is  
43  
44 304 analysed so that pathologists are aware that subjects are part of the study. However, they are  
45  
46 305 not aware of the exact details of the study protocol, and they are blinded to the sequence of  
47  
48 306 individual biopsy cores.  
49  
50

51  
52  
53 307 *Definition of overall Gleason grade and clinically significant prostate cancer*

54  
55 308 Clinically significant prostate cancer is defined as Gleason 4+3 or higher in overall Gleason  
56  
57 309 grade which is defined for each subject as the combination of the most frequent Gleason  
58  
59 310 grade and the highest Gleason grade.  
60

1  
2  
3 311 *Questionnaire*  
4

5 312 Prostate cancer related anxiety is measured with Memorial Anxiety Score for Prostate  
6  
7 313 Cancer anxiety score (MAX-PC) (18). The questionnaire will be collected at baseline, at six,  
8  
9 and 12 months.  
10  
11

12  
13 315 *Adverse events*  
14

15 316 Since anatomical MRI and DWI are not based on ionizing radiation, the risk for adverse  
16  
17 events in properly selected subjects is considered minimal if any. Claustrofobic subjects will  
18  
19 be excluded from the study. Commonly no side-effects or only mild side-effects are  
20  
21 associated with taking of sodium picosulfat drops (Laxoberon, Boehringer Ingelheim GmbH)  
22  
23 or Bisacodyl enema (Toilax, Orion Pharma Ltd) for bowel preparation but it is recommended  
24  
25 for subjects to maintain their water balance with increased water intake. No MRI contrast  
26  
27 agents will be given to the subjects. The type and the severity of the adverse events will be  
28  
29 defined during the MRI-visit by using the CTCAE4.0 classification.  
30  
31

32 324 TRUS guided biopsies are associated with risk of complications, the most important being  
33  
34 serious infections (0.5%) and bleeding (4%) complications. Adverse events related to TRUS  
35  
36 and prostate biopsies are recorded for 14 days after the biopsies. The type and the severity of  
37  
38 the complication are defined and recorded. The severity will be defined by using the Clavien-  
39  
40 Dindo classification (19).  
41  
42  
43  
44

45  
46 329 *Potential benefits and harms*  
47

48  
49 330 Potential harms include adverse events related to TRUS guided biopsies and the fact that a  
50  
51 fraction of clinically significant prostate cancer is left undiagnosed in subjects not undergoing  
52  
53 TRUS guided biopsies in the intervention arm. However, the study does not expose subjects  
54  
55 to any extra procedures since in normal clinical practice all included subjects would undergo  
56  
57 bpMRI and subsequent TRUS guided biopsies. Given the fact that TRUS guided biopsies are  
58  
59  
60

1  
2  
3 335 potentially harmful to the subject, subjects in the intervention arm may even have less  
4  
5 336 adverse events than subjects in the control arm. Also, leaving a fraction of clinically  
6  
7 337 significant prostate cancer un-diagnosed in the intervention arm does not harm the subjects  
8  
9 338 since a robust follow-up after the initial diagnostic procedure is included in the study design.  
10  
11  
12

### 13 339 ***Subject retention and protocol deviation***

14  
15 340 It is expected that subject retention rate is low, since all subjects have a suspicion of prostate  
16  
17 341 cancer and they want to be involved in diagnostic pathway. For the same reason, no protocol  
18  
19 342 deviations are expected. If subject decides to retain from the study or a study deviation  
20  
21 343 occurs, subjects are included in the final analysis if he has undergone prostate MRI and  
22  
23 344 TRUS-visits.  
24  
25  
26  
27

### 28 345 ***Sample size calculation***

29  
30 346 A two-stage sample size calculation was performed: 1, an initial calculation before the start  
31  
32 347 of the trial; 2, a predetermined blinded re-estimation after the recruitment of first 300  
33  
34 348 subjects.  
35  
36

- 37 349 1. The estimation of clinically significant prostate cancer rate was based on data from our  
38  
39 350 previous prospective trials (the IMPROD and the multi-IMPROD) (7, 8). Using a  
40  
41 351 clinically significant cancer rate of 25% in both arms, a non-inferiority margin of -8%,  
42  
43 352 a beta-level of 0.2, and an alpha-level of 0.05, it was estimated that 600 subjects will  
44  
45 353 be needed.  
46  
47  
48 354 2. The re-estimation of sample size was based on observation that clinically significant  
49  
50 355 prostate cancer was present in 20% of the first 300 subjects. Also, regarding the  
51  
52 356 potential difference in clinically significant cancer rates between the arms, the sample  
53  
54 357 size was evaluated in three different scenarios. Using a non-inferiority margin of -8%,  
55  
56 358 a beta-level of 0.2, and an alpha-level of 0.05, the scenarios were the following:  
57  
58  
59  
60

- 1  
2  
3 359 a. with a rate of 20.0% in both arms, 624 participants will be needed  
4  
5 360 b. with rates of 20.5% (control arm) and 19.5% (intervention arm), 814 subjects  
6  
7 will be needed  
8 361  
9  
10 362 c. with rates of 21.0% (control arm) and 19.0% (intervention arm), 1104 subjects  
11  
12 will be needed  
13 363

14 364 It was decided that the final sample size will be calculated according to scenario b. Using a  
15  
16 dropout rate of 2%, 830 subjects will be recruited.  
17 365  
18  
19

## 20 366 **Data handling**

### 21 22 367 *RedCap database*

23  
24 368 In addition to medical charts in each participating centre, study data are collected, managed  
25  
26 and stored pseudoanonymised in REDCap electronic data capture tool hosted at University of  
27 369  
28  
29 370 Turku (20, 21). Every participating centre holds a pseudoanonymisation key in their own server.  
30  
31

### 32 33 371 *Qualitative analysis of MRI data*

34  
35 372 Prostate cancer in the peripheral zone appears as round or ill-defined, low-signal-intensity  
36  
37 373 foci on T2-weighted images while central gland tumors appear as homogeneous low signal  
38  
39 374 intensity lesions with irregular margins and without a capsule. Invasion of the pseudocapsule  
40  
41 with lenticular extension into the urethra or anterior fibromuscular zone is commonly seen on  
42 375  
43  
44 376 T2-weighted images of central gland tumors (22). The central zone prostate cancers tend to  
45  
46 377 have higher Gleason scores compared with cancers located in peripheral zone (23).  
47  
48 378 Moreover, the central zone prostate cancers were shown to have higher pathological stage  
49  
50 379 (higher rate of extracapsular extension and seminal vesicle invasion) as well higher Gleason  
51  
52 380 score (23).  
53  
54  
55

### 56 57 381 *Quantitative analysis of DWI*

58  
59 382 The signal intensity of DWI will be fitting using monoexponential fit.  
60

1  
2  
3 383 Monoexponential calculation of apparent diffusion coefficient (ADC) is described by the  
4  
5 384 following equation (eq.1):  
6  
7

$$8 \quad 385 \quad ADC = -\frac{1}{b_2 - b_1} \ln \left[ \frac{SI(b_1)}{SI(b_0)} \right]$$

9  
10  
11 386 where SI( $b_1$ ) and SI( $b_0$ ) denotes the signal intensity at higher b-value ( $b_1$ ) and at  $b = 0$  mm<sup>2</sup>/s  
12  
13  
14 387 ( $b_1$ ).  
15  
16

### 17 388 ***Data analysis plan***

18  
19 389 The non-inferiority evaluation will be done based on one-sided 95% CI for the difference of  
20  
21  
22 390 proportions in control arm and intervention arm. The primary analysis is the proportion of  
23  
24 391 men with clinically significant cancer in each arm. Analysis will be done by logistic  
25  
26 392 regression, with randomization strata as covariate. The odds ratio and confidence interval  
27  
28  
29 393 between groups will be applied to the risk in the control group in order to calculate a risk  
30  
31 394 difference and confidence interval. A one-sided 95% confidence interval will be used to place  
32  
33 395 a bound on the maximum reduction in detection rates associated with the intervention arm. A  
34  
35 396 similar approach will be used for proportion of men with clinically non-significant prostate  
36  
37 397 cancer, biopsy rate, and biopsy-related complications. For the patient reported outcome of  
38  
39 398 biopsy-related anxiety, analysis will be by ANCOVA, with randomization strata as covariate.  
40  
41  
42 399 In this case, a two-sided 95% C.I. will be calculated.  
43  
44

45 400 To evaluate the rate of clinically significant prostate cancer during follow-up, we will use  
46  
47 401 time-to-event methods, with subjects censored at the time of their last biopsy or curative  
48  
49 402 treatment (if received for clinically non-significant prostate cancer). Cox proportional hazards  
50  
51 403 will be used to compare between groups, with randomization strata as covariate.  
52  
53

54 404 As a descriptive analysis, we will evaluate how biopsy rates in the intervention arm vary by  
55  
56 405 predicted risk produced by the model. We will first divide subjects into low (<5%),  
57  
58 406 intermediate (5-20%) and high ( $\geq 20\%$ ) predicted risk of high-grade disease and report the  
59  
60

1  
2  
3 407 rate of biopsy in each category. We will then calculate the probability of biopsy by the  
4  
5 408 predicted risk of high-grade cancer using locally weighted scatterplot smoothing (lowess).  
6  
7  
8 409 We will conduct two additional exploratory analyses. First, we will evaluate the hypothetical  
9  
10 410 results in the control group had biopsy been restricted to those meeting different biopsy  
11  
12 411 criteria - including PI-RADS 3 or higher; PI-RADS 4 or higher; PI-RADS 3 or higher or PSA  
13  
14 412 density  $> 0.2 \text{ ng / mL / mm}^3$  – reporting the number of biopsies that would have been  
15  
16 413 conducted and the number of clinically-significant cancers found for each strategy in  
17  
18 414 comparison to the observed strategy of biopsying all men. The results of these analyses will  
19  
20 415 be standardized per 1000 men presenting with elevated PSA. In the second exploratory  
21  
22 416 analysis, we will report the calibration of the prediction model in the control group.  
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3 417 **Ethics and dissemination**  
4

5 418 ***Ethics***  
6

7  
8 419 The study will be conducted in compliance with the current revision of Declaration of  
9  
10 420 Helsinki guiding physicians and medical research involving human subjects (64th World  
11  
12 421 Medical Association General Assembly, Fortaleza, Brazil 2013). The study (protocol version  
13  
14 422 2.0, Jan 04, 2021) is approved by the Ethics Committee of the Hospital District of Southwest  
15  
16 423 Finland (IORG number: 0001744, IBR number: 00002216), (trial number: 99 /1801/2019)  
17  
18 424 and registered (NCT04287088). The amended study protocol (version 2.1) including the  
19  
20 425 recalculated sample size will be send for ethical reading Jun 15, 2021. Any important  
21  
22 426 modifications and amendments to trial protocol will be approved by the Ethics committee and  
23  
24 427 all parties participating the study will be informed.  
25  
26  
27  
28

29 428 ***Patient and Public Involvement***  
30

31 429 Patients or the public were not involved in the design, and will not be involved in conduct, or  
32  
33 430 reporting, or dissemination plans of our research.  
34  
35  
36

37 431 ***Data monitoring***  
38

39 432 A risk-based data monitoring will be performed according to monitoring plan, Supplement 1.  
40  
41  
42

43 433 ***Insurance***  
44

45 434 The study subjectsts are insured during the study by the “Insurance against medicine-related  
46  
47 435 injuries” (In Finnish: “Lääkevahinkovakuutus”) under regulations currently in effect in all  
48  
49 436 participating centres.  
50  
51  
52

53 437 ***Study report and publications***  
54

55 438 Any formal presentation or publication of data collected from this research protocol will be  
56  
57 439 considered as a joint publication by the investigator(s) and other appropriate persons deemed  
58  
59 440 to have a significant academic output in the implementation of the study. Full reports of this  
60



1  
2  
3 441 study will be submitted to peer-reviewed journals in concerned fields (mainly radiology and  
4  
5 442 oncology).  
6  
7 443 Following completion of the trial, free public access to all data will be provided similar to our  
8  
9 444 previous single- (IMPROD, NCT01864135) and multi-center (Multi-IMRPOD,  
10  
11 445 NCT02241122) trials available at <http://petiv.utu.fi/improd/> and  
12  
13 446 <http://petiv.utu.fi/multiimprod/>, respectively.  
14  
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17

### 18 447 ***Study schedule***

19  
20 448 The study started in Feb 2020. All the subjects are expected to be recruited by May 2022. The  
21  
22 449 prospective follow-up will stop latest 2027. Long-term follow-up based on medical charts  
23  
24 450 will stop latest 2042.  
25  
26  
27

### 28 451 **Study centres**

29  
30 452 A detailed description of all study centres is provided in  
31  
32 453 <https://clinicaltrials.gov/ct2/show/NCT04287088>.  
33  
34 454 Central Finland Central Hospital, Jyväskylä, Finland, 40620  
35  
36 455 Satakunta Central Hospital, Pori, Finland, 28500  
37  
38 456 Tampere University Hospital, Tampere, Finland, 33520  
39  
40 457 Turku University Hospital, Turku, Finland, 20521  
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459 **References**

- 460 1. Seikkula HA, Kaipia AJ, Rantanen ME, Pitkaniemi JM, Malila NK, Bostrom PJ. Stage-  
461 specific mortality and survival trends of prostate cancer patients in Finland before and after  
462 introduction of PSA. *Acta Oncol.* 2017;56(7):971-7.
- 463 2. Wong MC, Goggins WB, Wang HH, Fung FD, Leung C, Wong SY, et al. Global  
464 Incidence and Mortality for Prostate Cancer: Analysis of Temporal Patterns and Trends in 36  
465 Countries. *Eur Urol.* 2016;70(5):862-74.
- 466 3. Mottet N., Bellmunt J., Briers E., Bolla M., Bourke L., Cornford P., De Santis M.,  
467 Henry A., Joniau S., Lam T., Mason M.D., Van den Poel H., Van den Kwast T.H., Rouvière  
468 O., Wiegel T.; members of the EAU – ESTRO – ESUR –SIOG Prostate Cancer Guidelines  
469 Panel. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer. Edn. presented at the  
470 EAU Annual Congress Copenhagen 2018. 978-94-92671-02-8. Publisher: EAU Guidelines  
471 Office. Place published: Arnhem, The Netherlands.
- 472 4. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al.  
473 Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS):  
474 a paired validating confirmatory study. *Lancet.* 2017;389(10071):815-22.
- 475 5. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala  
476 MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med.*  
477 2018;378(19):1767-77.
- 478 6. Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Mège-Lechevallier F, et al.  
479 Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-  
480 naïve patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol.*  
481 2019;20(1):100-9.
- 482 7. Jambor I, Bostrom PJ, Taimen P, Syvanen K, Kahkonen E, Kallajoki M, et al. Novel  
483 biparametric MRI and targeted biopsy improves risk stratification in men with a clinical  
484 suspicion of prostate cancer (IMPROD Trial). *J Magn Reson Imaging.* 2017;46(4):1089-95.
- 485 8. Jambor I, Verho J, Ettala O, Knaapila J, Taimen P, Syvanen KT, et al. Validation of  
486 IMPROD biparametric MRI in men with clinically suspected prostate cancer: A prospective  
487 multi-institutional trial. *PLoS Med.* 2019;16(6):e1002813.
- 488 9. Grönberg H, Eklund M, Picker W, Aly M, Jäderling F, Adolfsson J, et al. Prostate  
489 Cancer Diagnostics Using a Combination of the Stockholm3 Blood Test and Multiparametric  
490 Magnetic Resonance Imaging. *Eur Urol.* 2018;74(6):722-8.
- 491 10. Boesen L, Norgaard N, Logager V, Balslev I, Bisbjerg R, Thestrup KC, et al.  
492 Assessment of the Diagnostic Accuracy of Biparametric Magnetic Resonance Imaging for  
493 Prostate Cancer in Biopsy-Naïve Men: The Biparametric MRI for Detection of Prostate Cancer  
494 (BIDOC) Study. *JAMA Netw Open.* 2018;1(2):e180219.
- 495 11. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al.  
496 Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus  
497 Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided  
498 Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective  
499 Multicenter Clinical Study. *Eur Urol.* 2019;75(4):570-8.
- 500 12. Vickers A, Carlsson SV, Cooperberg M. Routine Use of Magnetic Resonance Imaging  
501 for Early Detection of Prostate Cancer Is Not Justified by the Clinical Trial Evidence. *Eur Urol.*  
502 2020;78(3):304-6.
- 503 13. J K, I J, IM P, O E, P T, J V, et al. Prebiopsy IMPROD Biparametric Magnetic  
504 Resonance Imaging Combined With Prostate-Specific Antigen Density in the Diagnosis of  
505 Prostate Cancer: An External Validation Study. *European urology oncology.* 2019.
- 506 14. Falagarío UG, Jambor I, Lantz A, Ettala O, Stabile A, Taimen P, et al. Combined Use  
507 of Prostate-specific Antigen Density and Magnetic Resonance Imaging for Prostate Biopsy

