The Göteborg-2 trial (Protocol Version 2.0 (replaces version 1.0 with amendments)

A prospective, randomized, population-based trial of prostate cancer screening with prostate-specific antigen testing followed by magnetic resonance imaging of the prostate in balancing the benefits and harms of screening

Sponsored by:

Karin and Christer Johansson´ s Foundation
The Swedish Cancer Society (Cancerfonden)
ALF (agreement between the Swedish State and the Swedish Regions for education and research)
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Chief Investigator	Co-chief investigator	Co-chief investigator

Jonas Wallström	Marianne Månsson
Co-chief investigator	Chief Statistician

Content

PARTICIPATING UNITS IN THE STUDY

This study will be carried out as a single site study with the trial administration located at the Department of Urology at Sahlgrenska University Hospital, Göteborg, Sweden.

Starting in 2015, men randomized to the study will emanate from the geographical catchment area, i.e. the city of Göteborg and 10 surrounding municipalities: Ale, Alingsås, Herrljunga, Härryda, Kungälv, Lerum, Mölndal, Partille, Vårgårda, and Öckerö.

The following departments will participate in the study:

1. Sahlgrenska Academy at University of Gothenburg

I. Department of Urology
II. Department of Radiology
III. Department of Pathology

2. Clinical Chemistry at Unilabs, Skövde, Sweden

3. Blood sampling units (See 5.2.1)

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STUDY MANAGEMENT

All questions concerning this protocol should be sent to Jonas Hugosson via email (jonas.hugosson@surgery.gu.se). The appropriate team member will respond with a "cc" to jonas.hugosson@surgery.gu.se. A response should generally be received within 24 hours (Monday-Friday).

For general inquiries about the Göteborg-2 trial, please visit the frequently asked questions (FAQ) on our website at https://www.g2screening.se or use the contact form on the website to contact us.

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

BPH	Benign Prostatic Hyperplasia
CI	Confidence Interval
CG	Control Group
DRE	Digital Rectal Examination
EORTC	European Organization for Research and Treatment of Cancer
ERSPC	European Randomized Study of Screening for Prostate Cancer
HRQOL	Health Related Quality Of Life
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
ITS	Intention To Screen
MRI	Magnetic Resonance Imaging
mpMRI	Multi-Parametric Magnetic Resonance Imaging
bpMRI	Bi-Parametric Magnetic Resonance Imaging
NND	Number Needed to Diagnose
NNI	Number Needed to Invite to screening
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
PSA	Prostate-Specific Antigen
QoL	Quality of Life
RCT	Randomized Controlled Trial
SG	Screening Group
STAI	State-Trait Anxiety Inventory

1 INTRODUCTION

Prostate cancer is a major public health problem in Sweden, where it is the most common male cancer and the most common cause of cancer-related death. Each year, approximately 2,500 men die from prostate cancer, accounting for 5% of all causes of deaths among Swedish males. Without early detection, prostate cancer is typically diagnosed at a late stage when curative treatment is no longer an option. Early detection of prostate cancer was made possible by the introduction of the blood test prostate-specific-antigen (PSA) in the early 80's [1]. In some countries, regular PSA-testing is advocated, whereas Swedish authorities and the Swedish National Board of Health and Welfare have long had restrictive attitudes towards general prostate cancer screening, with the concern that it does more harm than good.

1.1 Background and rationale

Curative treatment for localized PC is effective [1, 2] and prostate-specific antigen (PSA) testing can enable the detection of prostate cancer (PC) at an early, curable stage [3-5]. The main problem with PSA-testing is overdiagnosis and the subsequent risk of overtreatment [6-8]. Due to the low specificity of the PSA-test many men are subjected to unnecessary biopsies with associated discomfort and risk of side-effects such as infections and bleeding [9, 10]. The use of systematic biopsy technique, which was the standard clinical method until recently, together with the large number of slow-growing cancers in the prostate never causing harm, are the main mechanisms behind overdiagnosis [11, 12].

Reduction of PC mortality by regular PSA-testing has been convincingly demonstrated [13-15]. However, the beneficial mortality reduction is not presently considered to outweigh the harms of screening. A refined screening strategy that maintains the PC mortality reduction while avoiding unnecessary biopsies and detection of clinically insignificant cancers, is much needed. In recent years, there has been a fundamental shift in the diagnostic work up of men with clinical suspicion of PC with magnetic resonance imaging (MRI) performed before prostate biopsy to guide, and sometimes even omit, biopsy [16]. MRI of the prostate is intended to discriminate insignificant cancers from harmful ones, and in this manner avoid unnecessary biopsies and overdiagnosis [17-19]. The findings of the PRECISION study, and several others, confirmed this and led to the recent paradigm shift in patients with clinical suspicion of cancer [20-23].

In a pilot study embedded within the last screening round of the Göteborg-1 trial, we evaluated prebiopsy MRI in a screening setting with promising results; MRI-targeted biopsy detected almost as many clinically significant cancers as the strategy with systematic biopsy, while reducing the detection rate of insignificant cancers [24]. However, the role of MRI as a screening tool has not yet been documented in large-scale, randomized screening trials. To bring clarity to this matter we launched the "Göteborg-2 trial" in 2015, as a prospective, randomized, population-based trial of PC screening with PSA testing followed by prostate MRI. Herein, we describe the study design, procedures and the analysis plan.

