The Göteborg-2 trial

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:

The Swedish Cancer Society
ALF
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Biocare
Regional Cancer Center Western Region
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Protocol Chair: Professor Jonas Hugosson
Protocol Vice Chairs: Professor Mikael Hellström and Associate professor Sigrid Carlsson

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SITES PARTICIPATING IN THE STUDY

This study will be carried out as a multi-site study with the screening bureau located at the Department of Urology at the Sahlgrenska University Hospital, Göteborg, Sweden.

Starting in 2014, men randomized to the study will emanate from the geographical catchment area in the city of Göteborg and 6 surrounding counties: Öckerö, Kungälv, Ale, Partille, Härryda, and Mölndal.

In 2015, we intend to invite men also from the following 4 counties: Lerum, Alingsås, Vårgårda, and Herrljunga. If the budget permits, we intend to also invite men in Skaraborg county in 2016. (a separate ethical application will follow)

The following departments will participate in the study:

1. Sahlgrenska Academy at Göteborg University

    I. Department of Urology
    II. Department of Radiology

STUDY TEAM

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STUDY MANAGEMENT

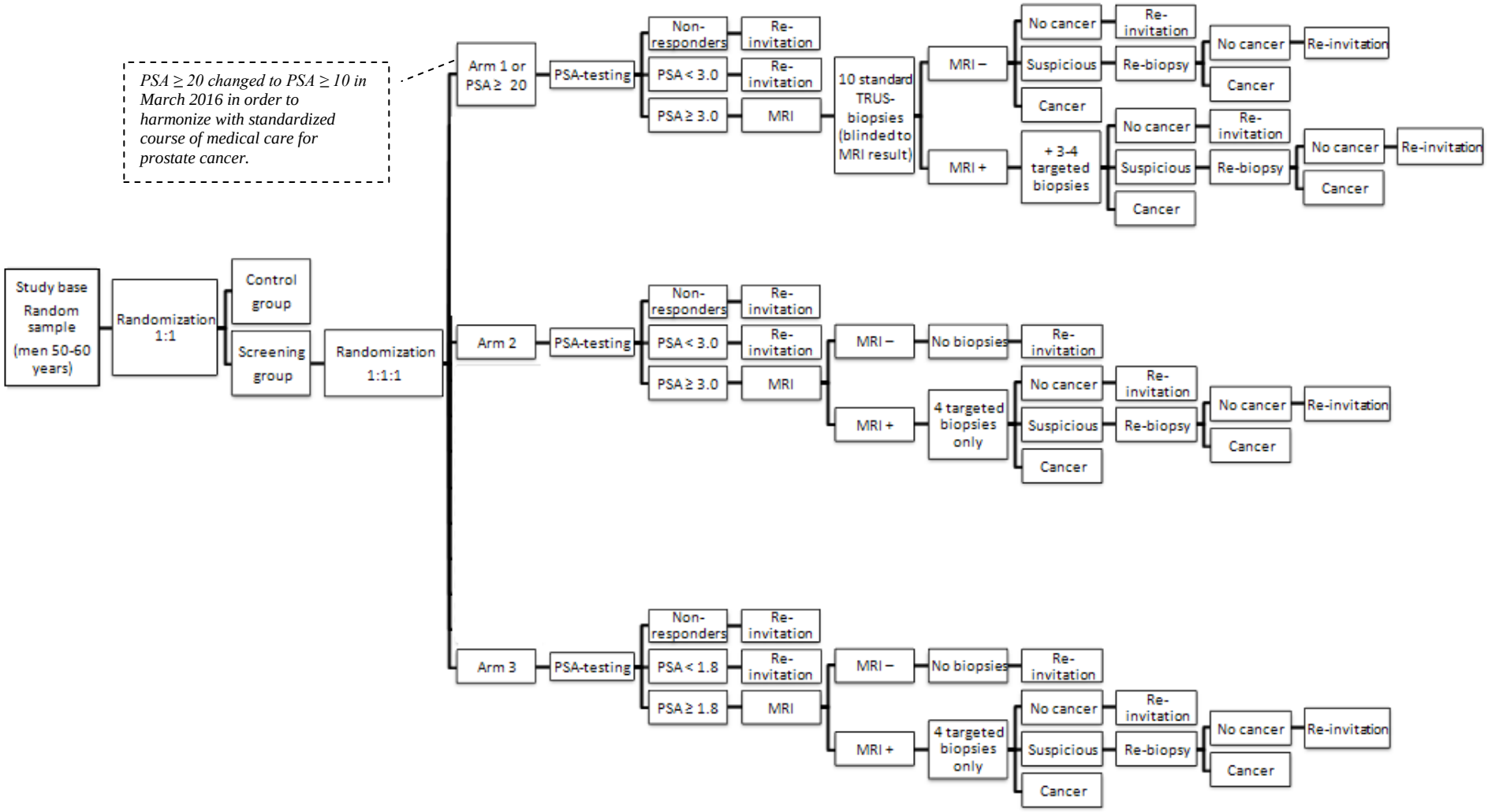
All questions concerning this protocol should be sent to jonas@urol.se via e-mail. The appropriate team member will respond with a "cc" to jonas@urol.se A response should generally be received within 24 hours (Monday-Friday).