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2  
3 508 Decision Planning: A Retrospective Multi-institutional Study Using the Prostate Magnetic  
4 509 Resonance Imaging Outcome Database (PROMOD). *Eur Urol Oncol*. 2020.  
5 510 15. NICE Guidance - Prostate Cancer: Diagnosis and Management: © NICE (2019)  
6 511 Prostate Cancer: Diagnosis and Management. *BJU international*. 2019;124(1).  
7 512 16. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al.  
8 513 Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging  
9 514 Reporting and Data System Version 2. *Eur Urol*. 2019;76(3):340-51.  
10 515 17. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014  
11 516 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason  
12 517 Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New  
13 518 Grading System. *Am J Surg Pathol*. 2016;40(2):244-52.  
14 519 18. Roth AJ, Rosenfeld B, Kornblith AB, Gibson C, Scher HI, Curley-Smart T, et al. The  
15 520 memorial anxiety scale for prostate cancer: validation of a new scale to measure anxiety in men  
16 521 with with prostate cancer. *Cancer*. 2003;97(11):2910-8.  
17 522 19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new  
18 523 proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*.  
19 524 2004;240(2):205-13.  
20 525 20. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic  
21 526 data capture (REDCap)--a metadata-driven methodology and workflow process for providing  
22 527 translational research informatics support. *J Biomed Inform*. 2009;42(2):377-81.  
23 528 21. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap  
24 529 consortium: Building an international community of software platform partners. *J Biomed*  
25 530 *Inform*. 2019;95:103208.  
26 531 22. Akin O, Sala E, Moskowitz CS, Kuroiwa K, Ishill NM, Pucar D, et al. Transition zone  
27 532 prostate cancers: features, detection, localization, and staging at endorectal MR imaging.  
28 533 *Radiology*. 2006;239(3):784-92.  
29 534 23. Vargas HA, Akin O, Franiel T, Goldman DA, Udo K, Touijer KA, et al. Normal central  
30 535 zone of the prostate and central zone involvement by prostate cancer: clinical and MR imaging  
31 536 implications. *Radiology*. 2012;262(3):894-902.  
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3 **539 Authors' contributions**  
4

5 540 OE was involved in drafting this protocol and participated in the conception, study design,  
6  
7 541 assessments, data interpretation, writing and submission of the manuscript. PB, HA, IJ, DS,  
8  
9 542 and AV contributed to the study design, assessments, data interpretation. MS, AK, HS, KS  
10  
11 543 took part in management, analysis and data interpretation. All authors read and approved the  
12  
13 544 final manuscript. OE takes the responsibility for the integrity of the work as a whole and have  
14  
15 545 access to the final trial dataset.  
16  
17  
18  
19  
20  
21

22 **546 Competing interest statement.**  
23

24 547 PT reports representation as a member on the Data Management Committee in the ProScreen  
25  
26 548 trial. AV is named as a co-inventor on US patent #: 9,672,329 for a statistical method to  
27  
28 549 predict the result of prostate biopsy. Patent has been commercialized and will receive  
29  
30 550 royalties from clinical use. AV is also a co-inventor of the 4kscore, a commercially available  
31  
32 551 reflex test for predicting prostate biopsy. He may receive royalties from sales of the test. He  
33  
34 552 owns stock options in Opko, which offers the test. Otherwise, no competing interest declared.  
35  
36  
37  
38  
39  
40

41 **553 Funding statement**  
42

43 554 This work is supported by academic grant from Finnish Cancer Society. The funding  
44  
45 555 organisation will not have any authority over study design; collection, management, analysis,  
46  
47 556 and interpretation of data; writing of the report; and the decision to submit the report for  
48  
49 557 publication.  
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**Table 1.** The anchors used to guide the shared 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.

559

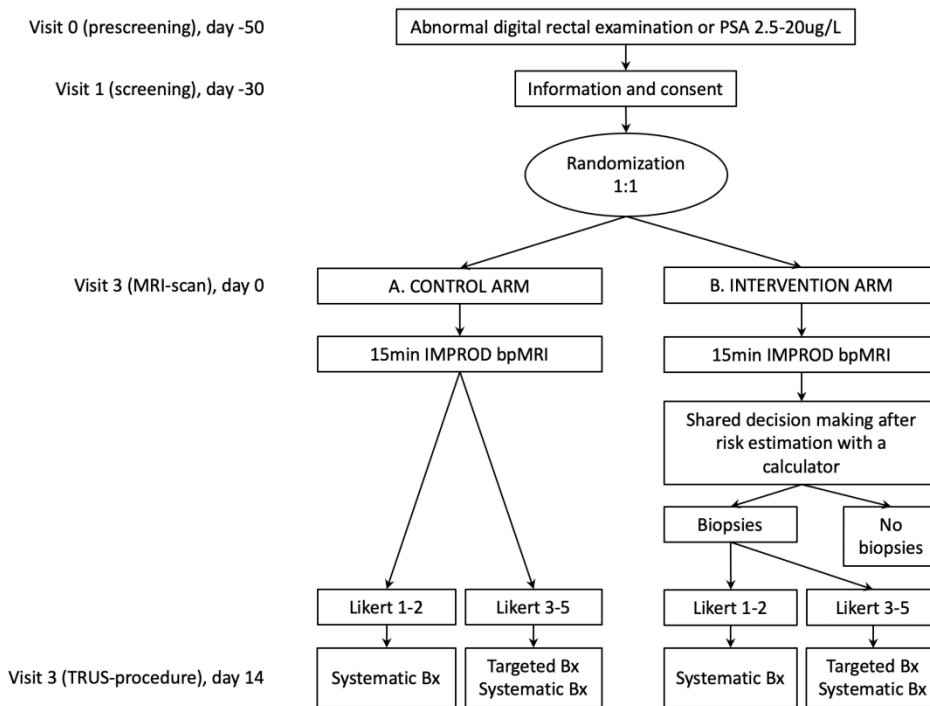


Figure 1. Study flow chart.

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**

- **1<sup>st</sup> 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.*

- **2<sup>nd</sup> 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.*

- **3<sup>rd</sup> 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**

- *1<sup>st</sup> monitoring visit 10h*
- *2<sup>nd</sup> monitoring visit 40h*
- *3<sup>rd</sup> 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



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

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <i>Rows 1-4</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <i>Rows 58-60 and Rows 424-430</i>
	2b	All items from the World Health Organization Trial Registration Data Set <i>Registered in <a href="http://clinicaltrials.gov">clinicaltrials.gov</a>, NCT03876912</i>
Protocol version	3	Date and version identifier <i>Row 58-60 and Rows 424-430</i>
Funding	4	Sources and types of financial, material, and other support <i>Row 558-562</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <i>Rows 5-16 and rows 544-550</i>
	5b	Name and contact information for the trial sponsor <i>Rows 17-21</i>
	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 <i>Rows 558-563</i>
	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) <i>Not applicable. However, a risk-based monitoring will be performed. Please see Item 21a and Supplemental document 1.</i>



## 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 <i>Research questions: rows 114-119</i> <i>Justification and relevant studies: rows 82-113</i> <i>Benefits and harms: rows 334-343</i>
	6b	Explanation for choice of comparators <i>Rows 106-113</i>
Objectives	7	Specific objectives or hypotheses <i>Rows 127-138</i>
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) <i>Rows 122-126</i>

## 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 <i>Rows 457-463</i>
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) <i>Rows 156-169</i>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <i>Rows 188-200</i>
	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) <i>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.</i>

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2		11c	Strategies to improve adherence to intervention protocols, and any
3			procedures for monitoring adherence (eg, drug tablet return,
4			laboratory tests)
5			<i>Not applicable. The one-time intervention is performed in controlled</i>
6			<i>circumstances i.e. in the urological out-patient clinic.</i>
7			
8		11d	Relevant concomitant care and interventions that are permitted or
9			prohibited during the trial
10			<i>Rows 205-207</i>
11			
12			
13	Outcomes	12	Primary, secondary, and other outcomes, including the specific
14			measurement variable (eg, systolic blood pressure), analysis metric
15			(eg, change from baseRow, final value, time to event), method of
16			aggregation (eg, median, proportion), and time point for each
17			outcome. Explanation of the clinical relevance of chosen efficacy and
18			harm outcomes is strongly recommended
19			<i>Rows 139-151</i>
20			
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23	Participant	13	Time schedule of enrolment, interventions (including any run-ins and
24	timeRow		washouts), assessments, and visits for participants. A schematic
25			diagram is highly recommended (see Figure)
26			<i>Figure 1</i>
27			
28	Sample size	14	Estimated number of participants needed to achieve study objectives
29			and how it was determined, including clinical and statistical
30			assumptions supporting any sample size calculations
31			<i>Rows 350-370</i>
32			
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34	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
35			target sample size
36			<i>Rows 172-179</i>
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### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

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43	Sequence	16a	Method of generating the allocation sequence (eg, computer-
44	generation		generated random numbers), and list of any factors for stratification.
45			To reduce predictability of a random sequence, details of any planned
46			restriction (eg, blocking) should be provided in a separate document
47			that is unavailable to those who enrol participants or assign
48			interventions
49			<i>Rows 182-187</i>
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52	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
53	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
54	mechanism		describing any steps to conceal the sequence until interventions are
55			assigned
56			<i>Rows 182-187</i>
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2	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
3			<i>Rows 182-187</i>
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6	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
7	(masking)		<i>Open label study. No blinding.</i>
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12		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
13			<i>Open label study. No blinding.</i>
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### Methods: Data collection, management, and analysis

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20	Data collection	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
21	methods		<i>Rows 372-375</i>
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29		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
30			<i>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.</i>
31			<i>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.</i>
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43	Data	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
44	management		<i>Rows 372-375</i>
45			
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50	Statistical	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
51	methods		<i>Rows 393-421</i>
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56		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
57			<i>Rows 393-421</i>
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- 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.*

## 10 **Methods: Monitoring**

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- 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.*

## 50 **Ethics and dissemination**

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- Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
- Rows 424-432*

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2	Protocol	25	Plans for communicating important protocol modifications (eg,
3	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
4			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
5			regulators)
6			<i>Rows 430-432</i>
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8	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
9			participants or authorised surrogates, and how (see Item 32)
10			<i>Rows 176-177</i>
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13		26b	Additional consent provisions for collection and use of participant data
14			and biological specimens in ancillary studies, if applicable
15			<i>Biological specimens (blood and urine) are collected. This is included in the</i>
16			<i>consent.</i>
17			
18	Confidentiality	27	How personal information about potential and enrolled participants will
19			be collected, shared, and maintained in order to protect confidentiality
20			before, during, and after the trial
21			<i>Rows 370-375</i>
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24	Declaration of	28	Financial and other competing interests for principal investigators for
25	interests		the overall trial and each study site
26			<i>No financial or other competing interest</i>
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29	Access to data	29	Statement of who will have access to the final trial dataset, and
30			disclosure of contractual agreements that limit such access for
31			investigators
32			<i>Rows 549-550</i>
33			
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35	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
36	post-trial care		compensation to those who suffer harm from trial participation
37			<i>No compensation.</i>
38			<i>Insurance: rows 439-441</i>
39			
40	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
41	policy		participants, healthcare professionals, the public, and other relevant
42			groups (eg, via publication, reporting in results databases, or other
43			data sharing arrangements), including any publication restrictions
44			<i>Rows 443-451</i>
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47		31b	Authorship eligibility guideRows and any intended use of professional
48			writers
49			<i>Eligibility for authorship in the primary report of the study includes a status of</i>
50			<i>principal or local investigator, a status of study radiologist or at least two of</i>
51			<i>the following: study design, obtaining funding, data collection, data analysis,</i>
52			<i>a key role in management of the study</i>
53			<i>No professional writers will be involved.</i>
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57		31c	Plans, if any, for granting public access to the full protocol, participant-
58			level dataset, and statistical code
59			<i>All images, datasets and statistical codes will be open access.</i>
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## 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

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\*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.

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# 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)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-053118.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Nov-2021
Complete List of Authors:	Ettala, Otto; University of Turku; TYKS Turku University Hospital, Department of Urology Jambor, Ivan; Icahn School of Medicine at Mount Sinai, Department of Radiology; TYKS Turku University Hospital, Medical Imaging Centre of Southwest Finland Montoya Perez, Ileana; University of Turku, Department of Computing; TYKS Turku University Hospital, Medical Imaging Centre of Southwest Finland Seppänen, Marjo; Satakunta Hospital District, Department of Urology Kaipia, Antti; Tampere University, Department of Urology; Tampere University Hospital, Department of Urology Seikkula, Heikki; Central Finland Central Hospital Syvänen, Kari T ; TYKS Turku University Hospital, Taimen, Pekka; TYKS Turku University Hospital, Department of Pathology; University of Turku, Institute of Biomedicine Verho, Janne; TYKS Turku University Hospital, Medical Imaging Centre of Southwest Finland Steiner, Aida; TYKS Turku University Hospital, Medical Imaging Centre of Southwest Finland Saunavaara, Jani; TYKS Turku University Hospital, Department of Medical Physics Saukko, Ekaterina ; Turku University Hospital, Sjöberg, Daniel; Memorial Sloan Kettering Cancer Center Department of Epidemiology & Biostatistics Vickers, Andrew; Memorial Sloan Kettering Cancer Center, Integrative Medicine Aronen, Hannu; TYKS Turku University Hospital, Medical Imaging Centre of Southwest Finland Boström, Peter; University of Turku; TYKS Turku University Hospital, Department of Urology
<b>Primary Subject Heading</b>:	Urology
Secondary Subject Heading:	Diagnostics, Patient-centred medicine, Oncology
Keywords:	Magnetic resonance imaging < RADIOLOGY & IMAGING, Urological tumours < UROLOGY, Prostate disease < UROLOGY, Urological tumours

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4 1 Individualized non-contrast MRI-based risk estimation and  
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7 2 shared decision making in men with a suspicion of prostate  
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10 3 cancer – protocol for multicentre randomised controlled trial  
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14 4 (multi-IMPROD2.0)  
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49 22 Word count: 4448 (article), 298 (abstract)

50 23 References: 25

51 24 Tables: 1

52 25 Figures: 1

53 26 Supplementary documents: 3  
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27 **Abbreviations**

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

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## 36 **Introduction**

37 EAU and NICE guidelines recommend that all men with a suspicion of prostate cancer  
38 should undergo pre-biopsy contrast-enhanced i.e. multiparametric prostate magnetic  
39 resonance imaging (mpMRI). Also, subsequent prostate biopsies should be performed if MRI  
40 is deemed as positive i.e. Prostate Imaging–Reporting and Data System (PI-RADS) scores 3-  
41 5. However, several retrospective post-hoc analyses have shown that this approach still leads  
42 to a large number of unnecessary biopsy procedures. For example, 88-96% of men with PI-  
43 RADS 3 finding are still diagnosed with clinically non-significant prostate cancer or no  
44 cancer at all.

## 45 **Methods and analysis**

46 This is a prospective, randomised, controlled, multicentre trial to demonstrate non-inferiority  
47 in clinically significant cancer detection rate between men undergoing prostate biopsies post-  
48 MRI and men undergoing prostate biopsies post-MRI only after a shared decision based on  
49 individualized risk estimation. Men without previous diagnosis of prostate cancer and with  
50 abnormal digital rectal examination findings and/ or prostate specific antigen (PSA) between  
51 2.5ug/L and 20.0ug/L are included. We aim at recruiting 830 men who are randomised 1:1  
52 fashion into control (all undergo biopsies after MRI) and intervention arms (the decision to  
53 perform biopsies is based on risk estimation and shared decision making). The primary  
54 outcome of the study is the proportion of men with clinically significant prostate cancer  
55 (Gleason 4+3 prostate cancer or higher) in the control. We will also compare the overall  
56 biopsy rate, benign biopsy rate, and the detection of non-significant prostate cancer between  
57 the two study groups.

## 58 **Ethics and dissemination**

59 The study (protocol version 2.0, Jan 04, 2021) is approved by the Ethics Committee of the  
60 Hospital District of Southwest Finland (IORG number: 0001744, IBR number: 00002216),

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

### 63 **Registration**

64 The study is registered at [clinicaltrials.gov](http://clinicaltrials.gov), NCT04287088.

### 65 **Strengths and limitations of this study**

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

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

82

## 83 Introduction

84 The incidence of prostate cancer continues to increase worldwide, mainly as a result of  
85 population aging, better diagnostic methods and potentially due to real increase in  
86 incidence. Although most of the prostate cancers are currently being diagnosed at early  
87 stage, at present 30% of prostate cancer in Finland are metastatic at diagnosis (1). In  
88 addition, prostate cancer continues to be the second leading cause of cancer death in men  
89 calling for better diagnostic methods (2).

90 Traditionally the diagnosis of prostate cancer is mostly based on the result of systematic  
91 transrectal ultrasonography (TRUS) guided biopsies (3). Recently, several prospective  
92 trials claimed that an alternative pathway using multiparametric (mpMRI) or biparametric  
93 (bpMRI) magnetic resonance imaging as a triage test reduces unnecessary biopsies,  
94 decreases the detection of clinically non-significant prostate cancer, and improves the  
95 detection of clinically significant prostate cancer (4-11). Therefore, in addition to men with  
96 previous negative prostate biopsies, EAU, AUA and NICE guidelines also recommend that  
97 all men with a suspicion of prostate cancer should undergo pre-biopsy MRI. Also,  
98 subsequent prostate biopsies should be performed if MRI is deemed as positive i.e. PI-  
99 RADS scores 3-5 (3).