[24]

2 STUDY OBJECTIVES AND OUTCOME MEASURES

This study design can be looked upon as an umbrella evaluating three major research questions: i) will omitting systematic biopsies in all men with elevated PSA (>= 3 ng/mL) and instead only biopsy MRI positive men, and only so with targeted biopsies, reduce the risk of detecting clinically insignificant cancers while still maintaining a sufficiently high detection rate of clinically significant cancers

ii) Will changing the PSA cut off from 3 ng/ml to 1.8 ng/ml decrease the risk of being detected with advanced, incurable cancer, instead allowing the cancer to be detected at an earlier, curable stage.

iii) Is a screening algorithm including prebiopsy MRI efficient to reduce prostate cancer mortality compared to the mortality in men randomized to a non-invited control group

2.1 Primary objectives

The primary objective of the trial is to evaluate whether changing the screening algorithm in men with PSA ≥ 3 ng/mL from systematic biopsy to MRI-targeted biopsy only, can reduce the risk of detecting clinically insignificant cancers.

2.2 Secondary objectives

1. To evaluate whether screening with pre-biopsy MRI and only MRI-targeted biopsy in men with PSA ≥ 3 ng/mL can maintain the detection rate of clinically significant cancer compared to systematic biopsy.

2.3 Additional objectives

1. To evaluate whether detection of clinically significant PC in a curable stage can be improved in screening with pre-biopsy MRI and only MRI-targeted biopsy if the PSA-cut off is lowered from 3 to 1.8 ng/mL. This study will also be described in details in a separate addendum to this protocol
2. To evaluate whether organized sequential screening with PSA followed by MRI can reduce prostate cancer mortality compared to the mortality in men randomized to a non-invited control group. This study will also be described in details in a separate addendum to this protocol.
3. To evaluate whether bi-parametric MRI is non-inferior to multi-parametric MRI in the detection of prostate cancer in a screening setting. This study will also be described in details in a separate addendum to this protocol (26).

2.4 Substudy objectives

A number of side-studies embedded within this trial will be performed evaluating technical aspects of multiparametric MRI (mpMRI) including the role of artificial intelligence, feasibility, logistics, costs, cost- effectiveness, quality of life, biomarkers, equitable care and health care disparities.

2.5 Outcome measures and times of assessments

Details of all outcome definitions and times of assessments are defined in table below.

Outcome definitions and times of assessments for the primary and secondary objectives

Objective	Definition	Time of assessment
Primary	Proportions of clinically insignificant cancers* Arm 1 vs Arm 2+3*	After completion of screening-round 1 (only screening visits in round 1 are analysed). Next assessment includes all screening visits up to 30th June 2022 and 2, 6 and 10 years thereafter
Secondary	Proportions of clinically significant cancers* Arm 1 vs Arm 2+3*.	After completion of screening-round 1 (only screening visits in round 1 are analysed). Next assessment includes all screening visits up to 30th June 2022 and 2, 6 and 10 years thereafter
Additional 1)	Proportions of clinically significant cancers Arm 2 vs Arm 3. See separate protocol	Including men who were invited and participated up to 30th June 2024 and 2, 6 and 10 years thereafter
Additional 2)	Cancer-specific incidence and mortality SG vs CG (intention to screen analysis). See separate protocol	12 years after randomization (31 December 2027) and every third year after.
Additional 3)	Sensitivity and specificity comparing multi- versus bi-parametric MRI. See separate protocol	After completion of screening round 1

SR = screening round. SG = Screening group. CG = control group

* The first analysis based upon screening round 1 will also include men in arm 3 ignoring cancers detected in the PSA range 1.8-2.99 and group them together with men in arm 2, but analysis coming after that including also subsequent screening rounds will only compare arm1 versus arm 2.

The primary definition of clinically significant PC is Gleason[1] Score ≥3 + 4 (also known as Grade Group 2-5) on biopsy but will also be analyzed with other definitions provided in Table page 25.

[1] Gleason grading (after Donald F Gleason 1920-2008) is the pathological grading of prostate needle biopsies. Gleason Score is based on recognizing the two most common morphological Gleason grade/pattern under the microscope, a primary and secondary grade, and then summing the two, e.g. 4+3=7. If there are more than two patterns present, and the worst grade is neither the primary nor the secondary grade, GS is based on the predominant + highest grade. The higher the score, the more aggressive the tumor is.

3 STUDY DESIGN

This is a population-based screening trial with randomization of men into either controls (not invited) or an intervention group invited for screening. Participating men are further randomly allocated into one out of three test arms with different designs following the flow chart in Figure 1. The rationale for randomizing participating men into three groups is based on the main obstacle with current gold standard, i.e. PSA and systematic biopsies which lead to an unacceptably high rate of over-diagnosis of small indolent cancers.
The hypothesis is that switching from systematic biopsies in all men with elevated PSA to targeted biopsies only, and only in men with positive MRI, will strongly decrease the risk of over-diagnosis and thus shift the balance between benefits versus harms so that screening for prostate cancer could be accepted as general health policy. The design is appropriate for testing this hypothesis and will hopefully provide level I evidence as to the preferred screening algorithm incorporating MRI as an adjunct to PSA as compared to the current gold standard, i.e. PSA and systematic biopsies. Performing systematic biopsies blinded to MRI result and thereafter targeted biopsies in arm 1 (see below) makes it possible i) to compare cancers detected by targeted biopsies only with ii) those detected by the combination of systematic and targeted biopsies and iii) those detected by systematic biopsies only. Hence the following comparisons between different diagnostic approaches can be performed after completion of screening round 1:

