Masaryk Memorial Cancer Institute

OECI CLINICAL Cancer Centre

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PROTOCOL

Prostate Cancer Screening With Abbreviated MRI Protocol

PROSTAPILOT

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Authors:	Michal Standara, MD; Jan Křístek, MD, PhD.
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1. Signature Page

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3. Table of Changes

Version	Supersedes	Change description	Valid from	Revised by
1	-	-	2022-04-01	M.Staník

2. Content

4. Basic Study Information

Basic study information		
Full name of study		Prostate Cancer Screening Using MRI With an Abbreviated Protocol
Abbreviated name of study		ProstaPilot
Expected length of study (Date from – to)		May 1, 2022 – June 30, 2025
Protocol number		NU22-09-00539 (MOU)
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Table 1 Basic study information

4.1. List of Abbreviations

bpMRI	Biparametric MRI
BPH	Benign prostate hyperplasia
BRCA	Breast Cancer tumor suppressor gene
CEITEC	Central European Institute of Technology project
CRF	case report form
CT	computed tomography
DCE	Dynamic contrast-enhanced sequence
DRE	Digital rectal examination
DWI	Diffusion-weighted image
EC	Ethic committee
EAU	European Association of Urology
ERSPC	European Randomized study of Screening for Prostate Cancer
GCP	Good clinical practice
GDPR	General Data Protection Regulation
GP	General practitioner
IBA LF	Institute of Biostatistics and Analyses, Faculty of Medicine
ICF	Informed Consent Form
ISF	Investigator's site file
ISUP	International Society of Urologic Pathologists, ISUP grade group classification system
MAFIL	Multimodal and Functional Imaging Laboratory
MMCI	Masaryk Memorial Cancer Institute
mpMRI	Multiparametric MRI
MRI	Magnetic resonance imaging
MU	Masaryk University
PACS	Picture archiving and communicating system
PHI	Prostate Health Index
PI	Principal investigator
PIRADS	Prostate Imaging Reporting and Data System
PSA	Prostate-specific antigen
PSAD	Prostate specific antigen density
SOP	Standard operational procedure
TMG	Trial Management Group
US	Ultrasonography

4.2. List of Tables

5. Introduction

Prostate cancer is the most common cancer in men in the Czech Republic, apart from nonmelanoma skin neoplasms; in recent years, its incidence in the population has been steadily increasing [1]. However, not all lesions have the potential to cause harm. These "insignificant" tumors make up an important and increasing proportion with age, about 30 % in men aged over 50 [2,3] have these insignificant lesions. Simultaneously, with increasing age and incidence of prostate cancer, the incidence of benign prostatic hyperplasia also increases. In current practice, testing of prostate-specific antigen (PSA) in serum does not make it possible to differentiate benign hyperplasia from cancer (especially significant), so it is not suitable for nationwide screening [4]. In the recommendations of the European Association of Urology (EAU), preventive PSA testing is reserved for higher-risk patients who are well informed about the possible risks of the test, including the possibility of detecting non-significant cancer [5]. A large international study, the European Randomized study of Screening for Prostate Cancer (ERSPC), shows that long-term PSA screening can lead to some reduction in mortality, though at the cost of a large number of biopsies. At least one-quarter of the study participants underwent a biopsy, authors report the positive biopsy in 24% of them [6].

The goal of nationwide screening is to capture as many clinically significant tumors as possible, i.e. those with the potential to affect the quality of life and survival. On the contrary, it is necessary to intentionally omit non-significant tumors, because their biopsy verification and subsequent potential treatment or even mere monitoring disproportionately burden the patient with risks and discomfort. At the same time, the resources of the health care system are wasted for services and care that do not have a positive impact on the patient's health.