100 That said, it is not clear whether the results of these trials reflect a true change in relative  
101 detection of significant and non-significant PCa or reflect upgrading associated with MRI  
102 (12). Moreover, several retrospective post-hoc analyses have shown that this approach still  
103 leads to a large number of unnecessary biopsy procedures. For example, 88-96% of men with  
104 PI-RADS 3 finding are still diagnosed with clinically non-significant prostate cancer or no  
105 cancer at all (5, 7, 8). In our retrospective post-hoc analyses we have shown that prostate  
106 specific antigen (PSA) density (PSA divided by prostate volume) combined with bpMRI is

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3 107 useful when determining the need to perform biopsies (13) This finding is supported by  
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5 108 retrospective analysis both in bpMRI (10) and mpMRI (14) settings.  
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8 109 The decision whether to perform biopsies or not is not just about MRI and PSA but a shared  
9  
10 110 decision making accounting for patient characteristics, such as co-morbidities, life-  
11  
12 111 expectancy, and expectations and values (15). Unfortunately, no risk tool utilising prostate  
13  
14 112 MRI and applying a truly individualized approach for each man have been evaluated in  
15  
16 113 prospective clinical trials (16, 17). Therefore, the concept of this trial is to generate a risk  
17  
18 114 calculator, based on MRI and clinical variables describing individual man's risk of having  
19  
20 115 clinically significant prostate cancer. This risk-estimation is then used as a basis for  
21  
22 116 discussion of the benefits and potential harms of proceeding with the prostate biopsy.  
23  
24 117 The aim of this prospective, randomised, multi-centre controlled, trial is to demonstrate non-  
25  
26 118 inferiority in clinically significant cancer detection rate between men undergoing prostate  
27  
28 119 biopsies post-MRI and men undergoing prostate biopsies post-MRI only after a shared  
29  
30 120 decision based on risk estimation. The aim is also to compare if there is a difference in  
31  
32 121 overall biopsy rate, benign biopsy rate, and the detection of non-significant prostate cancer  
33  
34  
35  
36 122 between the two study groups.  
37  
38  
39  
40 123

1  
2  
3 124 **Methods and analysis**  
4  
5

6 125 ***Study design***  
7

8 126 This is a prospective, randomised (allocation 1:1), controlled, multicentre trial to demonstrate  
9  
10 127 non-inferiority in clinically significant cancer detection rate between men undergoing  
11  
12 128 prostate biopsies post-MRI and men undergoing prostate biopsies post-MRI only after a  
13  
14 129 shared decision based on individualized risk estimation.  
15  
16  
17

18  
19 130 ***Objectives***

20  
21 131 ***Primary objective***  
22

23 132 A non-inferiority between significant prostate cancer detection rate in men undergoing  
24  
25 133 prostate biopsies post-MRI (control arm) and men undergoing prostate biopsies post-MRI  
26  
27 134 only after a shared decision based on individualised risk estimation (intervention arm)  
28  
29  
30

31 135 ***Secondary objectives***  
32

33 136 To compare the detection rate of clinically non-significant prostate cancer, intermediate risk  
34  
35 137 prostate cancer, and benign biopsies between arms.  
36  
37

38 138 To compare biopsy rates between the arms.  
39

40 139 To compare biopsy-related complications between the arms.  
41

42 140 To compare the detection rate of clinically significant prostate cancer during the five years of  
43  
44 141 follow-up between arms  
45

46 142 To study and compare anxiety related to the prostate cancer between arms  
47

48 143 To evaluate how biopsy rates in the experimental arm vary by predicted risk produced by the  
49  
50 144 risk model  
51  
52  
53

54  
55 145 ***Exploratory objectives***  
56

57 146 To evaluate the hypothetical results in the control group had biopsy been restricted to those  
58  
59 147 meeting different biopsy criteria  
60

1  
2  
3 148 To calibrate the prediction model in the control arm  
4

5 149 To evaluate if biomarkers could improve the prediction model in the control group  
6  
7

8 150  
9

10  
11 151 ***Outcomes***  
12

13 152 *Primary outcome*  
14

15 153 The proportion of men with clinically significant prostate cancer (Gleason 4+3 [ISUP grade  
16  
17

18 154 group, the GGG, 3]) prostate cancer or higher) in the control and intervention arms after  
19

20 155 primary diagnostic pathway  
21  
22

23 156 *Secondary outcomes*  
24

25 157 The proportion of men with clinically non-significant prostate cancer and intermediate risk  
26  
27

28 158 prostate cancer (Gleason 3+3 [GGG 1], and Gleason 3+4 [GGG 2]) and benign biopsies in  
29

30 159 the control and intervention arms after primary diagnostic pathway  
31  
32

33 160 The proportion of men undergoing biopsies in the control and intervention arms  
34

35 161 The proportion of men having biopsy-related complications in the control and intervention  
36  
37

38 162 arms  
39

40 163 The proportion of men with clinically significant prostate cancer (Gleason 4+3 [GGG 3],  
41

42 164 prostate cancer or higher) in the control and intervention arms during the five years of follow-  
43

44 165 up  
45

46 166 Total score of Memorial Sloan Kettering Cancer Centre Anxiety questionnaire in the control  
47

48 167 and intervention arms at baseline, at six and 12 months  
49

50 168 The probability of performing biopsy in experimental arm  
51  
52

53  
54 169 *Exploratory outcome measures*  
55

56 170 The number of biopsies and the number of clinically significant prostate cancer detected for  
57  
58

59 171 each biopsy criteria  
60



1  
2  
3 172 Calibration of the model using both Likert and PI-RADS2.1 criteria  
4

5 173 Calibration of the model using biomarkers such as the four kallikrein panel  
6  
7  
8 174

9  
10  
11 175 ***Sample selection***  
12

13 176 All men with clinical suspicion of prostate cancer living in the Hospital Districts of  
14

15 177 Southwest Finland, Satakunta, Keski-Suomi, and Pirkanmaa are potentially eligible. The  
16

17 178 study will enrol 830 subjects allocated in two groups.  
18  
19  
20

21 179 ***Inclusion criteria***  
22

23 180 - Age: 18 years or older  
24

25 181 - Language spoken: Finnish or Swedish  
26  
27

28 182 - Clinical suspicion of prostate cancer, based on: serum level of PSA from 2.5 ng/ml to  
29

30 183 20.0 ng/ml and/or abnormal digital rectal examination  
31  
32

33 184 - Mental status: The subject must be able to understand the meaning of the study  
34

35 185 - Informed consent: The subject must sign the appropriate Ethics Committee (EC)  
36

37 186 approved informed consent documents in the presence of the designated staff  
38  
39  
40

41 187 ***Exclusion criteria***  
42

43 188 - previous diagnosis of prostate cancer  
44

45 189 - any contraindications for MRI  
46  
47

48 190 - any other conditions that might compromise subject's safety, based on the clinical  
49

50 191 judgment of the responsible urologist  
51

52 192 - uni- or bilateral hip prosthesis  
53  
54

55 193 ***Study procedures***  
56

57 194 Study flow is presented in Figure 1.  
58  
59  
60

1  
2  
3 195 *Pre-screening (visit 0)* After a referral to participating centres, all subjects are evaluated for  
4  
5 196 inclusion and exclusion criteria. If eligible, the subject will receive an information sheet of  
6  
7 197 the study, the information sheet of shared decision-making process, and the time for the  
8  
9  
10 198 screening visit.

11  
12  
13 199 *Screening visit (visit 1)* During the screening visit at the urology out-patient clinic the study  
14  
15 200 design is discussed in detail with the local investigator (urologist). If willing to participate,  
16  
17 201 the subject will sign the informed consent. After consenting, subjects will complete baseline  
18  
19  
20 202 questionnaires, and baseline blood and urine samples are taken.

21  
22  
23 203 *MRI scan (visit 2)* MRI scan is performed according to the guidelines in each centre.  
24  
25 204 However, for study related requirements please refer to chapter “Study instruments”.

26  
27  
28  
29 205 *Randomisation* is performed before the TRUS-visit. Subjects are randomised 1:1 into two  
30  
31 206 arms: the control arm, and the intervention arm. Randomisation will be stratified by  
32  
33 207 categorised baseline PSA:  $<4$  ng / mL, 4-9.9 ng / mL,  $\geq 10$  ng / mL. Randomisation will be  
34  
35 208 performed using predefined allocation table implemented by the study statistician (EL). The  
36  
37 209 allocation table will be implemented in REDCap database and is in-accessible once uploaded,  
38  
39 210 hence ensuring allocation concealment.

40  
41  
42  
43  
44 211 *TRUS-visit (visit 3)* The visit follows a protocol used in normal outpatient clinic. MRI results  
45  
46 212 are discussed with the subject.

47  
48 213 *The control arm:* All subjects undergo TRUS guided biopsies. In subjects with Likert  
49  
50 214 scores of 1-2, 12-core systematic TRUS guided systematic biopsies are performed. In  
51  
52 215 subjects with Likert 3-5 score lesions, in addition to systematic biopsies, two targeted biopsy  
53  
54 216 cores are taken from each lesion (up to two lesions).

55  
56  
57 217 *The intervention arm:* The probability of clinically significant prostate cancer is  
58  
59 218 estimated using the risk calculator. The risks, and benefits of prostate biopsy, and patient

1  
2  
3 219 values are discussed. A shared decision whether to perform biopsies is made. If biopsies are  
4  
5 220 to be performed, in subjects with likert scores of 1-2, 12-core systematic TRUS guided  
6  
7 221 biopsies are performed and in subjects with Likert 3-5 score lesions, in addition to systematic  
8  
9 222 biopsies, two targeted biopsy cores are taken from each lesion (up to two lesions). If biopsies  
10  
11 223 are not performed, subjects are referred for a PSA follow-up.  
12  
13  
14

15 224 *Biopsy results (visit 4)* According to clinical guidelines in each centre, either a telephone  
16  
17 225 conference or a visit, subject is contacted to discuss the results of the biopsies and biopsy-  
18  
19 226 related adverse events. If biopsies are not taken, subjects are informed about follow-up  
20  
21 227 procedures.  
22  
23  
24

25 228 *Treatment* If diagnosed with prostate cancer, the subject and the treating physician, as part of  
26  
27 229 the multi-disciplinary team, will decide the treatment modality according to local, national  
28  
29 230 and international guidelines.  
30  
31  
32

33 231 *Follow-up* In subjects with benign biopsies or in subjects with no biopsies performed, PSA is  
34  
35 232 measured according to local guidelines in each centre but should be performed at least as  
36  
37 233 follows:  
38  
39

40 234       Years 1-2: every six months

41 235       Years 3-5: every 12 months

42  
43 236 Thereafter, follow-up is performed according to clinical guidelines in every centre. If  
44  
45 237 suspicion of prostate cancer persists after initial benign biopsies or in subjects with no  
46  
47 238 biopsies taken, the decision to perform biopsies and/or MRI is according to local guidelines  
48  
49 239 in each centre and/ or treating physician. However, if no such suspicion, re-visit (discussion  
50  
51 240 and consideration of MRI and/ or biopsies), should be performed at least as follows:  
52  
53  
54

55 241       1. PSA increases over 20

56  
57 242       2. PSA doubles during the follow-up  
58  
59  
60

1  
2  
3 243 A long-term follow-up of all subjects will be performed from medical charts, Finnish national  
4  
5 244 registries and if needed, contacting the subject, up to 20 years in order to have a  
6  
7 245 comprehensive data concerning incident prostate cancer in subjects without a diagnosis of  
8  
9 246 prostate cancer and clinical end points (biochemical relapse, metastasis, death) in subjects  
10  
11 247 with diagnosed prostate cancer.  
12  
13  
14

## 15 248 ***Study instruments***

### 16 249 *Prostate MRI*

17  
18 250 Subjects scheduled for the MRI examination will receive sodium picosulfate drops  
19  
20 251 (Laxoberon, Boehringer Ingelheim GmbH) and a Bisacodyl enema (Toilax, Orion Pharma  
21  
22 252 Ltd) for bowel preparation. Details of the MRI protocol are described in  
23  
24 253 <http://mrc.utu.fi/protocols/prostate>. In short, prostate MRI examinations prostate will be  
25  
26 254 performed using a 1.5T or 3T MR scanner. Body array coils will be used for image data  
27  
28 255 acquisition. No endorectal coil will be used. T2-weighted anatomic imaging will be  
29  
30 256 performed in axial and sagittal plane. Single-shot spin-echo echo-planar imaging will be used  
31  
32 257 for DWI and performed in three separate acquisitions using b-values of 500, 1500 and 2000.  
33  
34 258 The total scan time will be approximately 15-16min.  
35  
36 259 MRI will be interpreted using a IMPROD bpMRI Likert scoring system follows: 1,  
37  
38 260 significant cancer is highly unlikely to be present; 2, significant cancer is unlikely to be  
39  
40 261 present; 3, significant cancer is equivocal; 4, significant cancer is likely to be present; 5,  
41  
42 262 significant cancer is highly likely to be present (7, 8). The calculator and clinical judgement  
43  
44 263 are based on Likert scoring system. An additional classification of MRI lesions is performed  
45  
46 264 using a modified PI-RADS2.1 system (18).  
47  
48 265 All reports and data sets are uploaded to the central study server within seven days of the  
49  
50 266 MRI scan. A standardised form to report the MRI is used (18). All MRI data sets are reported  
51  
52 267 centrally by a designated central reader (IJ). Also, MRI data sets are re-reported by a local  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 268 radiologist (at least one year of prostate MRI experience). The readers are *all* blinded to all  
4  
5 269 clinical data such as PSA, age, and subject's past medical history.  
6  
7

8  
9 270 *TRUS and prostate biopsies*

10  
11 271 The time period between the MRI examination and TRUS guided biopsy will be a maximum  
12  
13 272 of 4 weeks. Prophylactic antibiotic treatment is given according to institutional guidelines. If  
14  
15 273 suspicious MRI-lesions are present, targeted biopsies followed by systematic TRUS guided  
16  
17 274 12-core biopsies are performed. Targeting is performed either with cognitive- or MRI-fusion  
18  
19 275 according to clinical guidelines in each centre. A maximum of two cores will be taken from  
20  
21 276 each MRI suspicious lesion. If more than two suspicious lesions are observed only two of  
22  
23 277 most suspicious ones are targeted. Therefore, four targeted biopsies at maximum are  
24  
25 278 performed.  
26  
27  
28

29  
30 279 *The risk estimation*

31  
32 280 To estimate the risk of clinically significant prostate cancer a calculator is developed and  
33  
34 281 implemented in eCRF, the RedCap. The calculator is based on our previous prospective MRI  
35  
36 282 studies (the IMPROD trial, NCT01864135 and the multi-IMPROD trial NCT02241122) and  
37  
38 283 it predicts the presence of biopsy Gleason  $\geq 4+3$  [GGG 3] prior to prostate biopsy, using  
39  
40 284 information on subject age, prostate volume, total PSA, 5-ARI use, and PI-RADS score.  
41  
42  
43

- 44 285 1. If the subject uses 5-ARI, modifications are needed to the subject's PSA and prostate  
45  
46 286 volume.
- 47  
48  
49 287 ○ Multiple PSA by 2
  - 50  
51 288 ○ Divide Prostate Volume by 0.7
- 52  
53  
54 289 2. Calculate cubic spline terms for PSA.
- 55  
56  
57 290 ○ The knot locations are  $t = (3.80, 6.60, 9.40, 18.47)$ , where  $t_1 = 3.80$ ,  $t_2 = 6.60$ . etc.
- 58  
59  
60

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

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 risk of Gleason  $\geq 3$  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.

1  
2  
3 310  
4  
5

6 311 *Laboratory evaluation*

8 312 As a part of a routine clinical practice blood tests including serum PSA, free-to-total PSA  
9 313 ratio, standard and differential blood counts, serum alkaline phosphatase, and serum  
10 314 testosterone are collected.

15  
16 315 *Serum and urine biomarkers*

17 316 Anticoagulated EDTA plasma (10 ml) and urine (min. 10 ml) are collected to investigate  
18 317 previously characterised biomarkers for prostate cancer detection such as the four kallikrein  
19 318 panel and potential new biomarkers. The blood and urine are drawn before the TRUS-visit.  
20 319 Subjects give their written consent to the sampling.

25  
26 320 *Histopathologic evaluation of tissue samples*

27 321 All histopathological biopsies are reported separately (core length, cancer length, Gleason  
28 322 grade) at each centre by expert pathologists, each with at least five years of experience in  
29 323 genitourinary pathology at the beginning of the trial, using the 2014 International Society of  
30 324 Urological Pathology Modified Gleason Grading System (19). The biopsy specimen is  
31 325 analysed so that pathologists are aware that subjects are part of the study. However, they are  
32 326 not aware of the exact details of the study protocol, and they are blinded to the sequence of  
33 327 individual biopsy cores.