- Pre-biopsy MRI and MRI-targeted biopsy only vs systematic biopsy and in case of a positive MRI also targeted biopsy (Arm 2-3 vs Arm1 (primary objective); can also be compared within Arm1)
- Pre-biopsy MRI and MRI-targeted biopsy vs systematic biopsy (Arm 2-3 vs Arm1; can also be compared within Arm1)
- Pre-biopsy MRI and systematic biopsy and in case of a positive MRI also targeted biopsy vs systematic biopsy (Within Arm1)
- Pre-biopsy MRI and in case of a positive MRI both targeted biopsy and systematic biopsy vs systematic biopsy (Within Arm1)
- Pre-biopsy MRI and in case of a positive MRI both targeted biopsy and systematic biopsy vs systematic biopsy and in case of a positive MRI also targeted biopsy (Within Arm1)
- Pre-biopsy MRI and in case of a positive MRI both targeted biopsy and systematic biopsy vs pre-biopsy MRI and MRI-targeted biopsy (Within Arm1)

After completion of multiple screening rounds

- Pre-biopsy MRI and MRI targeted biopsy only versus systematic biopsy and in case of a positive MRI also targeted biopsy (Arm 2 versus Arm 1)
- Changing PSA cut off from 3 to 1.8 ng/mL (Arm 2 versus Arm 3)

3.1 Selection and Study enrollment procedures

The study population will be identified from a random sample from the population register of men in the age group 50-60 (including age 60) years in the county of Göteborg and 10 surrounding municipalities: Ale, Alingsås, Herrljunga, Härryda, Kungälv, Lerum, Mölndal, Partille, Vårgårda, and Öckerö.

The extraction of the initial random study population will be carried out stratified on county, with respect to the number of inhabitants in that county.

3.2 Inclusion criteria

At date of randomization:

1. Alive
2. A registered address in the county of Gothenburg, Sweden or any of 10 specified surrounding municipalities
3. Age 50 to 60 years

3.3 Exclusion Criteria

At date of randomization:

1. A diagnosis of prostate cancer (will be excluded from analysis but will remain in the database (for future Ad Hoc analysis)
2. Emigration before randomization (date of emigration not updated in the Population Register at time of randomization)
3. Death before randomization (date of death not updated in the Population Register at time of randomization)

3.4 Randomization to Control Group and Screening Group

The Ethical committee at University of Gothenburg, working in accordance with Swedish rules and regulation, permits upfront randomization before consent. The first randomization, to control group and screening group, will be performed 1:1. Since January 2017, due to an observed lower than anticipated participation rate, the allocation was changed to 2:1 in order to reach a sufficient sample size in the SG to evaluate the primary objective at four years. The control group will be followed for prostate cancer incidence and prostate cancer mortality by cross-linking to the Regional Cancer registry as well as the Swedish Cause of death registry on the personal identification number, unique for each Swedish resident. The control group will thus constitute a pure control group receiving current clinical practice and standard care in Sweden today, which implies no regular organized PSA-testing (but opportunistic screening may occur). A mailed letter will inform men in the control group and that their participation is voluntarily (see 3.6 below).

When combining the men randomized with allocation ratio 1:1 up to January 22, 2017 with men randomized with ratio 1:2 thereafter, the distribution of follow-up times in the screening and control groups will differ. In order to achieve the same distribution of follow-up times in the two groups and hence make them comparable, only half of the men randomized to the control group up to January 22, 2017 will be considered. Therefore, a new variable called "active/non-active control group" was included in the database, where half of the men in the control group randomized up to January 22 2017 will be coded as "active", the rest of the control men as "non-active". The "active" men were randomly selected by taking year of birth and municipality into account, in the same way as they were balanced at randomization (see Amendment 4).

3.5 Allocation of Screening Group to three study arms

Men randomized to the screening group and who accept participation will be randomly allocated 1:1:1 into one of the three study arms. Allocation to study arm will occur automatically and instantly the first time a man has a PSA test delivered to the central database. PSA test results are delivered electronically directly into the database from the central laboratory and there is no manual interference.

3.6 Study participant information and consent

The Regional Ethics Review Board at University of Gothenburg approved the Göteborg-2 trial in January 2015, registration number 890-14. All men randomized to the SG or CG receive detailed information about the study by postal mail, on its design, benefits and risks, contact details, and a reference link to the study website. The website also includes a link to the Swedish National Board of Health and Welfare's written information about PSA-testing and its pros and cons. Men in both groups are informed that participation is voluntary and can be terminated at any time by a deliberate action of the participant (opt out procedure). Written informed consent is thus not requested from all participants in the main study but men who have a positive screening-test and are invited for prostate biopsy are asked to sign an informed consent where they permit study personal to take part of their medical records. Informed consent is also requested in some side studies.

Due to low participation rate following invitation reminders in screening round 2, invitation reminders are since February 27, 2019 only sent in the first screening round (see Amendment 7).

4 STUDY INTERVENTION

4.1 Intervention

Arm (1) (reference arm)

- Screen-negative: If the total-PSA level is “normal”, i.e. below the cut-off 3.0 ng/mL, no further testing or examination will be performed, but all men will be re-invited.

- Screen-positive: If the total-PSA level is “elevated” above the cut-off i.e. ≥ 3.0 ng/mL, the man will be invited for an MRI.

  All men will be recommended standard biopsy, i.e., digital rectal exam followed by TRUS-guided 12-core standard prostate biopsy according to the screening protocol. These standard biopsies will be taken with both the urologist and subject blinded to the MRI result. After these standard biopsies, the study nurse will show the urologist the result from the MRI examination, and in case of suspicious lesion at MRI, 3-4 targeted* biopsies in each of these lesions will be performed in the same séance; 3 targeted biopsies if one of the systematic biopsies already hit the area, and 4 targeted biopsies if otherwise.