In clinical practice, magnetic resonance imaging (MRI) is not yet recommended as an initial screening tool [5]. Two pilot studies were performed to assess the importance of MRI for the detection of prostate cancer in the general population. In 2016, Canadian authors [7] published the results of a study in 47 men, reporting multiparametric MRI examination as a better test for the prediction of prostate cancer than the PSA value (adjusted odds ratio 2.7, 95% CI 1.4–5.4, p = 0.004 vs. 1.1, 95 % CI 0.9–1.4, p = 0.21) in the general population. Among the 30 men with normal PSA (< 4ng / ml), the positive predictive value of MRI (PI-RADS score 4 or above) was 66.7 % and the negative predictive value of negative MRI (PI-RADS score below 4) was 85.7 % (p = 0.004).

Recently, the results of a larger study (406 men included) by British authors IP1-Prostagram have been published [8]. MRI, as shown in this study, has the potential to detect more clinically significant carcinomas in the general population than the PSA marker. The IP1-Prostagram study also verified that the abbreviated MRI acquisition protocol without the application of a contrast agent may be used for preventive examination.
Comparison of the currently standardized multiparametric MRI (consisting of T2-weighted sequences in at least two planes, a diffusion-weighted sequence and a dynamic post-contrast sequence) with biparametric (no contrast agent) and abbreviated biparametric (transverse plane only) protocol was performed by authors from the expert center in Nijmegen, the Netherlands [9] on a group of 699 men indicated for biopsy for high PSA, in all patients a systematic biopsy was performed as a reference; in MRI positive cases they underwent also a targeted biopsy. The sensitivity for significant cancer was 95 % for all protocols, the specificity was reduced only for the abbreviated biparametric protocol to 65 % compared with 69 % for the other protocols. Based on the results of this and other similar studies, the EAU guidelines [5] were changed to recommend MRI as a diagnostic tool of choice in clinical scenarios both before the first prostate biopsy and before re-biopsy after a previous negative one. A certain proportion of cancers is not visible in the MRI examination. According to a meta-analysis [10], the benefit of systematic biopsy for the detection of ISUP≥2 carcinomas is 8% of MRI negative patients, so it is

necessary to perform 13 systematic biopsies to detect one significant lesion missed on MRI, for ISUP≥3 cancer it is 3% (33 biopsies per one cancer).

5.1. Preliminary data at MMCI

Results of the IP1-Prostagram study [8], which the proposed study methodologically approaches:

	Positive test	Number of significant cancers detected	Number of nonsignificant cancers detected
MR (PI-RADS 3-5)	17.7 % (14.3-21.8 95% CI)	14	7
MR (PI-RADS 4-5)	10.6 % (7.9-14.0 95% CI)	11	5
PSA (≥3ng/ml)	9.9 % (7.3-13.2 95% CI)	7	6

Table 2 Results of the IP1-Prostagram study

Selected results of the COMPARE project (internal MMCI project, data not published):
The process of validation of clinical MRI prostate examinations is running in MMCI, 507 MRI examinations have been performed based on current indication criteria (i.e. staging, pre-biopsy, elevated PSA, active surveillance) by the time of writing the application, and patients have been comprehensively evaluated, including biopsies and histological samples after prostatectomy. The whole set across all indications contains 9.7 % of results marked as equivocal, i.e. PI-RADS 3. Despite the differences in the examined population, this clinical register can also be used for an evaluation of a screening project.

Validation of the biparametric MRI (bpMRI) at MMCI
Biparametric protocol efficacy has been tested by a simulated retrospective reading of more than one-year-old 51 consecutive non-selected exams without DCE sequence. Exams were anonymized and read by three uroradiologists with at least 2 years of experience in prostate MRI. Results were marked as negative if PI-RADS 1-3 and positive if PI-RADS 4-5 (PI-RADS 2 version).

	bpMRI/mpMRI concordance	bpMRI overrated	bpMRI underrated
Radiologist 1	86%	0%	14%
Radiologist 2	94%	4%	2%
Radiologist 3	84%	4%	12%

Table 3 Validation of the bpMRI at MMCI

All radiologists' bpMRI and original mpMRI results were compared against biopsy. Significant (ISUP≥2) cancer regarded as positive biopsy, 2 years of negative clinical follow up regarded as the equivalent of negative biopsy, positive PI-RADS scores only 4 or 5. The prevalence of significant cancer in this cohort was 39%.