34 328 *Definition of overall Gleason grade and clinically significant prostate cancer*

35 329 Clinically significant prostate cancer is defined as Gleason 4+3 [GGG 3] or higher in overall  
36 330 Gleason grade which is defined for each subject as the combination of the most frequent  
37 331 Gleason grade and the highest Gleason grade.

1  
2  
3 332 *Questionnaire*  
4

5 333 Prostate cancer related anxiety is measured with Memorial Anxiety Score for Prostate  
6  
7 334 Cancer anxiety score (MAX-PC) (20). The questionnaire will be collected at baseline, at six,  
8  
9 and 12 months.  
10  
11

12  
13 336 *Adverse events*  
14

15 337 Since anatomical MRI and DWI are not based on ionizing radiation, the risk for adverse  
16  
17 338 events in properly selected subjects is considered minimal if any. Claustrofobic subjects will  
18  
19 be excluded from the study. Commonly no side-effects or only mild side-effects are  
20  
21 339 associated with taking of sodium picosulfat drops (Laxoberon, Boehringer Ingelheim GmbH)  
22  
23 340 or Bisacodyl enema (Toilax, Orion Pharma Ltd) for bowel preparation, but it is recommended  
24  
25 341 for subjects to maintain their water balance with increased water intake. No MRI contrast  
26  
27 342 agents will be given to the subjects. The type and the severity of the adverse events will be  
28  
29 343 defined during the MRI-visit by using the CTCAE4.0 classification.  
30  
31 344

32  
33 345 TRUS guided biopsies are associated with risk of complications, the most important being  
34  
35 346 serious infections (0.5%) and bleeding (4%) complications. Adverse events related to TRUS  
36  
37 347 and prostate biopsies are recorded for 14 days after the biopsies. The type and the severity of  
38  
39 348 the complication are defined and recorded. The severity will be defined by using the Clavien-  
40  
41 349 Dindo classification (21).  
42  
43  
44  
45

46 350 *Potential benefits and harms*  
47

48  
49 351 Potential harms include adverse events related to TRUS guided biopsies and the fact that a  
50  
51 352 fraction of clinically significant prostate cancer is left undiagnosed in subjects not undergoing  
52  
53 353 TRUS guided biopsies in the intervention arm. However, the study does not expose subjects  
54  
55 354 to any extra procedures since in normal clinical practice all included subjects would undergo  
56  
57 355 bpMRI and subsequent TRUS guided biopsies. Given the fact that TRUS guided biopsies are  
58  
59  
60



1  
2  
3 356 potentially harmful to the subject, subjects in the intervention arm may even have less  
4  
5 357 adverse events than subjects in the control arm. Also, leaving a fraction of clinically  
6  
7 358 significant prostate cancer un-diagnosed in the intervention arm does not harm the subjects  
8  
9 359 since a robust follow-up after the initial diagnostic procedure is included in the study design.  
10  
11  
12

### 13 360 ***Subject retention and protocol deviation***

14  
15 361 It is expected that subject retention rate is low, since all subjects have a suspicion of prostate  
16  
17 362 cancer, and they want to be involved in diagnostic pathway. For the same reason, no protocol  
18  
19 363 deviations are expected. If subject decides to retain from the study or a study deviation  
20  
21 364 occurs, subjects are included in the final analysis if he has undergone prostate MRI and  
22  
23 365 TRUS-visits.  
24  
25  
26  
27

### 28 366 ***Sample size calculation***

29  
30 367 The concept of sample size re-calculation was brought up in protocol version 2.0 (Jan 04,  
31  
32 368 2021). A two-stage sample size calculation was performed: 1, an initial calculation before the  
33  
34 369 start of the trial; 2, a predetermined blinded re-estimation after the recruitment of first 300  
35  
36 370 subjects.  
37  
38  
39

- 40 371 1. The estimation of clinically significant prostate cancer rate was based on data from our  
41  
42 372 previous prospective trials (the IMPROD and the multi-IMPROD) (7, 8). Using a  
43  
44 373 clinically significant cancer rate of 25% in both arms, a non-inferiority margin of -8%,  
45  
46 374 a beta-level of 0.2, and an alpha-level of 0.05, it was estimated that 600 subjects will  
47  
48 375 be needed.
- 49  
50 376 2. The re-estimation of sample size is based on observation that clinically significant  
51  
52 377 prostate cancer is present in 20% of the first 300 subjects. Also, regarding the potential  
53  
54 378 difference in clinically significant cancer rates between the arms, the sample size is  
55  
56  
57  
58  
59  
60

1  
2  
3 379 evaluated in three different scenarios. Using a non-inferiority margin of -8%, a beta-  
4  
5 380 level of 0.2, and an alpha-level of 0.05, the scenarios are the following:

- 7  
8 381 a. with a rate of 20.0% in both arms, 624 participants will be needed  
9  
10 382 b. with rates of 20.5% (control arm) and 19.5% (intervention arm), 814 subjects  
11  
12 383 will be needed  
13  
14 384 c. with rates of 21.0% (control arm) and 19.0% (intervention arm), 1104 subjects  
15  
16  
17 385 will be needed

18  
19 386 It is decided that the final sample size will be calculated according to scenario b. Using a  
20  
21 387 dropout rate of 2%, 830 subjects will be recruited. The re-calculated sample size was  
22  
23 388 implemented in latest protocol amendment (version 2.1, Sep 21, 2021).

## 24 25 26 27 389 **Data handling**

### 28 29 390 *RedCap database*

30  
31 391 In addition to medical charts in each participating centre, study data are collected, managed  
32  
33 392 and stored pseudoanonymised in REDCap electronic data capture tool hosted at University of  
34  
35 393 Turku (22, 23). Every participating centre holds a pseudoanonymisation key in their own server.

### 36 37 38 39 394 *Quantitative analysis of DWI*

40  
41 395 The signal intensity of DWI will be fitting using monoexponential fit.  
42  
43 396 Monoexponential calculation of apparent diffusion coefficient (ADC) is described by the  
44  
45 397 following equation (eq.1):

$$46  
47  
48  
49 398 \quad \text{ADC} = -\frac{1}{b_2 - b_1} \ln \left[ \frac{SI(b_1)}{SI(b_0)} \right]$$

50  
51  
52  
53 399 where  $SI(b_1)$  and  $SI(b_0)$  denotes the signal intensity at higher b-value ( $b_1$ ) and at  $b = 0$  mm<sup>2</sup>/s  
54  
55 400 ( $b_1$ ).

1  
2  
3 401 ***Data analysis plan***  
4

5 402 The non-inferiority evaluation will be done based on one-sided 95% CI for the difference of  
6  
7 403 proportions in control arm and intervention arm. The primary analysis is the proportion of  
8  
9 404 men with clinically significant cancer in each arm. Analysis will be done by logistic  
10  
11 405 regression, with randomization strata as covariate. The odds ratio and confidence interval  
12  
13 406 between groups will be applied to the risk in the control group in order to calculate a risk  
14  
15 407 difference and confidence interval. A one-sided 95% confidence interval will be used to place  
16  
17 408 a bound on the maximum reduction in detection rates associated with the intervention arm. A  
18  
19 409 similar approach will be used for proportion of men with clinically non-significant prostate  
20  
21 410 cancer, biopsy rate, and biopsy-related complications. For the patient reported outcome of  
22  
23 411 biopsy-related anxiety, analysis will be by ANCOVA, with randomization strata as covariate.  
24  
25 412 In this case, a two-sided 95% C.I. will be calculated.  
26  
27  
28  
29

30 413 To evaluate the rate of clinically significant prostate cancer during follow-up, we will use  
31  
32 414 time-to-event methods, with subjects censored at the time of their last biopsy or curative  
33  
34 415 treatment (if received for clinically non-significant prostate cancer). Cox proportional hazards  
35  
36 416 will be used to compare between groups, with randomization strata as covariate.  
37  
38  
39

40 417 As a descriptive analysis, we will evaluate how biopsy rates in the intervention arm vary by  
41  
42 418 predicted risk produced by the model. We will first divide subjects into low (<5%),  
43  
44 419 intermediate (5-20%) and high ( $\geq 20\%$ ) predicted risk of high-grade disease and report the  
45  
46 420 rate of biopsy in each category. We will then calculate the probability of biopsy by the  
47  
48 421 predicted risk of high-grade cancer using locally weighted scatterplot smoothing (lowess).  
49  
50  
51  
52  
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54  
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57  
58  
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2  
3 422 We will conduct two additional exploratory analyses. First, we will evaluate the hypothetical  
4  
5 423 results in the control group had biopsy been restricted to those meeting different biopsy  
6  
7 424 criteria - including PI-RADS 3 or higher; PI-RADS 4 or higher; PI-RADS 3 or higher or PSA  
8  
9 425 density  $> 0.2 \text{ ng / mL / mm}^3$  – reporting the number of biopsies that would have been  
10  
11 426 conducted and the number of clinically-significant cancers found for each strategy in  
12  
13 427 comparison to the observed strategy of biopsying all men. The results of these analyses will  
14  
15 428 be standardized per 1000 men presenting with elevated PSA. In the second exploratory  
16  
17 429 analysis, we will report the calibration of the prediction model in the control group. The  
18  
19 430 calibration will be performed using two models: Likert and PI-RADS2.1 scores, and also  
20  
21 431 incorporating biomarkers such as the four kallikrein panel.  
22  
23  
24  
25  
26

27 432 *Patient and Public Involvement*  
28

29 433 Patients or the public were not involved in the design, and will not be involved in conduct, or  
30  
31 434 reporting, or dissemination plans of our research.  
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3 436 **Ethics and dissemination**  
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5 437 ***Ethics***  
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7 438 The study will be conducted in compliance with the current revision of Declaration of  
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9  
10 439 Helsinki guiding physicians and medical research involving human subjects (64th World  
11  
12 440 Medical Association General Assembly, Fortaleza, Brazil 2013). The study (initial approval,  
13  
14 441 protocol version 1.0, Sep 17, 2019; latest protocol version 2.1, Sep 21, 2021) is approved by  
15  
16 442 the Ethics Committee of the Hospital District of Southwest Finland (IORG number: 0001744,  
17  
18 443 IBR number: 00002216), (trial number: 99 /1801/2019) and registered (NCT04287088). The  
19  
20 444 amended study protocol (version 2.1) including the recalculated sample size will be send for  
21  
22 445 ethical reading Jun 15, 2021. Any important modifications and amendments to trial protocol  
23  
24 446 will be approved by the Ethics committee and all parties participating the study will be  
25  
26 447 informed.  
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32 448 ***Data monitoring***  
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34 449 A risk-based data monitoring will be performed according to monitoring plan, Supplement 1.  
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37 450 ***Insurance***  
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39 451 The study subjectsts are insured during the study by the “Insurance against medicine-related  
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41 452 injuries” (In Finnish: “Lääkevahinkovakuutus”) under regulations currently in effect in all  
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43 453 participating centres.  
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47 454 ***Study report and publications***  
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49 455 Any formal presentation or publication of data collected from this research protocol will be  
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51 456 considered as a joint publication by the investigator(s) and other appropriate persons deemed  
52  
53 457 to have a significant academic output in the implementation of the study. Full reports of this  
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55 458 study will be submitted to peer-reviewed journals in concerned fields (mainly radiology and  
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57 459 oncology).  
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3 460 Following completion of the trial, free public access to all data will be provided similar to our  
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5 461 previous single- (IMPROD, NCT01864135) and multi-center (Multi-IMRPOD,  
6  
7 462 NCT02241122) trials available at <http://petiv.utu.fi/improd/> and  
8  
9 463 <http://petiv.utu.fi/multiimprod/>, respectively.  
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### 13 464 ***Study schedule***

14  
15 465 The study started in Feb 2020. All the subjects are expected to be recruited by May 2022. The  
16  
17 466 prospective follow-up will stop latest 2027. Long-term follow-up based on medical charts  
18  
19 467 will stop latest 2042.  
20  
21  
22

### 23 468 **Study centres**

24  
25 469 A detailed description of all study centres is provided in  
26  
27 470 <https://clinicaltrials.gov/ct2/show/NCT04287088>.

28  
29 471 Central Finland Central Hospital, Jyväskylä, Finland, 40620

30  
31 472 Satakunta Central Hospital, Pori, Finland, 28500

32  
33 473 Tampere University Hospital, Tampere, Finland, 33520

34  
35 474 Turku University Hospital, Turku, Finland, 20521

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### 38 39 476 **Discussion**

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42 477 The trial is designed to show that as a triage test an individualized MRI-based risk estimation  
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44 478 is non-inferior to MRI-targeted biopsies in men with suspicion of prostate cancer. Although  
45  
46 479 one might argue that several risk scores for prostate cancer exists, the study is extremely  
47  
48 480 timely and relevant by establishing a contemporary risk score with data from prostate MRI,  
49  
50 481 and, more importantly, utilising the score in a scenario of shared decision making.

51  
52 482 There are some issues to discuss. First, the selection of GGG 3 or higher as a definition of  
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54 483 clinically significant prostate cancer instead of using Gleason GGG2 as a cut-off is of course  
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56 484 an issue for a debate. The overall Gleason score will be defined according to the most  
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3 485 common Gleason pattern and the highest Gleason pattern based on the combination of  
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5 486 Gleason patterns in targeted and systematic biopsies. Doing this will eventually lead to  
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7 487 saturation of the Gleason pattern of the targeted biopsies and most notably to a stage  
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9 488 migration towards higher overall Gleason grade. The approach is also supported by two  
10  
11 489 recent prostate MRI trials, the PROMIS and the National Cancer Institute (NCI) MRI-trial,  
12  
13 490 which both utilised GGG 3 as a definition of clinically significant prostate cancer (4, 24).

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16 491 Therefore, we consider the approach as justified.

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18  
19 492 Second, the usage of non-inferiority margin of -8% needs to be addressed. We acknowledge  
20  
21 493 that other prostate MRI trials utilising the non-inferiority setting have used a margin of -5%  
22  
23 494 (5, 25). However, it should be noted that the study designs are not comparable to our study.

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26 495 In the PRECISION and the trial by Klotz et al., novel technology i.e. MRI-guided biopsies  
27  
28 496 was compared to traditional technology the TRUS-guided biopsies and the outcome from the  
29  
30 497 technology dictated patient interventions. In that setting it is crucial that outcome after  
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32 498 interventional diagnostics is very similar or even superior to compared to traditional one. In  
33  
34 499 our trial patient characteristics and preferences, and clinicians' recommendation are taken  
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36 500 into account, and, therefore we feel that more liberal non-ineriority margin can be accepted.

37  
38 501 As in the end of the day the patient makes the decision.

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## 45 46 47 504 **References**

- 48  
49 505 1. Seikkula HA, Kaipia AJ, Rantanen ME, Pitkaniemi JM, Malila NK, Bostrom PJ. Stage-  
50 506 specific mortality and survival trends of prostate cancer patients in Finland before and after  
51 507 introduction of PSA. *Acta Oncol.* 2017;56(7):971-7.  
52  
53 508 2. Wong MC, Goggins WB, Wang HH, Fung FD, Leung C, Wong SY, et al. Global  
54 509 Incidence and Mortality for Prostate Cancer: Analysis of Temporal Patterns and Trends in 36  
55 510 Countries. *Eur Urol.* 2016;70(5):862-74.  
56  
57 511 3. Mottet N., Bellmunt J., Briers E., Bolla M., Bourke L., Cornford P., De Santis M.,  
58 512 Henry A., Joniau S., Lam T., Mason M.D., Van den Poel H., Van den Kwast T.H., Rouvière  
59 513 O., Wiegel T.; members of the EAU – ESTRO – ESUR –SIOG Prostate Cancer Guidelines  
60 514 Panel. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer. Edn. presented at the

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3 515 EAU Annual Congress Copenhagen 2018. 978-94-92671-02-8. Publisher: EAU Guidelines  
4 516 Office. Place published: Arnhem, The Netherlands.
- 5 517 4. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al.  
6 518 Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS):  
7 519 a paired validating confirmatory study. *Lancet*. 2017;389(10071):815-22.
- 8 520 5. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala  
9 521 MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med*.  
10 522 2018;378(19):1767-77.
- 11 523 6. Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Mège-Lechevallier F, et al.  
12 524 Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-  
13 525 naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol*.  
14 526 2019;20(1):100-9.
- 15 527 7. Jambor I, Bostrom PJ, Taimen P, Syvanen K, Kahkonen E, Kallajoki M, et al. Novel  
16 528 biparametric MRI and targeted biopsy improves risk stratification in men with a clinical  
17 529 suspicion of prostate cancer (IMPROD Trial). *J Magn Reson Imaging*. 2017;46(4):1089-95.
- 18 530 8. Jambor I, Verho J, Ettala O, Knaapila J, Taimen P, Syvanen KT, et al. Validation of  
19 531 IMPROD biparametric MRI in men with clinically suspected prostate cancer: A prospective  
20 532 multi-institutional trial. *PLoS Med*. 2019;16(6):e1002813.
- 21 533 9. Grönberg H, Eklund M, Picker W, Aly M, Jäderling F, Adolfsson J, et al. Prostate  
22 534 Cancer Diagnostics Using a Combination of the Stockholm3 Blood Test and Multiparametric  
23 535 Magnetic Resonance Imaging. *Eur Urol*. 2018;74(6):722-8.
- 24 536 10. Boesen L, Norgaard N, Logager V, Balslev I, Bisbjerg R, Thestrup KC, et al.  
25 537 Assessment of the Diagnostic Accuracy of Biparametric Magnetic Resonance Imaging for  
26 538 Prostate Cancer in Biopsy-Naive Men: The Biparametric MRI for Detection of Prostate Cancer  
27 539 (BIDOC) Study. *JAMA Netw Open*. 2018;1(2):e180219.
- 28 540 11. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al.  
29 541 Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus  
30 542 Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided  
31 543 Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective  
32 544 Multicenter Clinical Study. *Eur Urol*. 2019;75(4):570-8.
- 33 545 12. Vickers A, Carlsson SV, Cooperberg M. Routine Use of Magnetic Resonance Imaging  
34 546 for Early Detection of Prostate Cancer Is Not Justified by the Clinical Trial Evidence. *Eur Urol*.  
35 547 2020;78(3):304-6.
- 36 548 13. Knaapila J, Jambor I, Perez IM, Ettala O, Taimen P, Verho J, et al. Prebiopsy IMPROD  
37 549 Biparametric Magnetic Resonance Imaging Combined With Prostate-Specific Antigen Density  
38 550 in the Diagnosis of Prostate Cancer: An External Validation Study. *European urology*  
39 551 *oncology*. 2019.
- 40 552 14. Falagarío UG, Jambor I, Lantz A, Ettala O, Stabile A, Taimen P, et al. Combined Use  
41 553 of Prostate-specific Antigen Density and Magnetic Resonance Imaging for Prostate Biopsy  
42 554 Decision Planning: A Retrospective Multi-institutional Study Using the Prostate Magnetic  
43 555 Resonance Imaging Outcome Database (PROMOD). *Eur Urol Oncol*. 2020.
- 44 556 15. NICE Guidance - Prostate Cancer: Diagnosis and Management: © NICE (2019)  
45 557 Prostate Cancer: Diagnosis and Management. *BJU international*. 2019;124(1).
- 46 558 16. Kranse R, Roobol M, Schröder FH. A graphical device to represent the outcomes of a  
47 559 logistic regression analysis. *The Prostate*. 2008;68(15).
- 48 560 17. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, et al.  
49 561 Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *Journal of*  
50 562 *the National Cancer Institute*. 2006;98(8).