  - Men in whom MRI for any reason is not achievable or the result is inconclusive will only undergo systematic biopsies

Arm (2) (first experimental arm)

- Screen-negative: If the total-PSA level is “normal”, i.e., below 3.0 ng/mL, no further testing or examination will be performed. The man will be re-invited for screening identical to Arm (1).

- Screen-positive: If the total-PSA level is “elevated” ≥ 3.0 ng/mL, he will be offered MRI.
  - If the MRI is positive (PI-RADS 3-4), only targeted* biopsies will be performed, i.e. 4 biopsy cores targeted against each suspicious lesion, but no systematic biopsies.
  - If the MRI is positive (PI-RADS 5), targeted* biopsies will be performed, i.e., 4 biopsy cores targeted against each suspicious lesion but also systematic biopsies. Changed 2018-10-15 (see amendment 5)
  - If the MRI is negative no biopsies will be performed.
  - If the MRI is negative and PSA ≥ 10 and PSA density (PSAD), ≥ 0.1, systematic 12-core biopsies will be performed. PSA cut off changed 2016-03-01 from 20 to 10 ng/mL (see amendment 1).
  - Men in whom MRI for any reason is not achievable, or the MRI is technically inferior (for example in men with hip prothesis), are invited for urological examination with digital rectal examination (DRE) and transrectal ultrasound

(TRUS). These men are included in the intention to screen analysis but not in the per protocol analysis (see 6.2.1).

Arm (3) (experimental arm II)

- Identical to arm (2) except that the PSA-cut off is lower, ≥1.8 ng/mL.

Men in Arm 2 and 3 with cancer diagnosed at targeted biopsies during screening round 1 are recommended completion with systematic biopsies 6-12 weeks after the first biopsy.

* Targeted biopsy = biopsy targeted against MRI positive areas (suspicious for cancer)

4.2 Re-invitation intervals

On October 17, 2016, the re-invitation interval for those in arm 1+2 with PSA 2.4-2.99 was changed from 1 to 2 years. Men already informed that they would be re-invited after one year were notified that the invitation would be postponed one year.
Re-invitation interval algorithm:

Re-invitation intervals	
Arms 1+2 + 3	
PSA (ng/mL)	Interval (years)
≤0.59	8
0.6 – 1.19	4
≥ 1.2	2

Special re-invitation intervals	
Subjects	Interval (years)
Non-participation in any round	2*
Negative biopsy and/or negative MRI twice in a row	4
PSA ≥3, neither MRI nor biopsy performed	2
PSA ≥3, positive MRI, no biopsies performed	2

Men not participating at invitation in round 1 will receive a reminder after 3 and 9 months. In subsequent round no reminders will be sent out.

4.3 Upper age limit

On October 1, 2015, the algorithm for upper age limit, defined at time of study start (updated with new PSA-thresholds 2020), was updated (see amendment 2).

The new algorithm:

Upper age limit (no more screening)	
All arms	
PSA (ng/mL)	Age (years)
≤ 0.59	≥62
0.6 – 1.19	≥65
1.2 – 1.79	≥70
≥ 1.8	≥75

4.4 Special circumstances

Due to high risk of potentially lethal prostate cancer, all men with PSA ≥ 10.0 ng/mL, irrespective of Study Arm, will, for ethical reasons, be recommended 12 standard TRUS-biopsies plus additional targeted biopsies if positive MRI. Exceptions are those with PSAD < 0.1.

On March 1, 2016, the PSA level indicating high risk of lethal prostate cancer was adjusted from ≥ 20.0 ng/mL to PSA ≥ 10.0 ng/mL in order to harmonize with National standardized course of medical care (SVF) for prostate cancer.

Since October 15, 2018, all men with MRI showing a PI-RADS-score 5 in Arm 2 and Arm 3, should, apart from the targeted biopsies, also undergo systematic biopsies with 12 cores. All men with PI-RADS 5 lesions and negative biopsies should be re-evaluated at a radiology conference (round) and, if no adjustment of PI-RADS score, a new set of targeted biopsies should be carried out within 3 months.

The study design is depicted in Figure 1.

5 Study organisation and infrastructure

5.1 Outcome Ascertainment

The project is planned to run for an initial 4 years with an evaluation of the primary and some of the secondary objectives during year 4. Details of outcomes and times of assessments are given in Table 1 (p 19)

Prostate cancer diagnosis

Reporting of cancer to the National Prostate Cancer Register and the National Cancer Register is mandatory by Swedish law. All diagnoses made in the study will be continuously recorded in the study database. Every 3 months, cross-linkage on the study participants' personal identification number will also be performed with the study database and the cancer registries, to ensure accuracy and completeness of the diagnoses.

Prostate biopsies

One internal pathologist with 25 years of experience of prostate pathology will review the prostate biopsies in the study. To minimize heterogeneity in Gleason grading between different pathologists a secondary review of biopsies with a cancer diagnosis will be conducted by two external pathologists. The reviewers are blinded to the primary local assessment and work independently from each other. Each core harbouring cancer is reviewed separately. The final Gleason score for each patient is based upon these three verdicts. In case of agreement between at least two of the reviewers the Gleason score is set. In case all three reviewers differ from each other the "middle" assessment will be used. In the first screening round the internal pathologist is Dr. Carl-Gustaf Pihl with 25 years of experience of prostate pathology, and the external pathologists are Professor Lars Egevad at Karolinska Institute, Stockholm and Dr Ulrika Axcrona at University of Oslo.