	mpMRI	Radiologist 1 bpMRI	Radiologist 2 bpMRI	Radiologist 3 bpMRI
Sensitivity	100 %	90 %	100 %	95 %
Specificity	65 %	81 %	61 %	74 %
PPV	65 %	75 %	63 %	70 %
NPV	100 %	93 %	100 %	96 %
Accuracy	78 %	84 %	76 %	82 %
False positive rate	35 %	19 %	39 %	26 %
False negative rate	0 %	10 %	0 %	5 %

Table 4 Validation of the bpMRI at MMCI _II.part

Statistics of the MMCI Preventive Unit concerning PSA testing:
In 2019, 670 clients aged 50-69 were examined and tested for PSA. A total of 384 patients had not been examined in the previous 2 years and therefore were not tested for PSA. In all examined patients, the PSA value above 3 ng/ml occurred in 48 cases, i.e. in 7.16 %. This value is in concordance with literature data, e.g. in the IP1-Prostagram study, it was 9.9 %. These patients could potentially form the core of the study.

6. Study Objectives

Several studies have confirmed the benefit of MRI examination in patients at a high risk of cancer before prostate biopsy concerning a selection of patients who are very unlikely to bear a clinically significant cancer who can then avoid immediate biopsy. A limited number of pilot studies have shown the promising potential of MRI as an initial screening test in the general population.
We believe that the abbreviated MRI protocol is a suitable imaging test for prostate cancer screening, as it will allow the detection of a higher proportion of clinically significant lesions.

6.1. Primary Endpoints

Primary aim: To assess the importance of the imaging test in the screening of significant prostate cancer in asymptomatic men, compared with PSA screening.

Primary endpoint:
To determine the proportion of positive MRI findings (PI-RADS 4+) in the general population of men aged 50-69 years.

Further endpoints leading to the primary aim:

- To determine the distribution of PI-RADS scores in the screened population.
- To evaluate the proportion of significant and non-significant cancers in individual categories of PI-RADS scores in patients indicated for biopsy.
- To compare the combinations of tested biomarkers for the detection of significant and non-significant cancer.
- To evaluate the shift in the findings considering the results of the second round of screening.
- To estimate the relative sensitivity and specificity of MRI vs. laboratory markers.

6.2. Secondary Endpoints

Secondary aim: Feasibility evaluation of a larger-scale study of screening for significant prostate cancer using an imaging modality.

Secondary endpoints leading to the secondary aim:

- To evaluate the degree of concordance between radiologists performing MRI scoring.
- To determine the prevalence of complications after a biopsy.
- To evaluate the number of participants who:
  - agreed to be included in the study through used recruitment strategies.
  - contacted the team themselves with a request for testing.
  - signed the informed consent and were enrolled in the study.
  - visited a screening facility.
  - completed the designated examinations.
- To describe the success of different invitation methods on the second screening round.
- Tracking of individual inclusion and screening test costs.
- Monitoring of the numbers and reasons of participants who did not complete scheduled tests, follow-up examinations, or withdrew informed consent.

7. Study Design

7.1. Study Type

A prospective cross-sectional (with a longitudinal component, 2nd screening round) study evaluating the possibility of using the abbreviated bpMRI protocol technique for screening clinically significant prostate cancer in men from the general population.

7.2. Study Population

Clients of the MMCI Preventive Unit, patients invited by general practitioners, and other men from the community recruitment. We plan to include 300 participants – see Fig. 5 for detailed information about participant recruiting.