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2  
3 563 18. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al.  
4 564 Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging  
5 565 Reporting and Data System Version 2. *Eur Urol*. 2019;76(3):340-51.  
6 566 19. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014  
7 567 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason  
8 568 Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New  
9 569 Grading System. *Am J Surg Pathol*. 2016;40(2):244-52.  
10 570 20. Roth AJ, Rosenfeld B, Kornblith AB, Gibson C, Scher HI, Curley-Smart T, et al. The  
11 571 memorial anxiety scale for prostate cancer: validation of a new scale to measure anxiety in men  
12 572 with with prostate cancer. *Cancer*. 2003;97(11):2910-8.  
13 573 21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new  
14 574 proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*.  
15 575 2004;240(2):205-13.  
16 576 22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic  
17 577 data capture (REDCap)--a metadata-driven methodology and workflow process for providing  
18 578 translational research informatics support. *J Biomed Inform*. 2009;42(2):377-81.  
19 579 23. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap  
20 580 consortium: Building an international community of software platform partners. *J Biomed*  
21 581 *Inform*. 2019;95:103208.  
22 582 24. Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehralivand S, Gomella PT, et al.  
23 583 MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis. *The New*  
24 584 *England journal of medicine*. 2020;382(10).  
25 585 25. Klotz L, Chin J, Black PC, Finelli A, Anidjar M, Bladou F, et al. Comparison of  
26 586 Multiparametric Magnetic Resonance Imaging-Targeted Biopsy With Systematic Transrectal  
27 587 Ultrasonography Biopsy for Biopsy-Naive Men at Risk for Prostate Cancer: A Phase 3  
28 588 Randomized Clinical Trial. *JAMA oncology*. 2021;7(4).  
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3 **591 Authors' contributions**  
4

5 592 OE was involved in drafting this protocol and participated in the conception, study design,  
6  
7 593 assessments, data interpretation, writing and submission of the manuscript. PB, HA, IJ, DS,  
8  
9  
10 594 and AV contributed to the study design, assessments, data interpretation. MS, AK, HS, KS  
11  
12 595 took part in management, analysis and data interpretation. All authors read and approved the  
13  
14 596 final manuscript. OE takes the responsibility for the integrity of the work as a whole and have  
15  
16  
17 597 access to the final trial dataset.  
18  
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22 **598 Competing interest statement.**  
23

24 599 PT reports representation as a member on the Data Management Committee in the ProScreen  
25  
26  
27 600 trial. AV is named as a co-inventor on US patent #: 9,672,329 for a statistical method to  
28  
29 601 predict the result of prostate biopsy. Patent has been commercialized and will receive  
30  
31 602 royalties from clinical use. AV is also a co-inventor of the 4kscore, a commercially available  
32  
33 603 reflex test for predicting prostate biopsy. He may receive royalties from sales of the test. He  
34  
35  
36 604 owns stock options in Opko, which offers the test. Otherwise, no competing interest declared.  
37  
38  
39  
40

41 **605 Funding statement**  
42

43 606 This work is supported by academic grant from Finnish Cancer Society. The funding  
44  
45 607 organisation will not have any authority over study design; collection, management, analysis,  
46  
47  
48 608 and interpretation of data; writing of the report; and the decision to submit the report for  
49  
50 609 publication.  
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3 611 **Figure legends**  
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5 612 Figure 1. Study flow chart.  
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For peer review only

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

<b>Risk category</b>	<b>Actual risk</b>	<b>Recommendation</b>
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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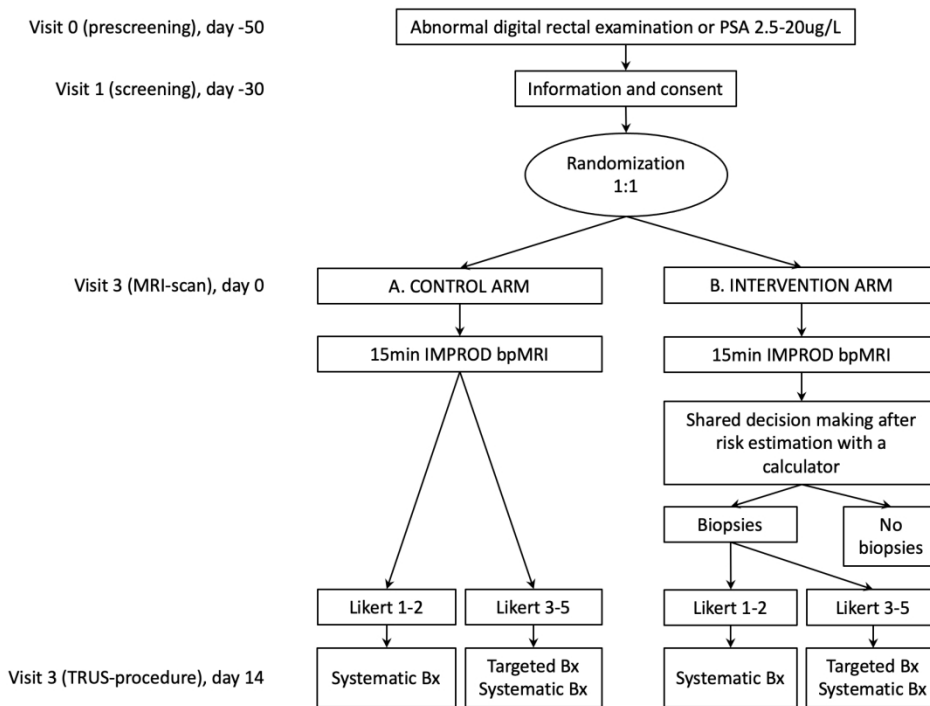


Figure 1. Study flow chart.

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**

- **1<sup>st</sup> 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.*

- **2<sup>nd</sup> 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.*

- **3<sup>rd</sup> 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**

- *1<sup>st</sup> monitoring visit 10h*
- *2<sup>nd</sup> monitoring visit 40h*
- *3<sup>rd</sup> 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



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
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <i>Rows 1-4</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <i>Rows 58-60 and Rows 424-430</i>
	2b	All items from the World Health Organization Trial Registration Data Set <i>Registered in <a href="http://clinicaltrials.gov">clinicaltrials.gov</a>, <a href="https://doi.org/10.1186/1745-6215-12-112">NCT03876912</a> <a href="https://doi.org/10.1186/1745-6215-12-112">NCT04287088</a></i>
Protocol version	3	Date and version identifier <i>Row 58-60 and Rows 424-430</i>
Funding	4	Sources and types of financial, material, and other support <i>Row 558-562</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <i>Rows 5-16 and rows 544-550</i>
	5b	Name and contact information for the trial sponsor <i>Rows 17-21</i>
	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 <i>Rows 558-563</i>
	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) <i>Not applicable. However, a risk-based monitoring will be performed. Please see Item 21a and Supplemental document 1.</i>

## 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 <i>Research questions: rows 114-119</i> <i>Justification and relevant studies: rows 82-113</i> <i>Benefits and harms: rows 334-343</i>
	6b	Explanation for choice of comparators <i>Rows 106-113</i>
Objectives	7	Specific objectives or hypotheses <i>Rows 127-138</i>
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) <i>Rows 122-126</i>

## 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 <i>Rows 457-463</i>
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) <i>Rows 156-169</i>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <i>Rows 188-200</i>
	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) <i>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.</i>



1			
2		11c	Strategies to improve adherence to intervention protocols, and any
3			procedures for monitoring adherence (eg, drug tablet return,
4			laboratory tests)
5			<i>Not applicable. The one-time intervention is performed in controlled</i>
6			<i>circumstances i.e. in the urological out-patient clinic.</i>
7			
8		11d	Relevant concomitant care and interventions that are permitted or
9			prohibited during the trial
10			<i>Rows 205-207</i>
11			
12			
13	Outcomes	12	Primary, secondary, and other outcomes, including the specific
14			measurement variable (eg, systolic blood pressure), analysis metric
15			(eg, change from baseRow, final value, time to event), method of
16			aggregation (eg, median, proportion), and time point for each
17			outcome. Explanation of the clinical relevance of chosen efficacy and
18			harm outcomes is strongly recommended
19			<i>Rows 139-151</i>
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22			
23	Participant	13	Time schedule of enrolment, interventions (including any run-ins and
24	timeRow		washouts), assessments, and visits for participants. A schematic
25			diagram is highly recommended (see Figure)
26			<i>Figure 1</i>
27			
28	Sample size	14	Estimated number of participants needed to achieve study objectives
29			and how it was determined, including clinical and statistical
30			assumptions supporting any sample size calculations
31			<i>Rows 350-370</i>
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33			
34	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
35			target sample size
36			<i>Rows 172-179</i>
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### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

42			
43	Sequence	16a	Method of generating the allocation sequence (eg, computer-
44	generation		generated random numbers), and list of any factors for stratification.
45			To reduce predictability of a random sequence, details of any planned
46			restriction (eg, blocking) should be provided in a separate document
47			that is unavailable to those who enrol participants or assign
48			interventions
49			<i>Rows 182-187</i>
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52	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
53	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
54	mechanism		describing any steps to conceal the sequence until interventions are
55			assigned
56			<i>Rows 182-187</i>
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2	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
3			<i>Rows 182-187</i>
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6	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
7	(masking)		<i>Open label study. No blinding.</i>
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12		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
13			<i>Open label study. No blinding.</i>
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### Methods: Data collection, management, and analysis

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20	Data collection	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
21	methods		<i>Rows 372-375</i>
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29		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
30			<i>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.</i>
31			<i>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.</i>
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43	Data	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
44	management		<i>Rows 372-375</i>
45			
46			
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50	Statistical	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
51	methods		<i>Rows 393-421</i>
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56		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
57			<i>Rows 393-421</i>
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- 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.*

## 10 **Methods: Monitoring**

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- 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.*

## 50 **Ethics and dissemination**

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- Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
- Rows 424-432*

1			
2	Protocol	25	Plans for communicating important protocol modifications (eg,
3	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
4			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
5			regulators)
6			<i>Rows 430-432</i>
7			
8	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
9			participants or authorised surrogates, and how (see Item 32)
10			<i>Rows 176-177</i>
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12			
13		26b	Additional consent provisions for collection and use of participant data
14			and biological specimens in ancillary studies, if applicable
15			<i>Biological specimens (blood and urine) are collected. This is included in the</i>
16			<i>consent.</i>
17			
18	Confidentiality	27	How personal information about potential and enrolled participants will
19			be collected, shared, and maintained in order to protect confidentiality
20			before, during, and after the trial
21			<i>Rows 370-375</i>
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24	Declaration of	28	Financial and other competing interests for principal investigators for
25	interests		the overall trial and each study site
26			<i>No financial or other competing interest</i>
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29	Access to data	29	Statement of who will have access to the final trial dataset, and
30			disclosure of contractual agreements that limit such access for
31			investigators
32			<i>Rows 549-550</i>
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35	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
36	post-trial care		compensation to those who suffer harm from trial participation
37			<i>No compensation.</i>
38			<i>Insurance: rows 439-441</i>
39			
40	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
41	policy		participants, healthcare professionals, the public, and other relevant
42			groups (eg, via publication, reporting in results databases, or other
43			data sharing arrangements), including any publication restrictions
44			<i>Rows 443-451</i>
45			
46			
47		31b	Authorship eligibility guideRows and any intended use of professional
48			writers
49			<i>Eligibility for authorship in the primary report of the study includes a status of</i>
50			<i>principal or local investigator, a status of study radiologist or at least two of</i>
51			<i>the following: study design, obtaining funding, data collection, data analysis,</i>
52			<i>a key role in management of the study</i>
53			<i>No professional writers will be involved.</i>
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57		31c	Plans, if any, for granting public access to the full protocol, participant-
58			level dataset, and statistical code
59			<i>All images, datasets and statistical codes will be open access.</i>
60			

## 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

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\*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.

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

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4 1 Individualised non-contrast MRI-based risk estimation and  
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7 2 shared decision making in men with a suspicion of prostate  
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10 3 cancer: protocol for multicentre randomised controlled trial  
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14 4 (multi-IMPROD2.0)  
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51 24 Tables: 1

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27 **Abbreviations**

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

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## 36 **Introduction**

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

## 45 **Methods and analysis**

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

## 58 **Ethics and dissemination**

59 The study (protocol version 2.0, January 04, 2021) was approved by the Ethics Committee of  
60 the Hospital District of Southwest Finland (IORG number: 0001744, IBR number: 00002216;

1  
2  
3 61 trial number: 99 /1801/2019). Participants are required to provide written informed consent.

4  
5 62 Full reports of this study will be submitted to peer-reviewed journals, mainly urology and  
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8 63 radiology.

9  
10 64 **Registration**

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12 65 The study is registered at ClinicalTrials.gov, NCT04287088.

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14 66  
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17 67 **Strengths and limitations of this study**

- 18  
19 68 • A strength of the study is the use of well-established IMPROD biparametric MRI  
20  
21 69 protocol (<http://mrc.utu.fi/protocols/prostate>), which is a result of long-term research  
22  
23 70 on diffusion weighted imaging, data acquisition and post-processing of MRI images.  
24  
25 71 • Another strength is that all data will be publicly available, like data from previous  
26  
27 72 IMPROD-trials (IMPROD-study, <http://petiv.utu.fi/improd/>, multi-IMRPOD-study,  
28  
29 73 <http://petiv.utu.fi/multiimprod/>).
- 30  
31 74 • Although study participants are recruited from several centres, the vast majority of  
32  
33 75 them are Caucasian in origin and, therefore, the generalisability of the results might  
34  
35 76 be limited.
- 36  
37 77 • The relatively low prevalence of opportunistic screening for prostate cancer in  
38  
39 78 Finland will have an impact on the baseline characteristics of the study population;  
40  
41 79 therefore, the generalisability of the results to nationalities with higher levels of  
42  
43 80 screening might be limited.

44  
45 81 **Keywords:** clinically significant prostate cancer, prostate MRI, risk estimation, shared  
46  
47 82 decision making

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49 83

## 84 Introduction

85 The incidence of prostate cancer continues to increase worldwide, mainly as a result of  
86 population ageing, better diagnostic methods and probably due to a real increase in  
87 incidence. Although most prostate cancers are currently being diagnosed at an early stage,  
88 30% of prostate cancers in Finland now are metastatic at diagnosis (1). Prostate cancer also  
89 continues to be the second leading cause of cancer deaths in men calling, for better  
90 diagnostic methods (2).

91 Traditionally, the diagnosis of prostate cancer is mostly based on the result of systematic  
92 transrectal ultrasonography (TRUS) guided biopsies (3). Recently, several prospective  
93 trials claimed that an alternative pathway using multiparametric magnetic resonance  
94 imaging (mpMRI) or biparametric magnetic resonance imaging (bpMRI) as a triage test  
95 reduces unnecessary biopsies, decreases the detection of clinically non-significant prostate  
96 cancer and improves the detection of clinically significant prostate cancer (4-11).