Reference for biopsy outcome

For analysing the endpoints based on prostate biopsies, different sets of biopsies will be taken into account (see table below). Adding systematic biopsies at a second occasion in men with cancer detected with targeted biopsies in arms 2 and 3 is an attempt to compensate for possible sampling errors due to the fact that MR positive and MR negative cancers were primarily biopsied with two different techniques. Only systematic biopsies taken within one year after the diagnostic biopsy are taken into account (arms 2 and 3).
If MRI, for any reason, is not achievable or inconclusive, see 4.1
Additional biopsies taken after what here is stated are not considered

Arm 1	**Arm, 1**	**Arm 2 and 3 (PSA < 10 ng/mL or PSA ≥ 10 and PSAD < 0.1)**		**Arm 2 and 3 (PSA ≥10 ng/mL and PSAD ≥0.1)**	
MRI pos*	MRI neg	MRI pos **, ***	MRI neg	MRI pos*	MRI neg
12 systematic plus 3-4 targeted biopsies	12 systematic biopsies	4 targeted biopsies. If cancer. 12 additional cores at a later occasion	No biopsies	12 systematic plus 3-4 targeted* biopsies	12 systematic biopsies

* If the MRI positive sector is sampled with one core in the systematic biopsies, 3 extra targeted biopsies are sampled from that sector, otherwise 4 biopsies
** If MRI shows PI-RADS 5, 12 systematic biopsies are added (not in screening round 1)
***If cancer is found in the targeted biopsies patients are rescheduled for systematic biopsies

Prostatectomy specimen

Prostatectomy specimen will be processed according to Swedish standard (KVAST document) and reviewed at the department of Pathology at Sahlgrenska University Hospital. Tumor volume will be assessed by the planimetric method. Endpoint definitions for prostatectomy specimen are given in table 3, p

Prostate cancer mortality

The project is planned to continue to allow evaluating long-term effects on prostate cancer mortality. In the Göteborg-1 trial [9], an independent Cause of death (COD) committee consisting of 3 urology professors, blinded to study allocation, reviewed the cause of death following a standardized algorithm. A similar COD committee will be used in this study.

5.2 Equipment

Laboratory evaluations (blood draw)

Blood sampling will be offered at blood draw units and primary care facilities in Göteborg and surrounding municipalities. Analyses of PSA and serum creatinine (only for men undergoing mpMRI) will be performed by Unilabs, Skövde.

Participating blood collection sites:
Nötkärnan Bergsjön vårdcentral och BVC
Nötkärnan Masthugget Familjeläkare och BVC
Nötkärnan Kortedala Vårdcentral och BVC
Nötkärnan Hovås Askim Familjeläkare och BVC
Nötkärnan Friskväderstorget Vårdcentral och BVC
Nötkärnan Kållered Familjeläkare och BVC
Carlanderska sjukhuset, Laboratoriet
Carlanderska sjukhuset, Urologkliniken
Noltorp vårdcentral
Vårdcentralen Kusten
Unilabs provtagning Almedal

Imaging (MRI)

A 3 Tesla MRI system with a pelvic surface coil is available for this study at the Dept. of Radiology, Sahlgrenska University Hospital. The imaging protocol is multi-parametric (mpMRI) including T2-weighted, diffusion weighted (DWI) and dynamic contrast-enhanced (DCE) sequences. A “positive MRI” or abnormal / suspicious lesion, will be defined by means

of a centralized evaluation at the radiology department, using the most recent version of the European Society of Urogenital Radiology (ESUR) criteria Prostate Imaging Reporting and Data system (PI-RADS) score. A PI-RADS score of 3-5 will be considered "positive". A standardized template will be used to report up to three lesions. For each lesion, PI-RADS score, size (largest diameter and its perpendicular diameter), prostate zone (peripheral, transition zone, or both) and location of lesion center (according to the sector system described below) will be recorded. All MRI examinations will be evaluated in consensus by two out of three study radiologists, with 4-10 years of experience in the prostate MR imaging field.

Multiparametric MRI is since April 1st, 2019, and onward only used in screening round 1 (see addendum 7).
All men referred for MRI in subsequent screening rounds (from screening round 2 and forth) undergo bi-parametric MRI (bpMRI) without the dynamic contrast-enhanced MRI sequence.

PI-RADS v2.1 has been used since June 1, 2019 (see Amendment 8).

Histopathological specimens (prostate biopsies)

Biopsy of the prostate will be carried out by a limited number of urologists (n=5), with several years of prostate biopsy experience (5-30 years), using existing equipment at the Dept. of Urology, Sahlgrenska University Hospital. Biopsies are conducted by a B&K equipment and directed by transrectal ultrasound (TRUS) guidance. Fusion biopsies will be used in selected cases but cognitive directed biopsies will be the standard.

On December 14, 2016, the number of cores in systematic biopsies was increased from 10 to 12 cores (see Amendment 9). All 12 cores are directed against the posterior aspect of the prostate. We use the same sector-system as in the National Swedish Prostate Cancer Registry (NPCR) which comprises 12 posterior and 12 anterior sectors. In case of a positive MRI finding in one of the sectors included in the systematic biopsies among men in Arm 1, one of the targeted cores from that sector is appointed as belonging to the "systematic biopsies" and the remaining three cores as targeted. In case of a MRI lesion in a sector not included in the systematic biopsies all 4 cores are designated as targeted.

The MRIs of men with PI-RADS 5 and a negative biopsy will, since January 16, 2020, be demonstrated at a prostate MRI radiology conference and these men will be re-invited after 3 months for a repeated targeted biopsy.