Source	Advantages	Disadvantage	Maximum estimated number
MMCI Preventive Unit	Motivated client Complete documentation Personal contact	Often a non-local client	* up to 576
General practitioners and urologists	General population Documentation available Recommendation by a trusted person	Rarely not -pretested by PSA Administrative costs	** 30 / GP office
Advertising and social networks	Simultaneous popularization of health prevention and presentation of the institute		up to 100

Table 5 Methods of recruiting patients

** In 2019, 384 clients with no previous PSA testing in the last 2 years were examined in the MMCI Preventive Unit, with an expected first round of recruitment of 1.5 years 384 * 1.5 = 576.*
*** According to a survey among general practitioners.*

7.3. Sample size

Our primary endpoint is to determine the proportion of positive MRI findings (PI-RADS 4-5). We therefore aim to produce a two-sided 95 % confidence interval with a width equal to 6 percent points (approximately +/- 3 percent points). In line with findings from Prostagram study, we expect 11 % of positive individuals. Due to prevalent opportunistic screening in the Czech Republic, we also considered potential estimate of prevalence of positives lowered by 5 percent points (6 %). In that case, a sample of 275 men (minimum for 1st round) would be adequate to achieve target confidence interval width. We performed sample size computations in PASS 13 software [13], considering exact (Clopper–Pearson) confidence interval formula.

7.4. Inclusion Criteria

Inclusion criteria:

- Age 50-69 years
- Life expectancy over 10 years
- Ability to undergo all planned procedures (without contraindications to MRI or biopsy)
- No known prostate cancer or prostate biopsy in the past (interventions for BPH are not a restriction)
- No PSA test or prostate MRI in the past 2 years.
- No signs of prostatitis or urinary tract infection in the past 6 months.
- Signed informed consent.

7.5. Exclusion Criteria

Exclusion criteria:

- Contraindications to MRI
- Hip replacement
- Known BRCA1/BRCA2 mutation

7.6. Criteria for termination of patient participation in the study

1) Patient decision, patient non-cooperation.
2) Inability of the patient to undergo the tests/procedures established by the study protocol.
3) The attending physician's decision in the event that termination of participation in the study is in the patient's best interest.
4) Detection of prostate cancer / histologically confirmed diagnosis.

8. Methodology

8.1. Tests and Procedures performed

Laboratory examination:

- Serum PSA evaluation
- PHI calculation (Prostate Health Index) to be performed only if the PSA values are in the range of 2-10 ng/l [14]

Magnetic resonance (MRI)

- MRI of the prostate (abbreviated biparametric protocol)

MRI specifications:

- Protocol with anatomical T2 sequence and diffusion-weighted images (DWI), according to the standards [15].
- Typical complete examination time does not exceed 20 minutes, planned acquisition time less than 15 minutes.
- No contrast agent or spasmolytics is injected.

Digital rectal examination (DRE)

- Digital rectal examination (DRE) as part of a clinical visit at a urologist in patients with a positive PSA test
- Biopsy - if indicated, with pathological examination followed

8.2. Blinding, Study Arm

- Every test evaluator (radiologist/urologist) does not know the results of other tests.
- MRI reports entered in the registry obligatorily before the biopsy.
- The patient is not informed which test was positive and resulted in an indication for biopsy.
- The pathologist does not know the results of MRI or laboratory tests.
- Single-arm study

8.3. Study design

The MRI is assessed with the PI-RADS 2.1 system, each finding is reported on a scale of 1-5. To minimize the detection of non-significant cancers and to reduce the number of biopsies according to the results of the IP1-Prostagram study [8], a PI-RADS value of 4-5 was chosen as a positive test representation. Consensual double reading by 2 experienced uroradiologists (at least 400 mpMRI of the prostate read by the beginning of the study [16]). Men with a positive MR test are planned for a targeted MRI/US fusion and systematic prostate biopsy.

Men with a positive blood marker (either PSA, PSAD, or PHI) are planned for a systematic 12 core biopsy. Positive test results are PSA ≥ 3, integrated marker PSAD ≥ 0.15 [17], and PHI ≥ 35.
Study participants are invited to repeat the screening tests after 2 years by letter. If they do not respond to a written offer, also by e-mail and SMS. The workflow of the project is graphically illustrated in [Table 6].