97 Therefore, in addition to men with previous negative prostate biopsies, European  
98 Association of Urology, American Urological Association and UK National Institute for  
99 Health and Care Excellence guidelines also recommend that all men with a suspicion of  
100 prostate cancer should undergo pre-biopsy MRI. Also, subsequent prostate biopsies should  
101 be performed if MRI is deemed positive, i.e. PI-RADS scores 3-5 (3).

102 That said, it is not clear whether the results of these trials reflect a true change in relative  
103 detection of significant and non-significant or reflect upgrading associated with MRI (12).

104 Moreover, several retrospective post-hoc analyses have shown that this approach still leads to  
105 many unnecessary biopsy procedures. For example, 88-96% of men with PI-RADS 3 finding  
106 are still diagnosed with clinically non-significant prostate cancer or no cancer at all (5, 7, 8).

107 In our retrospective post-hoc analyses, we have shown that prostate specific antigen (PSA)  
108 density (PSA divided by prostate volume) combined with bpMRI is useful when determining

1  
2  
3 109 the need to perform biopsies (13). This finding is supported by retrospective analysis both in  
4  
5 110 bpMRI (10) and mpMRI (14) settings.

6  
7 111 The decision on whether to or not perform biopsies is not just about MRI and PSA but a  
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9 112 shared decision making accounting for patient characteristics, such as co-morbidities, life-  
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11 113 expectancy and expectations and values (15). Unfortunately, no risk tool utilising prostate  
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13 114 MRI and applying a truly individualised approach for each man has been evaluated in  
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15 115 prospective clinical trials (16, 17). Therefore, the aim of this trial is to generate a risk  
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17 116 calculator based on MRI and clinical variables describing an individual risk of having  
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19 117 clinically significant prostate cancer. This risk-estimation is then used as a basis for  
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21 118 discussion of the benefits and potential harms of proceeding with the prostate biopsy.  
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24 119 The aim of this prospective, randomised, multi-centre controlled, trial is to demonstrate non-  
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26 120 inferiority in clinically significant cancer detection rate between men undergoing prostate  
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28 121 biopsies post-MRI and men undergoing prostate biopsies post-MRI only after a shared  
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30 122 decision based on risk estimation. The aim is also to compare whether there is a difference in  
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32 123 overall biopsy rate, benign biopsy rate and the detection of non-significant prostate cancer  
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35 124 between the two study groups.  
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3 126 **Methods and analysis**  
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6 127 ***Study design***  
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8 128 This is a prospective, randomised (allocation 1:1), controlled, multicentre trial to demonstrate  
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10 129 non-inferiority in clinically significant cancer detection rate between men undergoing  
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12 130 prostate biopsies post-MRI and men undergoing prostate biopsies post-MRI only after a  
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14 131 shared decision based on individualised risk estimation.  
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19 132 ***Objectives***

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21 133 ***Primary objective***

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23 134 A non-inferiority between significant prostate cancer detection rate in men undergoing  
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25 135 prostate biopsies post-MRI (control arm) and men undergoing prostate biopsies post-MRI  
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27 136 only after a shared decision based on individualised risk estimation (intervention arm)  
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31 137 ***Secondary objectives***

32  
33 138 To compare the detection rate of clinically non-significant prostate cancer, intermediate risk  
34  
35 139 prostate cancer and benign biopsies between the arms.

36 140 To compare biopsy rates between the arms.

37  
38 141 To compare biopsy-related complications between the arms.

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40 142 To compare the detection rate of clinically significant prostate cancer during the five years of  
41  
42 143 follow-up between the arms

43  
44 144 To study and compare anxiety related to prostate cancer between the arms

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46 145 To evaluate how biopsy rates in the experimental arm vary by predicted risk produced by the  
47  
48 146 risk model

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50 147 To evaluate inter-reader variability between central and local radiologists  
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54 148 ***Exploratory objectives***  
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3 149 To evaluate the hypothetical results in the control group had biopsy been restricted to those  
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5 150 meeting different biopsy criteria

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7 151 To calibrate the prediction model in the control arm

8 152 To evaluate if biomarkers could improve the prediction model in the control group

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16 154 **Outcomes**

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18 155 *Primary outcome*

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20 156 The proportion of men with clinically significant prostate cancer (Gleason 4+3 [International  
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22 Society of Urological pathology grade group, the GGG, 3]) prostate cancer or higher) in the  
23 157  
24 control and intervention arms after primary diagnostic pathway

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28 159 *Secondary outcomes*

29  
30 160 The proportion of men with clinically non-significant prostate cancer and intermediate risk  
31  
32 prostate cancer (Gleason 3+3 [GGG 1] and Gleason 3+4 [GGG 2]) and benign biopsies in the  
33 161  
34 control and intervention arms after primary diagnostic pathway

35 162 The proportion of men undergoing biopsies in the control and intervention arms

36  
37 163 The proportion of men having biopsy-related complications in the control and intervention  
38  
39 164 arms

40 165  
41  
42 166 The proportion of men with clinically significant prostate cancer (Gleason 4+3 [GGG 3],  
43  
44 prostate cancer or higher) in the control and intervention arms during the five years of follow-  
45 167  
46 up

47 168  
48  
49 169 Total score of Memorial Sloan Kettering Cancer Centre Anxiety questionnaire in the control  
50  
51 and intervention arms at baseline, at six months and at 12 months

52 170  
53  
54 171 The rate of biopsy in patients with low (<5%), intermediate (5-20%) and high ( $\geq$ 20%)  
55  
56 predicted risk of clinically significant prostate cancer

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3 173 Kendall rank correlation coefficient between central and local reader reported PI-RADS  
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5 174 scores

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9 175 *Exploratory outcome measures*

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11 176 The number of biopsies and the number of clinically significant prostate cancers detected in  
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13 177 patients with PI-RADS 3 or higher, PI-RADS 4 or higher, PI-RADS 3 or higher or PSA  
14  
15 178 density higher than 0.2 ng/mL/mm<sup>3</sup>

16  
17  
18 179 Calibration of the model using both Likert and PI-RADS2.1 criteria

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20 180 Calibration of the model using future biomarkers aiming to improve prostate cancer  
21  
22 181 diagnostics

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25 182

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28 183 ***Sample selection***

29  
30 184 All men with clinical suspicion of prostate cancer living in the Hospital Districts of  
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32 185 Southwest Finland, Satakunta, Keski-Suomi and Pirkanmaa are potentially eligible. The  
33  
34 186 study will enrol 830 subjects allocated into two groups.

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38 187 *Inclusion criteria*

39  
40 188 - Age: 18 years or older

41  
42 189 - Language spoken: Finnish or Swedish

43  
44 190 - Clinical suspicion of prostate cancer, based on: serum level of PSA from 2.5 -20.0 ng/ml  
45  
46 191 and/or abnormal digital rectal examination

47  
48 192 - Mental status: The subject must be able to understand the meaning of the study

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50 193 - Informed consent: The subject must sign the appropriate Ethics Committee (EC)  
51  
52 194 approved informed consent documents in the presence of the designated staff

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54  
55 195 *Exclusion criteria*

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57  
58 196 - Previous diagnosis of prostate cancer



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3 197 - Any contraindications for MRI  
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5 198 - Any other conditions that might compromise subject's safety, based on the clinical  
6  
7 judgment of the responsible urologist  
8 199  
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10 200 - Uni- or bilateral hip prosthesis  
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13 201 ***Study procedures***  
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15 202 The study flow is presented in Figure 1.  
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203 *Pre-screening (visit 0):* After a referral to participating centres, all subjects are evaluated for  
204 inclusion and exclusion criteria. If eligible, the subject will receive a study information sheet,  
205 an information sheet of the shared decision-making process and a time for the screening visit.

206 *Screening visit (visit 1):* During the screening visit at the urology out-patient clinic the study  
207 design is discussed in detail with the local investigator (urologist). If willing to participate,  
208 the subject will sign the informed consent form (Supplement 1). Thereafter, subjects will  
209 complete baseline questionnaires and baseline blood and urine samples are taken.

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

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

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

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

224 *The intervention arm:* The probability of clinically significant prostate cancer is  
225 estimated using the risk calculator. The risks and benefits of prostate biopsy and patient  
226 values are discussed. A shared decision regarding whether to perform biopsies is made. If

1  
2  
3 227 biopsies are to be performed, in subjects with Likert scores of 1-2, 12-core systematic TRUS  
4  
5 228 guided biopsies are performed and in subjects with Likert 3-5 score lesions-systematic  
6  
7 229 biopsies and two targeted biopsy cores are taken from each lesion (up to two lesions). If  
8  
9  
10 230 biopsies are not performed, subjects are referred for a PSA follow-up.  
11  
12

13 231 *Biopsy results (visit 4):* According to clinical guidelines in each centre, either by telephone  
14  
15 232 conference or a visit, the subject is contacted to discuss the results of the biopsies and biopsy-  
16  
17 233 related adverse events. If biopsies are not taken, subjects are informed about follow-up  
18  
19  
20 234 procedures.  
21  
22

23 235 *Treatment:* If diagnosed with prostate cancer, the subject and the treating physician, as part  
24  
25 236 of the multi-disciplinary team, will decide the treatment modality according to local, national  
26  
27  
28 237 and international guidelines.  
29  
30

31 238 *Follow-up* In subjects with benign biopsies or in subjects with no performed biopsies, PSA is  
32  
33 239 measured according to local guidelines in each centre but should be performed at least as  
34  
35  
36 240 follows:  
37

38 241 Years 1-2: every six months  
39

40 242 Years 3-5: every 12 months  
41  
42

43 243 Thereafter, follow-up is performed according to clinical guidelines in every centre. If  
44  
45 244 suspicion of prostate cancer persists after initial benign biopsies or in subjects with no  
46  
47 245 biopsies taken, the decision to perform biopsies and/or MRI is according to local guidelines  
48  
49 246 in each centre and/or the treating physician. However, if there is no such suspicion, a re-visit  
50  
51 247 (discussion and consideration of MRI and/or biopsies), should be performed at least as  
52  
53  
54 248 follows:  
55

56 249 1. PSA increases over 20 ng / mL  
57

58  
59 250 2. PSA doubles during the follow-up  
60

1  
2  
3 251 A long-term follow-up of all subjects will be performed from medical charts, Finnish national  
4  
5 252 registries and if needed, contacting the subject, for up to 20 years to have a comprehensive  
6  
7 253 data concerning incident prostate cancer in subjects without a diagnosis of prostate cancer  
8  
9 254 and clinical end points (biochemical relapse, metastasis, death) in subjects with diagnosed  
10  
11 255 prostate cancer.

## 15 256 ***Study instruments***

### 17 257 *Prostate MRI*

18 258 Subjects scheduled for the MRI examination will receive sodium picosulfate drops  
19  
20 259 (Laxoberon, Boehringer Ingelheim GmbH) and a Bisacodyl enema (Toilax, Orion Pharma  
21  
22 260 Ltd) for bowel preparation. Details of the MRI protocol are described in  
23  
24 261 <http://mrc.utu.fi/protocols/prostate>. In short, prostate MRI examinations will be performed  
25  
26 262 using a 1.5T or 3T MR scanner. Body array coils will be used for image data acquisition. No  
27  
28 263 endorectal coil will be used. T2-weighted anatomic imaging will be performed in the axial  
29  
30 264 and sagittal planes. Single-shot spin-echo echo-planar imaging will be used for diffusion  
31  
32 265 weighted imaging (DWI) and performed in three separate acquisitions using b-values of 0,  
33  
34 266 100, 200, 350, 500 s/mm<sup>2</sup>; 0, 1500 s/mm<sup>2</sup>; and 0, 2000 s/mm<sup>2</sup>. Apparent diffusion  
35  
36 267 coefficient (ADC) maps are calculated from each acquisition, but the one calculated from the  
37  
38 268 acquisition with low b-values (0-500 s/mm<sup>2</sup>) is considered to be the most reliable. The total  
39  
40 269 scan time will be approximately 15-16 minutes.

41 270 MRI will be interpreted using an IMPROD bpMRI Likert scoring system as follows: 1,  
42  
43 271 significant cancer is highly unlikely to be present; 2, significant cancer is unlikely to be  
44  
45 272 present; 3, significant cancer is equivocal; 4, significant cancer is likely to be present; 5,  
46  
47 273 significant cancer is highly likely to be present (7, 8). The calculator and clinical judgement  
48  
49 274 are based on a Likert scoring system. An additional classification of MRI lesions is  
50  
51 275 performed using a modified PI-RADS2.1 system (18).

1  
2  
3 276 All reports and data sets are uploaded to the central study server within seven days of the  
4  
5 277 MRI scan. A standardised form to report the MRI is used (18). All MRI data sets are reported  
6  
7 278 centrally by a designated central reader (IJ). The reported PI-RADS score of central reading  
8  
9  
10 279 is used for the risk calculator and for the MRI guided biopsies. To assess inter-reader  
11  
12 280 variability, MRI data sets are also re-reported retrospectively by a local radiologist in each  
13  
14 281 centre (at least one year of prostate MRI experience). The readers are *all* blinded to all  
15  
16 282 clinical data such as PSA, age and the subject's past medical history.

### 20 283 *TRUS and prostate biopsies*

21  
22 284 The period between the MRI examination and TRUS guided biopsy will be a maximum of 4  
23  
24 285 weeks. Prophylactic antibiotic treatment is given according to institutional guidelines. If  
25  
26 286 suspicious MRI-lesions are present, targeted biopsies followed by systematic TRUS guided  
27  
28 287 12-core biopsies are performed. Targeting is performed either with cognitive- or MRI-fusion  
29  
30 288 according to clinical guidelines in each centre. A maximum of two cores will be taken from  
31  
32 289 each MRI suspicious lesion. If more than two suspicious lesions are observed only two of  
33  
34 290 most suspicious ones are targeted. Therefore, a maximum of four targeted biopsies are  
35  
36 291 performed.

### 41 292 *The risk estimation*

42  
43 293 To estimate the risk of clinically significant prostate cancer a calculator is developed and  
44  
45 294 implemented in eCRF, the RedCap. The calculator is based on our previous prospective MRI  
46  
47 295 studies (the IMPROD trial, NCT01864135 and the multi-IMPROD trial NCT02241122) and  
48  
49 296 it predicts the presence of biopsy Gleason  $\geq 4+3$  [GGG 3] prior to prostate biopsy, using  
50  
51 297 information on subject age, prostate volume, total PSA, 5-ARI use and PI-RADS score.

- 52 298 1. If the subject uses 5-ARI, modifications are needed to the subject's PSA and prostate  
53  
54 299 volume.

300 ○ Multiple PSA by 2

301 ○ Divide Prostate Volume by 0.7

302 2. Calculate cubic spline terms for PSA.

303 ○ The knot locations are  $t = (3.80, 6.60, 9.40, 18.47)$ , where  $t_1 = 3.80$ ,  $t_2 = 6.60$ . etc.

304 
$$PSASpline_{j+1} = \max(PSA - t_j, 0)^3 - \max(PSA - t_3, 0)^3 * \frac{t_4 - t_j}{t_4 - t_3} + \max(PSA - t_4, 0)^3$$

305 
$$* \frac{t_4 - t_j}{t_4 - t_3} \text{ for } j = 1, 2$$

305 3. Calculate the regression model linear predictor

306 
$$X\beta = -6.97314184 + 0.064172722 * \{Age\} + -0.008141264 * \{Prostate Volume\}$$

307 
$$+ -0.182694534 * \{PSA\} + 0.006136442 * \{PSASpline2\} +$$

308 
$$-0.013049396 * \{PSASpline3\} + 1.37637197 * \{Likert == 3\}$$

309 
$$+ 2.50939431 * \{Likert == 4\} + 4.07331563 * \{Likert == 5\}$$

307 4. Convert linear predictor to the risk of Gleason  $\geq 3$  on biopsy (will be a probability  
308 between 0 and 1)

309 
$$Risk = \frac{e^{X\beta}}{1 + e^{X\beta}}$$

1  
2  
3 310 *Shared decision making*  
4

5 311 All consented subjects will be provided an information sheet on the concept of shared  
6  
7 312 decision. The sheet will describe the biopsy pathway, the risks and benefits related to the  
8  
9 313 biopsies and the application of the risk calculator. At the end of the sheet, there will be  
10  
11 314 questions related to the subject's values of life, especially related to the risk of prostate  
12  
13 315 cancer, its treatment and treatment related side effects.  
14  
15  
16  
17

18 316 In the TRUS-visit (visit 3), the information sheet is used to aid the discussion with subjects  
19  
20 317 randomised to the intervention arm. The risk of clinically significant cancer is calculated and  
21  
22 318 a shared decision regarding whether to perform biopsies is made.  
23  
24

25 319 The details of the protocol and execution of the trial and the concept of shared decision-  
26  
27 320 making are discussed with all investigators during the investigator meeting before the start of  
28  
29 321 the trial. The concept of the calculator is also discussed and its use is demonstrated. The  
30  
31 322 anchor guides to the shared decision making are presented in Table 1.  
32  
33  
34

35 323 *Laboratory evaluation*  
36

37 324 As a part of routine clinical practice blood tests including serum PSA, free-to-total PSA ratio,  
38  
39 325 standard and differential blood counts, serum alkaline phosphatase and serum testosterone are  
40  
41 326 collected.  
42  
43  
44  
45

46 327 *Serum and urine biomarkers*  
47

48 328 Anticoagulated EDTA plasma (10 ml) and urine (a minimum of 10 ml) are collected to  
49  
50 329 investigate previously characterised biomarkers for prostate cancer detection such as the four  
51  
52 330 kallikrein panel and potential new biomarkers. The blood and urine are samples drawn before  
53  
54 331 the TRUS-visit. Subjects give their written consent to the sampling.  
55  
56  
57

58 332 *Histopathologic evaluation of tissue samples*  
59  
60

1  
2  
3 333 All histopathological biopsies are reported separately (core length, cancer length, Gleason  
4  
5 334 grade) at each centre by expert pathologists, each with at least five years of experience in  
6  
7  
8 335 genitourinary pathology at the beginning of the trial. Reports are made using the 2014  
9  
10 336 International Society of Urological Pathology Modified Gleason Grading System (19). The  
11  
12 337 biopsy specimen is analysed so that pathologists are aware that the subjects are part of the  
13  
14  
15 338 study. However, they are not aware of the exact details of the study protocol and they are  
16  
17 339 blinded to the sequence of individual biopsy cores.