6 STATISTICAL CONSIDERATIONS

6.1 Sample Size Calculation

The hypothesis is that the MRI-targeted biopsy only strategy would reduce insignificant cancer with 50%. Based on previous studies and expert knowledge, we assumed that the proportion of men diagnosed with insignificant cancer among men with PSA ≥ 3 in Arm 1 (reference arm) would be 9%. This gave a sample size of N=1,164 men with PSA ≥ 3 ng/mL to achieve 80% power, when having a two-sided test alternative and significance level 5%. Furthermore, we hypothesized that 7% among men attending PSA-screening would have an elevated PSA and that the participation rate would be 50%, which lead to the sample size N=33,260 altogether in the three screening-arms. Accounting for uncertainty in the hypothesized proportion of insignificant cancers and in the proportion of men with PSA ≥ 3

ng/mL among those screened, lead to the final sample size of N=36,000 for the SG. With an allocation rate of 1:2 between the CG and SG, altogether, N=54,000 men are needed to be included in the study.

6.2 Analysis plan for the primary and secondary endpoints

6.2.1 Primary objective (Detection of insignificant cancer)

- Hypothesis

  The proportion of men with insignificant cancer detected by PSA testing with threshold 3 ng/mL, systematic biopsies and MRI-targeted biopsies (p_1) will be different from the proportion detected when omitting systematic biopsies (p_2):
  H_0 (null hypothesis): $p_1 = p_2$
  H_A (alternative hypothesis): $p_1 \neq p_2$
  Although the hypothesis of the investigators is one-sided, that MRI-targeted biopsies only will lower the proportion, the test is two-sided to allow for a significant effect in both directions.

- Analysis populations

  First assessment (after completion of screening round 1): All men in arm 1 will be compared to all men in arm 2 and 3 combined. However, for men in arm 3, cancers detected in men with PSA < 3 ng/mL will be ignored.
  Later assessments: the analysis will compare all men in arm 1 with all men in arm 2.

  The analyses will primarily be carried out according to the intention to treat (ITT) principle, which here means that all men will be included in the analysis and belong to the arm they were allocated to, irrespective of whether they completed the intended diagnostic pathway with MRI and biopsies or not.

  Furthermore, per protocol analyses will be carried out including only men who strictly follow the protocol.

  An additional analyses will compare men in arm 1 who underwent MRI followed by systematic and possible targeted biopsies (if MRI positive) with those in arm 2 and 3 who underwent MRI and also targeted biopsies but ignoring results from possible systematic biopsies if those were taken at the primary biopsy and the targeted biopsies were benign.

- Analysis

  Outcome measure is the relative difference of the proportion of insignificant cancers detected in arms 2 and 3 combined vs arm 1 (the cancers detected in men with PSA below 3 ng/mL in arm 3 will be ignored). In later assessments only arm 1 and 2 will be included. The result will be presented as a point estimate with a two-sided 95% confidence interval, and a p-value of the hypothesis test. Significance testing will only be carried out for the first definition of insignificant cancer (Gleason grade 3+3).
  The score method will be used for testing and confidence intervals (27). A p-value below 5% will be considered statistically significant.

6.2.2 Secondary objective (Detection of significant cancer)

The detection of significant cancers will be analysed in the same way as the detection of insignificant cancers except that no hypothesis testing will be performed.

6.2.3 Endpoint Definitions

Several different definitions of significant and insignificant cancer will be considered, see Table below. The main result and conclusion of the study results will be based upon the first definition of significant (Gleason score >6) versus insignificant cancer (Gleason=6) based on findings in core biopsies. Clinically significant cancer is for the first definition defined as not fulfilling the criteria for clinically insignificant cancer but we also added two definitions used in the PROMIS study. The different definitions of clinically insignificant cancer will be based on pathology evaluation in core biopsies, see section 5.1, and in prostatectomy specimen, when available. The pathology evaluation includes Gleason score and tumor size.

Endpoint definitions

Definition of insignificant cancer	Gleason biopsy	Cancer involvement in biopsies	Prostatectomy outcome	Comments
First definition	GS=6	Any	Any	
Second definition	GS=6	Maximum 2 sectors involved, T1c, PSAD<0.15 and unilateral involvement	Any	
Third definition	GS=6	Maximum 2 sectors involved, T1c, PSAD<0.15 and unilateral involvement	GS=6, no EPE Tumor volume < 0.5 cc	Biopsy criteria only to use if no prostatectomy is performed
Fourth definition	GS≤7	Maximum 2 sectors involved, T1c, PSAD<0.15 and unilateral involvement	GS≤7, no EPE Tumor volume < 0.5 cc	Biopsy criteria only to use if no prostatectomy is performed
Definition of significant cancer				
First definition	GS>6	any	Any	
Second definition	GS>3+4	A maximum core cancer length of>= 6 mm	Any	Gleason Biopsy and/or cancer involvement
Third definition	GS>3+3	A maximum core cancer length of>= 4 mm	Any	Gleason Biopsy and/or cancer involvement

Another endpoint in this study is primary treatment split into i) treated with radical prostatectomy ii) treated by radical radiation therapy iii) hormonal therapy iiii) surveillance and iiiii) other treatments. No significance testing will be performed.

6.3 Substudies

For the substudies separate analysis plans will be written prior to any analysis.

6.4 Statistical software

The statistical analysis will be performed using R Statistical Software, version ≥ 4.0.4 (Foundation for Statistical Computing, Vienna, Austria).

7 TRIAL MANAGEMENT

7.1 Study secretariat

We will use the same structural organization as in a previous study (Göteborg-1). With 25 years of prior experience from running a 20,000-men screening trial (Göteborg-1), it is expected that this trial can be carried out utilizing the same organization and a fully equipped screening center. The infrastructure for performing this study already exists. We will use the same processes (except for MRI) as in the Göteborg-1 trial.