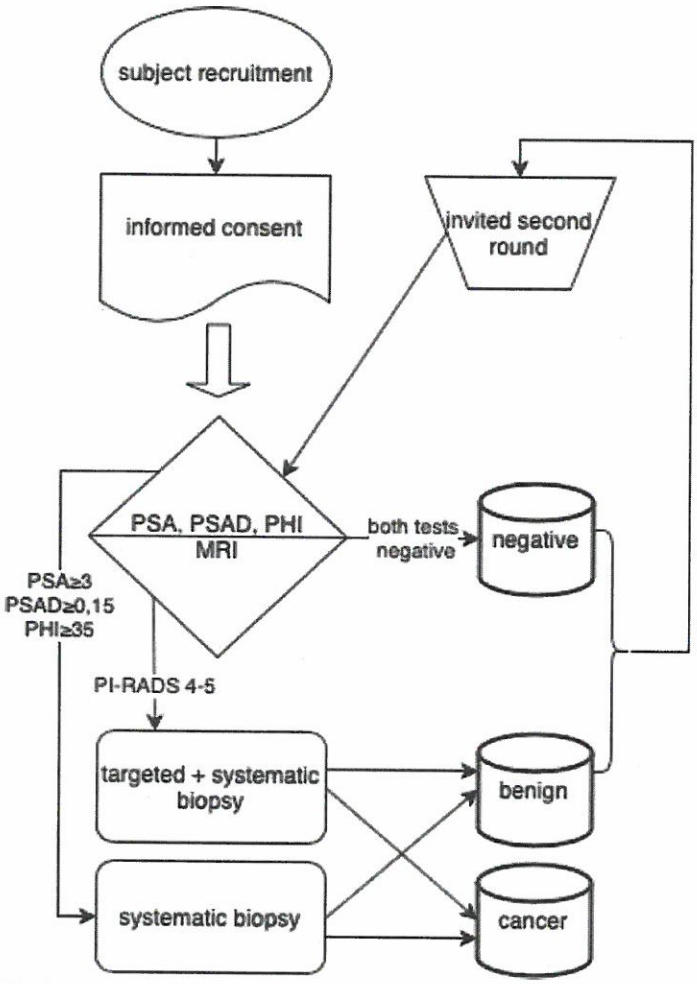

Table 6 The workflow of the study

Definition of clinically significant cancer: ISUP Grade Group ≥ 2.

8.4. Project Time Schedule

	MMCI	MAFIL	IBA LF
2022-preparation phase (1-2 months)	Coordination of preparatory work. Preparation of data register.	Data transfer and scheduling tests.	Design of statistical data plan and model for data collection.
2022	Scheduling MRI examinations and blood sampling. MRI reporting. Supervising the register. Patient consultation and biopsy.	MRI examination - 140 patients.	Ongoing analyses and proposals for methodological corrections.
2023	Scheduling MRI examinations and blood sampling. MRI reporting. Supervising the register. Patient consultation and biopsy. Evaluation of the first screening round.	MRI examination - 160 patients.	Evaluation of the first round of screening. Cooperation on the interim report.
2024	Invitation to the second round. Scheduling MRI examinations and blood sampling. MRI reporting. Supervising the register. Patient consultation and biopsy. Evaluation of the first screening round.	MRI examination - 120 patients.	Evaluation of the first round of screening. Publication of results.
2025	Invitation to the second round. Scheduling MRI examinations and blood sampling. MRI reporting. Supervising the register. Patient consultation and biopsy. Study evaluation and publication.	MRI examination - 80 patients.	Evaluation of the second round of screening. Preparation of the final report. Publication of results.

Table 7 Project Time schedule

8.5. Data Management, Documentation

The principal investigator must keep all adequate and sufficient records to document the workflow of the study and to verify the data collected. These documents are divided into two categories - ISF (Investigator's Site File) documentation and source documentation kept in electronic form in the hospital information system (laboratory and clinical data).
All basic documents required for the correct execution of the clinical trial will be kept at the center (at the health service provider) for at least 15 years after the end of the clinical trial in accordance with the applicable legislation. If necessary, they will be accessible for inspection - audit.