18  
19  
20 340 *Definition of overall Gleason grade and clinically significant prostate cancer*

21  
22 341 Clinically significant prostate cancer is defined as Gleason 4+3 [GGG 3] or higher in overall  
23  
24 342 Gleason grade which is defined for each subject as the combination of the most frequent  
25  
26 343 Gleason grade and the highest Gleason grade.

27  
28  
29  
30 344 *Questionnaire*

31  
32  
33 345 Prostate cancer related anxiety is measured with Memorial Anxiety Score for Prostate  
34  
35 346 Cancer anxiety score (MAX-PC) (20). The questionnaire will be collected at baseline, at six  
36  
37 347 months and at 12 months.

38  
39  
40 348 *Adverse events*

41  
42  
43 349 Since anatomical MRI and DWI are not based on ionizing radiation, the risk for adverse  
44  
45 350 events in properly selected subjects is considered minimal, if any. Claustrofobic subjects will  
46  
47 351 be excluded from the study. Commonly, no side-effects or only mild side-effects are  
48  
49 352 associated with taking sodium picosulfat drops (Laxoberon, Boehringer Ingelheim GmbH) or  
50  
51 353 Bisacodyl enema (Toilax, Orion Pharma Ltd) for bowel preparation, but it is recommended  
52  
53 354 for subjects to maintain their water balance with increased water intake. No MRI contrast  
54  
55 355 agents will be given to the subjects. The type and severity of the adverse events will be  
56  
57 356 defined during the MRI-visit by using the CTCAE4.0 classification.  
58  
59  
60



1  
2  
3 357 TRUS-guided biopsies are associated with risk of complications, the most important being  
4  
5 358 serious infections (0.5%) and bleeding (4%) complications. Adverse events related to TRUS  
6  
7 359 and prostate biopsies are recorded for 14 days after the biopsies. The type and severity of the  
8  
9 360 complication are defined and recorded. The severity will be defined by using the Clavien-  
10  
11 361 Dindo classification (21).

### 12 13 14 15 362 ***Potential benefits and harms***

16  
17 363 Potential harms include adverse events related to TRUS guided biopsies and the fact that a  
18  
19 364 fraction of clinically significant prostate cancer is left undiagnosed in subjects not undergoing  
20  
21 365 TRUS guided biopsies in the intervention arm. However, the study does not expose subjects  
22  
23 366 to any extra procedures since in normal clinical practice all included subjects would undergo  
24  
25 367 bpMRI and subsequent TRUS guided biopsies. TRUS-guided biopsies are potentially  
26  
27 368 harmful to the subject, however, subjects in the intervention arm may have even fewer  
28  
29 369 adverse events than subjects in the control arm. Furthermore, leaving a fraction of clinically  
30  
31 370 significant prostate cancer un-diagnosed in the intervention arm does not harm the subjects  
32  
33 371 since a robust follow-up after the initial diagnostic procedure is included in the study design.

### 34 35 36 37 372 ***Subject retention and protocol deviation***

38  
39  
40 373 It is expected that the subject retention rate is low, since all subjects have a suspicion of  
41  
42 374 prostate cancer and they want to be involved in the diagnostic pathway. For the same reason,  
43  
44 375 no protocol deviations are expected. Subjects who decide to refrain from the study are  
45  
46 376 included in the final analysis, if they have undergone prostate MRI and TRUS-visits.

### 47 48 49 50 377 ***Sample size calculation***

51  
52 378 The concept of sample size re-calculation was brought up in protocol version 2.0 (January 04,  
53  
54 379 2021). A two-stage sample size calculation was performed: first, an initial calculation before  
55  
56  
57  
58  
59  
60

1  
2  
3 380 the start of the trial; second, a predetermined blinded re-estimation after the recruitment of  
4  
5 381 the first 300 subjects.

6  
7  
8 382 1. The estimation of the clinically significant prostate cancer rate was based on data from  
9  
10 383 our previous prospective trials (the IMPROD and the multi-IMPROD) (7, 8). Using a  
11  
12 384 clinically significant cancer rate of 25% in both arms, a non-inferiority margin of -8%,  
13  
14 385 a beta-level of 0.2 and an alpha-level of 0.05, it was estimated that 600 subjects would  
15  
16 386 be needed.

17  
18  
19 387 2. The re-estimation of sample size is based on the observation that clinically significant  
20  
21 388 prostate cancer is present in 20% of the first 300 subjects. Also, regarding the potential  
22  
23 389 difference in clinically significant cancer rates between the arms, the sample size is  
24  
25 390 evaluated in three different scenarios. Using a non-inferiority margin of -8%, a beta-  
26  
27 391 level of 0.2 and an alpha-level of 0.05, the scenarios are as follows:

28  
29  
30 392 a. with a rate of 20.0% in both arms, 624 participants will be needed

31  
32  
33 393 b. with rates of 20.5% (control arm) and 19.5% (intervention arm), 814 subjects  
34  
35 394 will be needed

36  
37  
38 395 c. with rates of 21.0% (control arm) and 19.0% (intervention arm), 1104 subjects  
39  
40 396 will be needed

41  
42 397 It is decided that the final sample size will be calculated according to scenario b. Using a  
43  
44 398 dropout rate of 2%, 830 subjects will be recruited. The re-calculated sample size was  
45  
46 399 implemented in the latest protocol amendment (version 2.1, September 21, 2021).

#### 400 **Data handling**

##### 401 *RedCap database*

402 In addition to medical charts in each participating centre, study data are collected, managed  
403 and stored pseudoanonymised in REDCap electronic data capture tool hosted at the

1  
2  
3 404 University of Turku (22, 23). Every participating centre holds a pseudonymisation key in its  
4  
5 405 own server.

6  
7  
8  
9 406 *Quantitative analysis of DWI*

10  
11 407 The signal intensity of DWI will be fitted using monoexponential fit.

12  
13 408 Monoexponential calculation of apparent diffusion coefficient (ADC) is described by the  
14  
15 409 following equation (eq.1):

16  
17  
18  
19 410 
$$ADC = -\frac{1}{b_2 - b_1} \ln \left[ \frac{SI(b_1)}{SI(b_0)} \right]$$

20  
21  
22 411 where SI( $b_1$ ) and SI( $b_0$ ) denotes the signal intensity at higher b-value ( $b_1$ ) and at  $b = 0$  mm<sup>2</sup>/s  
23  
24 412 ( $b_1$ ).

25  
26  
27  
28 413 ***Data analysis plan***

29  
30 414 The non-inferiority evaluation will be done based on one-sided 95% confidence interval (CI)  
31  
32 415 for the difference of proportions in the control arm and intervention arm. The primary  
33  
34 416 analysis is the proportion of men with clinically significant cancer in each arm. Analysis will  
35  
36 417 be done by logistic regression, with randomisation strata as covariate. The odds ratio and  
37  
38 418 confidence interval between groups will be applied to the risk in the control group to  
39  
40 419 calculate a risk difference and confidence interval. A one-sided 95% confidence interval will  
41  
42 420 be used to place a bound on the maximum reduction in detection rates associated with the  
43  
44 421 intervention arm. A similar approach will be used for the proportion of men with clinically  
45  
46 422 non-significant prostate cancer, biopsy rate and biopsy-related complications. For the patient  
47  
48 423 reported outcome of biopsy-related anxiety, analysis will be by ANCOVA, with  
49  
50 424 randomisation strata as covariate. In this case, a two-sided 95% C.I. will be calculated.  
51  
52 425 To evaluate the rate of clinically significant prostate cancer during follow-up, we will use  
53  
54 426 time-to-event methods, with subjects censored at the time of their last biopsy or curative  
55  
56  
57  
58  
59  
60

1  
2  
3 427 treatment (if received for clinically non-significant prostate cancer). Cox proportional hazards  
4  
5 428 will be used to compare between groups, with randomisation strata as covariate.

6  
7 429 As a descriptive analysis, we will evaluate how biopsy rates in the intervention arm vary by  
8  
9 430 the predicted risk produced by the model. We will first divide subjects into low (<5%),  
10  
11 431 intermediate (5-20%) and high ( $\geq 20\%$ ) predicted risk of high-grade disease and report the  
12  
13 432 rate of biopsy in each category. We will then calculate the probability of biopsy by the  
14  
15 433 predicted risk of high-grade cancer using locally weighted scatterplot smoothing (lowess).  
16  
17 434 We will conduct two additional exploratory analyses. First, we will evaluate the hypothetical  
18  
19 435 results in the control group had biopsy been restricted to those meeting different biopsy  
20  
21 436 criteria - including PI-RADS 3 or higher; PI-RADS 4 or higher; PI-RADS 3 or higher or PSA  
22  
23 437 density  $> 0.2$  ng / mL / mm<sup>3</sup> – reporting the number of biopsies that would have been  
24  
25 438 conducted and the number of clinically-significant cancers found for each strategy in  
26  
27 439 comparison to the observed strategy of taking biopsies from all men. The results of these  
28  
29 440 analyses will be standardised per 1000 men presenting with elevated PSA. The inter-reader  
30  
31 441 variability between central and local reader-reported PI-RADS scores will be analysed using  
32  
33 442 the Kendall tau-b. In the second exploratory analysis, we will report the calibration of the  
34  
35 443 prediction model in the control group. The calibration will be performed using two models:  
36  
37 444 Likert and PI-RADS2.1 scores and by incorporating.

#### 38 39 40 41 42 43 44 45 445 *Patient and Public Involvement*

46  
47 446 Patients or the public were not involved in the design, and will not be involved in the  
48  
49 447 conduct, reporting or dissemination plans of our research.

50  
51  
52  
53 448

1  
2  
3 449 **Ethics and dissemination**  
4

5 450 ***Ethics***  
6

7  
8 451 The study will be conducted in compliance with the current revision of the Declaration of  
9  
10 452 Helsinki guiding physicians and medical research involving human subjects (64th World  
11  
12 453 Medical Association General Assembly, Fortaleza, Brazil, 2013). The study (initial approval,  
13  
14 454 protocol version 1.0, September 17, 2019; latest protocol version 2.1, September 21, 2021) is  
15  
16 455 approved by the Ethics Committee of the Hospital District of Southwest Finland (IORG  
17  
18 456 number: 0001744, IBR number: 00002216), (trial number: 99 /1801/2019) and registered  
19  
20 457 (NCT04287088). Any important modifications and amendments to trial protocol will be  
21  
22 458 approved by the Ethics Committee and all parties participating in the study will be informed.  
23  
24  
25

26  
27 459 ***Data monitoring***  
28

29 460 Risk-based data monitoring will be performed according to the monitoring plan (Supplement  
30  
31 461 2).  
32  
33

34  
35 462 ***Insurance***  
36

37 463 The study subjects are insured during the study by the “Insurance against medicine-related  
38  
39 464 injuries” (In Finnish: “Lääkevahinkovakuutus”) under regulations currently in effect in all  
40  
41 465 participating centres.  
42  
43  
44

45 466 ***Study report and publications***  
46

47 467 Any formal presentation or publication of data collected from this research protocol will be  
48  
49 468 considered as a joint publication by the investigator(s) and other appropriate persons deemed  
50  
51 469 to have a significant academic output in the implementation of the study. Full reports of this  
52  
53 470 study will be submitted to peer-reviewed journals in concerned fields (mainly radiology and  
54  
55 471 oncology).  
56  
57  
58  
59  
60

1  
2  
3 472 Following completion of the trial, free public access to all data will be provided like to our  
4  
5 473 previous single- (IMPROD, NCT01864135) and multi-centre (Multi-IMRPOD,  
6  
7 474 NCT02241122) trials available at <http://petiv.utu.fi/improd/> and  
8  
9 475 <http://petiv.utu.fi/multiimprod/>, respectively.  
10  
11  
12

### 13 476 ***Study schedule***

14  
15 477 The study started in February 2020. All the subjects are expected to be recruited by May  
16  
17 478 2022. The prospective follow-up will stop in 2027. Long-term follow-up based on medical  
18  
19 479 charts will stop in 2042.  
20  
21  
22

### 23 480 **Study centres**

24  
25 481 A detailed description of all study centres is provided in  
26  
27 482 <https://clinicaltrials.gov/ct2/show/NCT04287088>.

28  
29 483 Central Finland Central Hospital, Jyväskylä, Finland, 40620

30  
31 484 Satakunta Central Hospital, Pori, Finland, 28500

32  
33 485 Tampere University Hospital, Tampere, Finland, 33520

34  
35 486 Turku University Hospital, Turku, Finland, 20521

36  
37 487

### 38 39 488 **Discussion**

40  
41 489 The trial is designed to show that as a triage test an individualised MRI-based risk estimation  
42  
43 490 is non-inferior to MRI-targeted biopsies in men with suspicion of prostate cancer. Although  
44  
45 491 one might argue that several risk scores for prostate cancer exist, the study is extremely  
46  
47 492 timely and relevant by establishing a contemporary risk score with data from prostate MRI  
48  
49 493 and, more importantly, utilising the score in a scenario of shared decision making.

50  
51 494 However, some issues should be discussed. First, the selection of GGG 3 or higher as a  
52  
53 495 definition of clinically significant prostate cancer instead of using Gleason GGG2 as a cut-off  
54  
55 496 is debatable. The overall Gleason score will be defined according to the most common

1  
2  
3 497 Gleason pattern and the highest Gleason pattern based on the combination of Gleason  
4  
5 498 patterns in targeted and systematic biopsies. This will eventually lead to saturation of the  
6  
7 499 Gleason pattern of the targeted biopsies and most notably to a stage migration towards higher  
8  
9 500 overall Gleason grades. The approach is also supported by two recent prostate MRI trials, the  
10  
11 501 PROMIS and the National Cancer Institute (NCI) MRI-trial, which both utilised GGG 3 as a  
12  
13 502 definition of clinically significant prostate cancer (4, 24). Therefore, we consider the  
14  
15 503 approach justified.

16  
17 504 Second, a non-inferiority margin of -8% needs to be addressed. We acknowledge that other  
18  
19 505 prostate MRI trials utilising the non-inferiority setting have adopted a margin of -5% (5, 25).  
20  
21 506 However, the study designs are not comparable to our study. In the PRECISION and the trial  
22  
23 507 by Klotz et al., novel technology, i.e. MRI-guided biopsies, was compared to traditional  
24  
25 508 technology, the TRUS-guided biopsies and the outcome from the technology dictated patient  
26  
27 509 interventions. In that setting, it is crucial that the outcome after interventional diagnostics is  
28  
29 510 analogous or even superior compared to traditional ones. In our trial, patient characteristics  
30  
31 511 and preferences and clinicians' recommendations are taken into account and, therefore, we  
32  
33 512 are confident that a more liberal non-inferiority margin can be accepted. Ultimately, the  
34  
35 513 patient makes the decision.

36  
37 514 The cohort should also be addressed. It is purely of Caucasian origin and consists of Finnish  
38  
39 515 men, a population presenting with a low level of opportunistic screening for prostate cancer.  
40  
41 516 Therefore, the results may not be directly generalised to men of non-Caucasian origin or  
42  
43 517 populations with higher rates of opportunistic prostate cancer screening.