7.2 Advisory board

An advisory board with 4-5 members will meet with the study board when needed. This committee will advise the study board in recommending possible extensions of the study and changes/amendments in the protocol. The Advisory board will also be asked for advise in other questions brought up by the study board. The Advisory board will be recruited from national and international experts in the field. For participants, see Appendix 2.

8 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

8.1 Database

The study database will be kept at a server at University of Gothenburg for 35 years.

8.2 Monitoring

Data will be prospectively and continuously recorded in the screening database. Several quality data checks will be performed.

8.3 Adverse Event Reporting

Adverse events (see toxicity) from MRI and TRUS biopsy will be recorded continuously and summarized once a year. This summary will be discussed within the study board and possibly together with the Advisory board. The study protocol follows principally clinical recommendations from the Swedish Board of Health and Welfare. One critical point in this study is a potential risk to delay diagnosis of serious cancer when omitting biopsy in men with a negative MRI (and a PSA < 10) in Arm 2 and 3. Therefore, analysis of the incidence of interval cancers in these men is planned as well as studying the characteristics of cancers detected at follow-up screens in men with elevated PSA and negative MRI in previous screening rounds. These data will be presented to the Advisory Board for recommendations. No other stopping rules are specified within the protocol.

9 ETHICAL CONSIDERATIONS

9.1 Ethical Committee Approval and Informed Consent

The Ethics Review Committee at the University of Göteborg approved the pilot study (Diarie no 13-138). Application for the main study was sent to The Ethics Review Committee as of November 14, 2014. All men randomized to screening will be invited by mail. The invitation contains detailed information about the study, its design, benefits and risks, contact details and a reference to our website with a link to the Swedish National Board of Health and Welfare's written information about PSA testing and its pros and cons. Hence, men who show up for PSA testing are assumed to have read the information provided in the invitation letter and thus make an active choice to participate. Taking a PSA test, as well as undergoing MRI and prostate biopsy tissue sampling, is considered standard clinical practice by the Swedish ethical committees. All men who show up for prostate biopsies at the urology clinic will fill out a standardized health form, which is also used in clinical practice. Here, the patient must check a box "Are we allowed to store your samples in a bio bank? yes/no."

Separate information about a side study of biomarkers and genetics will be administered. Individuals, who want to participate in this study, will have to sign a separate informed consent at the urology clinic

9.2 Subject Confidentiality

Data integration will ensure privacy of human subjects. For data analysis, data will be re-coded for anonymity. Full access to the database will be held by Chief investigator (Jonas Hugosson), data manager (Helén Ahlgren), and study nurse (Maria Nyberg). All inquiries for data analysis must be approved by the chief investigator prior to data extraction and only anonymized data will be used in analyses.

9.3 Harms, benefits and equipoise

This study aims to evaluate whether a new screening algorithm can improve on the ratio of harms to benefits resulting in that benefits will outweigh the harms.

9.3.1 Potential risks for study participants

Information on potential risks associated with the screening procedures will be mailed to the participants together with the invitation letter. The questions in the questionnaire are of private nature and may evoke feelings of discomfort. If the men experience discomfort upon completion of the questionnaire, they have the possibility to contact a study nurse.

Screening for prostate cancer

Potential risks include anxiety, over-diagnosis, side-effects from biopsies and treatment and negative impact on quality of life but also the risk of delaying diagnosis in men with aggressive cancer. The test interval in this study is longer compared to what is recommended in national and international guidelines. Participating in a screening study like this may give men a false security.

The main downside with PSA testing is the risk of over-diagnosis and subsequent overtreatment of a disease that would otherwise not have caused symptoms or death during the lifespan of a typical man. Such slow-growing cancers do however not have to be treated immediately, but can be monitored (active surveillance). Treatment for localized prostate cancer can lead to impaired erectile function. Radiation is associated with a minor risk of proctitis and urinary urgency, while surgery leads to bothersome urinary leakage in <5%.

Another important ethical aspect regarding prostate cancer screening is that the balance between benefits and harm may vary between individuals, and that the benefit for some men may be significantly less than the potential risks of over- diagnosis of harmless tumors, especially in older men with other co-morbidities, as well as the risks of side effects of treatment in the form of impotence and urinary incontinence. By informing men of the pros and cons of PSA testing and its consequences upstream, i.e., before screening takes place this allows the individual to make an active choice to participate.

To review the risks with both over-diagnosis and delayed diagnosis a close follow-up is planned. See also 8.3

Blood test

Potential risks include anxiety, bruising, and vaso-vagal reactions.

MRI

Potential risks include anxiety, claustrophobia, noise, immobilization for 30-45 minutes. Contraindications are asked for before MRI including: metal implants, pacemaker, kidney failure, contrast medium hypersensitivity.

Low risk gadolinium contrast medium (Dotarem) will be utilized. Plasma-creatinin will be measured for all men undergoing MRI. Height and weight will be measured and eGFR

calculated (kidney function). An eGFR <45 ml/min is an absolute contraindication to MRI in the study. Use of contrast-medium at MRI was discontinued in 2019 except for those who were invited in for their first time. After completion of screening round 1 in 2021 no contrast medium has been given.

Prostate biopsies

Potential risks include discomfort, pain, blood in urine, blood in semen, blood in stool, urinary tract infection, fever and sepsis. Men are informed about these risks at biopsy and given instructions what to do and information who to call in the event of an adverse event.

Survey

The surveys may cause some degree of distress in certain subjects. Questionnaires of various kinds have been carried out for a long time and several of the forms are previously tested on several individuals and have been perceived as easy to understand and can be completed in a short time and without stress.