The ISF documentation includes the informed consent of participants, questionnaires at the entry and at the end the study, MRI images recorded in the PACS system and clinical and diagnostic data of the participants, which will be recorded in the COMPARE register, in pseudonymized form under studyID. In all ISF documents except the ICF, participants will be identified by an StudyID and not by name. A list of included participants (the so-called Identification key) will be kept at the place of study and it will include: participant's name, birthdate, personal identification number and the assigned StudyID. The identification key will be held by the study coordinators.

In the COMPARE database, validation rules are set to ensure data quality control and mistakes are eliminated during regular data reviews using the system of queries.

9. Statistical Processing

9.1. Statistical Analytical Plan and Methodology

It will be published together with the final report.

10. Ethical and Legislative Requirements

The processing of personal data of persons involved in study ProstaPilot is carried out in accordance with the requirements and provisions of Act No 101/2000 Coll, On the protection of personal data and on Amendments to certain Acts, as amended or with legal regulation replacing this Act, and in accordance with Regulation (EU) 2016/679 of the European parliament and of the Council on protection of nature persons with regard to the processing of personal data and on the free movement of such data (hereinafter „GDPR"). Both the controller and the processor are obliged to observe the rules and obligations coming from GDPR, as well as to set up the relevant processes for data subject's rights fulfilment.

The clinical study ProstaPilot was discussed and approved by the local ethics committee at the MMCI.Before enrolment, each participant will be informed in detail about the mentioned study by a physician and then asked to sign the Informed Consent Form (ICF) to participate in this study. Each participant will be informed about the possible risks of the involvement in this study, as well as about the possibility of his discontinuation in the study at any time without any consequences. The participant will be informed about the precautions that will be taken due to the personal data protection as well.
Sufficient time will be given to the participant to read thoroughly the written patient information and ICF. All his questions will be satisfactorily answered so that he can make a responsible decision whether he agrees to participate in the study or not. Signed ICF will be stored in the ISF folder at the clinical study center of MMCI. After signing the ICF, the participant receives a studyID from the coordinator of ProstaPilot study. The identification key is available only to the coordinator, not to the physicians involved, due to the blinding of the study.
The information about giving the participant´s content should be confirmed in the COMPARE register.A new patient cannot be registered without this confirmation.
Study coordinators enter participant´s data into the COMPARE register under a unique studyID and they are the only persons who can identify participants based on the studyID. Physician-radiologist accessing the registry and entering MRI data cannot directly identify the participant in the registry, resp. in the study. IBA LF is responsible for data analysis and processes only pseudonymous data. Participants are informed about the transfer of data in pseudonymous form when giving informed consent. IBA LF is obliged to take appropriate technical and organizational precautions to protect personal data.
The patient may claim his rights either with the study coordinator or with the data protection officer at the MMCI. Contacts are provided in the ICF and on the study voucher.

11. Rules for Publishing

All publication outputs of the clinical study will be carried out by a team of study investigators under the leadership of the principal investigator. The submission of each publication is subject to the consent of the principal investigator. The results of this study may be published or presented at scientific meetings after the approval of the PI and always after anonymizing the subjects' personal data in accordance with Act No. 101/2000 Coll., On the Protection of Personal Data and in accordance with Regulation (EU) 2016/679 (GDPR).

12. .Quality Control and Quality Assurance

To supervise the quality of the clinical study, the sponsor has established a working group "Trial Management Group" (TMG), whose aim will be to ensure whether this study is conducted in accordance with the protocol, standard operating procedures (SOPs), GCP and all applicable legal requirements. It will be verified whether the data records are complete, true and in accordance with the source documentation.

TMG will review continously:

- Deviation from the protocol (major findings) – their assessment and proposal of corrective and preventive actions, especially in relation to the security of participants and preservation of data integrity

If necessary, it will evaluate other events:

- potential changes – amendments to the protocol
- assessment of reasons for interruption or early termination of the clinical study
- potential new security risks
- possible continuation of the study/possibility of including other subjects

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