44  
45 518

46  
47 519

48  
49 520

50  
51 521

522 **References**

- 523 1. Seikkula HA, Kaipia AJ, Rantanen ME, Pitkaniemi JM, Malila NK, Bostrom PJ. Stage-  
524 specific mortality and survival trends of prostate cancer patients in Finland before and after  
525 introduction of PSA. *Acta Oncol.* 2017;56(7):971-7.
- 526 2. Wong MC, Goggins WB, Wang HH, Fung FD, Leung C, Wong SY, et al. Global  
527 Incidence and Mortality for Prostate Cancer: Analysis of Temporal Patterns and Trends in 36  
528 Countries. *Eur Urol.* 2016;70(5):862-74.
- 529 3. Mottet N., Bellmunt J., Briers E., Bolla M., Bourke L., Cornford P., De Santis M.,  
530 Henry A., Joniau S., Lam T., Mason M.D., Van den Poel H., Van den Kwast T.H., Rouvière  
531 O., Wiegel T.; members of the EAU – ESTRO – ESUR –SIOG Prostate Cancer Guidelines  
532 Panel. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer. Edn. presented at the  
533 EAU Annual Congress Copenhagen 2018. 978-94-92671-02-8. Publisher: EAU Guidelines  
534 Office. Place published: Arnhem, The Netherlands.
- 535 4. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al.  
536 Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS):  
537 a paired validating confirmatory study. *Lancet.* 2017;389(10071):815-22.
- 538 5. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala  
539 MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med.*  
540 2018;378(19):1767-77.
- 541 6. Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Mège-Lechevallier F, et al.  
542 Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-  
543 naïve patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol.*  
544 2019;20(1):100-9.
- 545 7. Jambor I, Bostrom PJ, Taimen P, Syvanen K, Kahkonen E, Kallajoki M, et al. Novel  
546 biparametric MRI and targeted biopsy improves risk stratification in men with a clinical  
547 suspicion of prostate cancer (IMPROD Trial). *J Magn Reson Imaging.* 2017;46(4):1089-95.
- 548 8. Jambor I, Verho J, Ettala O, Knaapila J, Taimen P, Syvanen KT, et al. Validation of  
549 IMPROD biparametric MRI in men with clinically suspected prostate cancer: A prospective  
550 multi-institutional trial. *PLoS Med.* 2019;16(6):e1002813.
- 551 9. Grönberg H, Eklund M, Picker W, Aly M, Jäderling F, Adolfsson J, et al. Prostate  
552 Cancer Diagnostics Using a Combination of the Stockholm3 Blood Test and Multiparametric  
553 Magnetic Resonance Imaging. *Eur Urol.* 2018;74(6):722-8.
- 554 10. Boesen L, Norgaard N, Logager V, Balslev I, Bisbjerg R, Thestrup KC, et al.  
555 Assessment of the Diagnostic Accuracy of Biparametric Magnetic Resonance Imaging for  
556 Prostate Cancer in Biopsy-Naïve Men: The Biparametric MRI for Detection of Prostate Cancer  
557 (BIDOC) Study. *JAMA Netw Open.* 2018;1(2):e180219.
- 558 11. van der Leest M, Cornel E, Israël B, Hendriks R, Padhani AR, Hoogenboom M, et al.  
559 Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus  
560 Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided  
561 Biopsy in Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective  
562 Multicenter Clinical Study. *Eur Urol.* 2019;75(4):570-8.
- 563 12. Vickers A, Carlsson SV, Cooperberg M. Routine Use of Magnetic Resonance Imaging  
564 for Early Detection of Prostate Cancer Is Not Justified by the Clinical Trial Evidence. *Eur Urol.*  
565 2020;78(3):304-6.
- 566 13. Knaapila J, Jambor I, Perez IM, Ettala O, Taimen P, Verho J, et al. Prebiopsy IMPROD  
567 Biparametric Magnetic Resonance Imaging Combined With Prostate-Specific Antigen Density  
568 in the Diagnosis of Prostate Cancer: An External Validation Study. *European urology*  
569 *oncology.* 2019.



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2  
3 570 14. Falagario UG, Jambor I, Lantz A, Ettala O, Stabile A, Taimen P, et al. Combined Use  
4 571 of Prostate-specific Antigen Density and Magnetic Resonance Imaging for Prostate Biopsy  
5 572 Decision Planning: A Retrospective Multi-institutional Study Using the Prostate Magnetic  
6 573 Resonance Imaging Outcome Database (PROMOD). *Eur Urol Oncol*. 2020.
- 8 574 15. NICE Guidance - Prostate Cancer: Diagnosis and Management: © NICE (2019)  
9 575 Prostate Cancer: Diagnosis and Management. *BJU international*. 2019;124(1).
- 10 576 16. Kranse R, Roobol M, Schröder FH. A graphical device to represent the outcomes of a  
11 577 logistic regression analysis. *The Prostate*. 2008;68(15).
- 13 578 17. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, et al.  
14 579 Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *Journal of*  
15 580 *the National Cancer Institute*. 2006;98(8).
- 16 581 18. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al.  
17 582 Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging  
18 583 Reporting and Data System Version 2. *Eur Urol*. 2019;76(3):340-51.
- 19 584 19. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014  
20 585 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason  
21 586 Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New  
22 587 Grading System. *Am J Surg Pathol*. 2016;40(2):244-52.
- 24 588 20. Roth AJ, Rosenfeld B, Kornblith AB, Gibson C, Scher HI, Curley-Smart T, et al. The  
25 589 memorial anxiety scale for prostate cancer: validation of a new scale to measure anxiety in men  
26 590 with with prostate cancer. *Cancer*. 2003;97(11):2910-8.
- 27 591 21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new  
28 592 proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*.  
29 593 2004;240(2):205-13.
- 31 594 22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic  
32 595 data capture (REDCap)--a metadata-driven methodology and workflow process for providing  
33 596 translational research informatics support. *J Biomed Inform*. 2009;42(2):377-81.
- 34 597 23. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap  
35 598 consortium: Building an international community of software platform partners. *J Biomed*  
36 599 *Inform*. 2019;95:103208.
- 38 600 24. Ahdoot M, Wilbur AR, Reese SE, Lebastchi AH, Mehravivand S, Gomella PT, et al.  
39 601 MRI-Targeted, Systematic, and Combined Biopsy for Prostate Cancer Diagnosis. *The New*  
40 602 *England journal of medicine*. 2020;382(10).
- 41 603 25. Klotz L, Chin J, Black PC, Finelli A, Anidjar M, Bladou F, et al. Comparison of  
42 604 Multiparametric Magnetic Resonance Imaging-Targeted Biopsy With Systematic Transrectal  
43 605 Ultrasonography Biopsy for Biopsy-Naive Men at Risk for Prostate Cancer: A Phase 3  
44 606 Randomized Clinical Trial. *JAMA oncology*. 2021;7(4).
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3 **609 Authors' contributions**  
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5 610 Otto Ettala, Ivan Jambor, Ileana Montoya Perez, Kari Syvänen, Pekka Taimen, Jani  
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7 611 Saunavaara, Daniel D. Sjöberg, Andrew Vickers, Hannu Aronen, Peter J. Boström  
8  
9  
10 612 contributed to the planning of the study. Otto Ettala, Ivan Jambor, Marjo Seppänen, Antti  
11  
12 613 Kaipia, Heikki Seikkula, Kari Syvänen, Pekka Taimen, Janne Verho, Aida Steiner, Ekaterina  
13  
14 614 Saukko, Peter J. Boström participated in the conduction of the study. All authors contributed  
15  
16  
17 615 to the reporting of the study.  
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22 **616 Competing interest statement.**  
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24 617 PT reports representation as a member of the Data Management Committee in the ProScreen  
25  
26 618 trial. AV is named as a co-inventor on US patent #: 9,672,329 for a statistical method to  
27  
28 619 predict the result of prostate biopsy. Patent has been commercialised and will receive  
29  
30 620 royalties from clinical use. AV is also a co-inventor of the 4kscore, a commercially available  
31  
32 621 reflex test for predicting prostate biopsy. He may receive royalties from sales of the test. He  
33  
34 622 owns stock options in Opko, which offers the test. Otherwise, no competing interest was  
35  
36 623 declared.  
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44 **624 Funding statement**  
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46 625 This work is supported by an academic grant from the Finnish Cancer Society. Grant number  
47  
48 626 is not applicable. The funding organisation will not have any authority over study design;  
49  
50 627 collection, management, analysis and interpretation of data; writing of the report; and the  
51  
52 628 decision to submit the report for publication.  
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3 **630 Figure legends**  
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6 631 Figure 1. Study flow chart. Bx, prostate biopsies; IMPROD bpMRI, bi-parametric magnetic  
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8 632 resonance imaging of prostate performed according to IMPROD MRI protocol  
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10 633 (<http://mrc.utu.fi/protocols/prostate>); PSA, prostate specific antigen; TRUS, transrectal  
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12 634 ultrasound of prostate.  
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**Table 1.** The anchors used to guide the shared 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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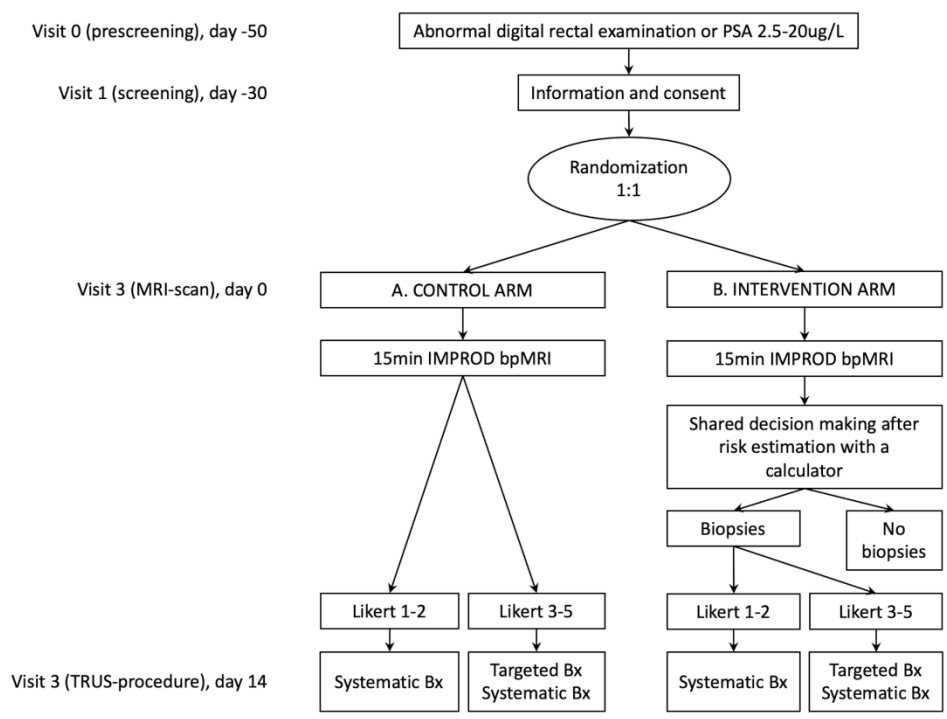


Figure 1. Study flow chart. Bx, prostate biopsies; IMPROD bpMRI, bi-parametric magnetic resonance imaging of prostate performed according to IMPROD MRI protocol (<http://mrc.utu.fi/protocols/prostate>); PSA, prostate specific antigen; TRUS, transrectal ultrasound of prostate.

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 suostumukseni, minusta keskeyttämiseen ja suostumukseni 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**

- **1<sup>st</sup> 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.*

- **2<sup>nd</sup> 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.*

- **3<sup>rd</sup> 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**

- *1<sup>st</sup> monitoring visit 10h*
- *2<sup>nd</sup> monitoring visit 40h*
- *3<sup>rd</sup> 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

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Signature



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
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <i>Rows 1-4</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <i>Rows 58-60 and Rows 424-430</i>
	2b	All items from the World Health Organization Trial Registration Data Set <i>Registered in <a href="http://clinicaltrials.gov">clinicaltrials.gov</a>, <a href="https://doi.org/10.1186/17454219120000000000000000000000">NCT03876912</a> <a href="https://doi.org/10.1186/17454219120000000000000000000000">NCT04287088</a></i>
Protocol version	3	Date and version identifier <i>Row 58-60 and Rows 424-430</i>
Funding	4	Sources and types of financial, material, and other support <i>Row 558-562</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <i>Rows 5-16 and rows 544-550</i>
	5b	Name and contact information for the trial sponsor <i>Rows 17-21</i>
	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 <i>Rows 558-563</i>
	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) <i>Not applicable. However, a risk-based monitoring will be performed. Please see Item 21a and Supplemental document 1.</i>



## 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 <i>Research questions: rows 114-119</i> <i>Justification and relevant studies: rows 82-113</i> <i>Benefits and harms: rows 334-343</i>
	6b	Explanation for choice of comparators <i>Rows 106-113</i>
Objectives	7	Specific objectives or hypotheses <i>Rows 127-138</i>
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) <i>Rows 122-126</i>

## 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 <i>Rows 457-463</i>
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) <i>Rows 156-169</i>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <i>Rows 188-200</i>
	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) <i>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.</i>

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2		11c	Strategies to improve adherence to intervention protocols, and any
3			procedures for monitoring adherence (eg, drug tablet return,
4			laboratory tests)
5			<i>Not applicable. The one-time intervention is performed in controlled</i>
6			<i>circumstances i.e. in the urological out-patient clinic.</i>
7			
8		11d	Relevant concomitant care and interventions that are permitted or
9			prohibited during the trial
10			<i>Rows 205-207</i>
11			
12			
13	Outcomes	12	Primary, secondary, and other outcomes, including the specific
14			measurement variable (eg, systolic blood pressure), analysis metric
15			(eg, change from baseRow, final value, time to event), method of
16			aggregation (eg, median, proportion), and time point for each
17			outcome. Explanation of the clinical relevance of chosen efficacy and
18			harm outcomes is strongly recommended
19			<i>Rows 139-151</i>
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22			
23	Participant	13	Time schedule of enrolment, interventions (including any run-ins and
24	timeRow		washouts), assessments, and visits for participants. A schematic
25			diagram is highly recommended (see Figure)
26			<i>Figure 1</i>
27			
28	Sample size	14	Estimated number of participants needed to achieve study objectives
29			and how it was determined, including clinical and statistical
30			assumptions supporting any sample size calculations
31			<i>Rows 350-370</i>
32			
33			
34	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
35			target sample size
36			<i>Rows 172-179</i>
37			

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

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43	Sequence	16a	Method of generating the allocation sequence (eg, computer-
44	generation		generated random numbers), and list of any factors for stratification.
45			To reduce predictability of a random sequence, details of any planned
46			restriction (eg, blocking) should be provided in a separate document
47			that is unavailable to those who enrol participants or assign
48			interventions
49			<i>Rows 182-187</i>
50			
51			
52	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
53	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
54	mechanism		describing any steps to conceal the sequence until interventions are
55			assigned
56			<i>Rows 182-187</i>
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1			
2	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
3			<i>Rows 182-187</i>
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5			
6	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
7	(masking)		<i>Open label study. No blinding.</i>
8			
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12		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
13			<i>Open label study. No blinding.</i>
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### Methods: Data collection, management, and analysis

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20	Data collection	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
21	methods		<i>Rows 372-375</i>
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29		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
30			<i>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.</i>
31			<i>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.</i>
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43	Data	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
44	management		<i>Rows 372-375</i>
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50	Statistical	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
51	methods		<i>Rows 393-421</i>
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56		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
57			<i>Rows 393-421</i>
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- 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.*

## 10 **Methods: Monitoring**

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- 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.*

## 50 **Ethics and dissemination**

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- Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
- Rows 424-432*

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2	Protocol	25	Plans for communicating important protocol modifications (eg,
3	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
4			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
5			regulators)
6			<i>Rows 430-432</i>
7			
8	Consent or assent	26a	Who will obtain informed consent or assent from potential trial
9			participants or authorised surrogates, and how (see Item 32)
10			<i>Rows 176-177</i>
11			
12			
13		26b	Additional consent provisions for collection and use of participant data
14			and biological specimens in ancillary studies, if applicable
15			<i>Biological specimens (blood and urine) are collected. This is included in the</i>
16			<i>consent.</i>
17			
18	Confidentiality	27	How personal information about potential and enrolled participants will
19			be collected, shared, and maintained in order to protect confidentiality
20			before, during, and after the trial
21			<i>Rows 370-375</i>
22			
23			
24	Declaration of	28	Financial and other competing interests for principal investigators for
25	interests		the overall trial and each study site
26			<i>No financial or other competing interest</i>
27			
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29	Access to data	29	Statement of who will have access to the final trial dataset, and
30			disclosure of contractual agreements that limit such access for
31			investigators
32			<i>Rows 549-550</i>
33			
34			
35	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
36	post-trial care		compensation to those who suffer harm from trial participation
37			<i>No compensation.</i>
38			<i>Insurance: rows 439-441</i>
39			
40	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
41	policy		participants, healthcare professionals, the public, and other relevant
42			groups (eg, via publication, reporting in results databases, or other
43			data sharing arrangements), including any publication restrictions
44			<i>Rows 443-451</i>
45			
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47		31b	Authorship eligibility guideRows and any intended use of professional
48			writers
49			<i>Eligibility for authorship in the primary report of the study includes a status of</i>
50			<i>principal or local investigator, a status of study radiologist or at least two of</i>
51			<i>the following: study design, obtaining funding, data collection, data analysis,</i>
52			<i>a key role in management of the study</i>
53			<i>No professional writers will be involved.</i>
54			
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57		31c	Plans, if any, for granting public access to the full protocol, participant-
58			level dataset, and statistical code
59			<i>All images, datasets and statistical codes will be open access.</i>
60			

## 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

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\*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.

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