9.3.2 Potential benefits for study participants

Screening for prostate cancer

Potential benefits include early detection and treatment of prostate cancer at a curable stage, prevention of metastatic disease, morbidity, and disease-specific death.

If the hypothesis is proven to be true, that PSA+MRI reduces the risk of finding insignificant tumors, the major problem with over-diagnosis will be diminished. The number of men who need to be biopsied will be reduced and hence the negative consequences of PSA testing. Most likely, targeted biopsies, guided by MRI findings, will increase the likelihood that a significant cancer is found. Lowering the PSA threshold may enable more men to have their cancer detected at a curable stage. In our previous study (Göteborg-1), regular PSA-testing decreased prostate cancer mortality by 44% and the present study is likely to further reduce mortality from prostate cancer through detection of significant tumors and effective treatment at a curable stage and reduced over-diagnosis.

9.4 Benefit: Risk Endpoints

9.4.1 Exit Examination Analysis

An ordinal overall clinical response will be used, on the individual level, as suggested by Chuang-Stein (Chuang-Stein, 1994).

	Efficacy (no over-diagnosis)	No efficacy (over-diagnosis)
No serious side-effects from screening procedures	Category 1	Category 3
Serious side-effects from screening procedures	Category 2	Category 4

Side-effect leading to withdrawal	Category 5

Clinical outcomes

Efficacy: no detection of insignificant disease (no over-diagnosis).
No efficacy: detection of insignificant disease (over-diagnosis).

Toxicity: The following toxicity will be recorded

- Non-serious side-effects from MRI: Contrast medium hypersensitivity requiring medication
- Serious side-effects from MRI: Any major side-effect from MRI requiring hospitalization or causing death
- Non-serious side-effects from Biopsy. Profuse bleeding or infection or pain needing medical attention.
- Serious side-effects from Biopsy: Any major side-effect requiring hospitalization or causing death.

- QoL: reduced HRQoL during screening process (patient-reported outcome assessed by questionnaires)

10 PUBLICATION OF RESEARCH FINDINGS

The results of the study and sub-studies will be reported as standard scientific manuscripts in peer-reviewed medical journals.

Comments in the end:
The study population will be identified from a random sample from the population register of men in the age group 50-60 years in the county of Göteborg and six surrounding municipalities, and as such, be truly population-based and generalizable to the entire male population of this age. Since randomization to screening versus control is performed upfront and without informed consent, this allows evaluating the effectiveness of screening on prostate-cancer mortality and to more accurately estimate this effect if population-based screening were introduced. This is in contrast to if the study had been designed as an efficacy trial with informed consent prior to randomization, which may instead introduce healthy screenee bias. The current design will minimize this bias, although it is known from Göteborg-1 that non-attendees to screening have a higher risk of prostate cancer mortality, than attendees (Bergdahl 2009)

A limitation of the study is that the vast majority of Swedes in this age group are Caucasians. However, there was no predefined selection per ethnicity. Nevertheless, the results of the study may not be generalizable to non-caucasion populations.

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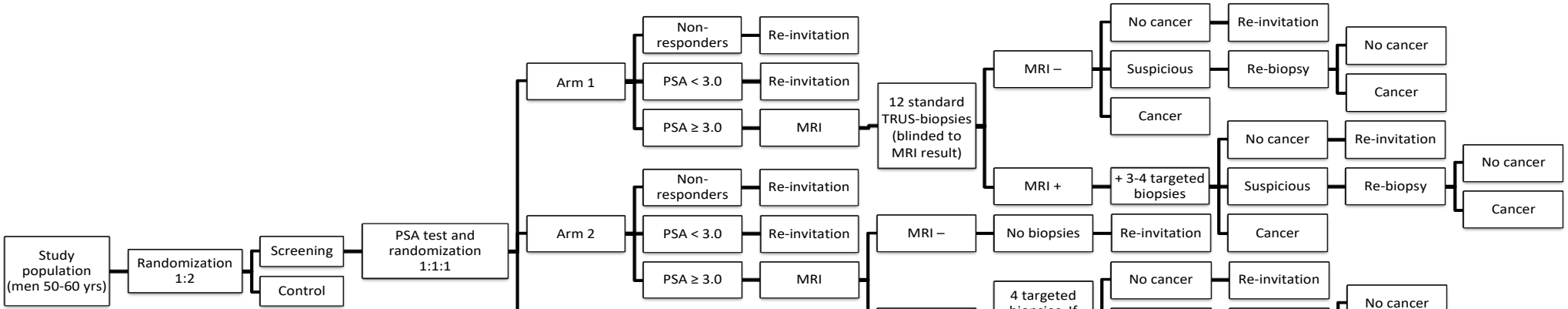
Figure 1



Men with PSA ≥ 10.0 ng/mL. Due to high risk of serious prostate cancer, these men in Arm 2 and 3 will, for safety reasons and not delaying diagnosis, be recommended 12 systematic TRUS-biopsies plus additional targeted biopsies if positive MRI (similar strategy as in arm 1)

Definition of MRI results
Negative (-) = PI-RADS score 1 or 2
Positive (+) = PI-RADS score 3, 4 or 5

Targeted biopsies
Biopsy targeted against MRI positive areas with 4 biopsies against each lesion or 3 biopsies if 1 systematic biopsy has already been directed to that area in arm 1

Upper age limit	
PSA (ng/mL)	Age
≤0.59	>62
0.6-1.19	>65
1.2-1.79	>70
Non responder	>70
≥1.8	>75

Re-invitation intervals	
Arm 1+2+3	
PSA (ng/mL)	Interval (yrs)
≤0.59	8
0.6-1.19	4
≥1.2	2