For general inquiries about the Göteborg-2 trial, please visit the frequently asked questions (FAQ) on our website at http://www.gbg2.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
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
SC	Screening Group
STAI	State Trait Anxiety Inventory

SCHEMA The Göteborg-2 trial



1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

This is the world's first large-scale, prospective, randomized screening trial for prostate cancer incorporating magnetic resonance imaging (MRI) as a screening tool before prostate biopsy. The study seeks to evaluate whether a screening algorithm using prostate-specific antigen (PSA) and MRI with targeted biopsies can improve the ratio of harms to benefits as compared to PSA and systematic biopsies. If there is scientific support for this hypothesis, this study will be the introduction to a paradigm shift in the future of screening and fundamentally change the way we think about early detection of prostate cancer.

H_0 = null hypothesis
H_A = alternative hypothesis
SG = screening group
CG = control group
p = proportion

Prostate cancer mortality at 12 years

H_0: $p_{CG} = p_{SG}$ = i.e. there is *no* difference between the proportion of prostate cancer deaths between the CG and the SG at the evaluation at 12 years.

H_A: $p_{CG} > p_{SC}$ = We hypothesize that the proportion of prostate cancer deaths in the SG is ≥ 50% that of the CG, at 12 years, corresponding to an absolute reduction in prostate cancer mortality from 0.5% in the CG to 0.25% in the SG.

Insignificant prostate cancer at 4 years

i. H_0: $p_1 = p_2$ = i.e. there is no difference between the proportion of insignificant prostate cancer between arm 2 vs arm 1 at the evaluation at 4 years.

H_A: $p_1 > p_2$ = We hypothesize that the proportion of insignificant prostate cancer in arm 2 will be ≥ 50% lower than in arm 1, at 4 years.

ii. H_0: $p_1 = p_3$ = i.e. there is no difference between the proportion of insignificant prostate cancer between arm 3 vs arm 1 at 4 years.

H_A: $p_1 > p_3$ = We hypothesize that the proportion of insignificant prostate cancer in arm 3 will be ≥ 30% lower than in arm 1, at 4 years.

Significant prostate cancer at 4 years

i. H_0: $p_1 = p_2$ = i.e. there is *no* difference between the proportion of significant prostate cancer between arm 2 vs arm 1 at the evaluation at 4 years.

H_A: $p_1 > p_2$ = We hypothesize that the proportion of significant prostate cancer in arm 2 is at least 80% of that in arm 1, at 4 years.

ii. H_0: $p_1 = p_3$ = i.e. there is *no* difference between the proportion of significant prostate cancer between arm 3 vs arm 1 at 4 years.

H_A: $p_1 > p_3$ = We hypothesize that the proportion of significant prostate cancer in arm 3 is at least equal to (≥100%) that in arm 1, at 4 years.

1.2 Primary Objective

To evaluate whether screening with PSA+MRI can reduce prostate cancer mortality at 12 years, compared to the control group.

1.3 Secondary Objectives

To evaluate whether screening with PSA+MRI and targeted biopsies can reduce the risk of detecting insignificant prostate cancer (over-diagnosis), defined as no Gleason* grade 4 or 5 in prostate biopsies compared to PSA and systematic biopsies (gold standard), while maintaining detection of significant prostate cancer, defined as any Gleason grade 4 or 5 in prostate biopsies.

To evaluate whether screening with PSA+MRI and targeted biopsies can reduce the number of unnecessary biopsies and whether detection of significant cancer can be improved if the PSA-cut off is lowered.

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* 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.

1.4 Substudy Objectives

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

2.0 INTRODUCTION

2.1 Background

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 where curative treatment is no longer an option. Early detection for prostate cancer was made possible by the introduction of the blood test prostate-specific-antigen (PSA) in the early 80's (*Stamey, 1987*). 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.

Prostate cancer is unique among solid tumors that many men die with rather than from the disease, because of the slow-growing nature of the disease and its detection in elderly men. Therefore, the major dilemma with current screening is the high risk of over-diagnosis (30-50%) i.e. detection of small very slow-growing, insignificant tumors, that would never have given rise to clinical symptoms during a man's life-time.(*Draisma 2003*). Moreover, the PSA test is a sensitive measure of increased risk for prostate cancer, but due to low specificity, it is an imperfect screening tool as most men with a modestly elevated PSA (3-10 ng/mL) do not have prostate cancer at biopsy, but instead a benign enlargement that causes the elevation. This implies that many men undergo unnecessary, uncomfortable and risky prostate biopsies to rule out cancer. Further, over-diagnosis may subsequently lead to overtreatment. Treatments for localized prostate cancer include surgery or radiation, both associated with a substantial risk of irreversible complications); erectile dysfunction, urinary leakage and bowel disturbances. (*Sanda, 2008, Resnick 2013*) These, oftentimes long-term, side-effects may lead to tremendous suffering for the individual and negatively impact a man's quality of life.(*Carlsson 2010, Heijnsdijk 2012, Steineck 2002*)

Many Swedish men participate in opportunistic screening. Today, it is estimated that more than 50% of Swedish men between 55-70 years old have had a PSA test.(*Bratt 2010, Jonsson 2011, Nordström 2013*). The current standard of care to follow-up men with elevated PSA-levels, is recommendation of 10-16 laterally directed systematic, but non-targeted biopsies, meaning covering the peripheral zones in the whole prostate gland. However, it is well-known from autopsy studies that 20-40% of men in the screening age (50-70 years) have small insignificant low grade tumors *(Sakr 1994, Haas 2007)*, and therefore, such a biopsy strategy will unconditionally detect cancers that are not clinically relevant, leading to a high risk of over-diagnosis and subsequent risk of over-treatment. There are no randomized trials using other than PSA and biomarkers as screening tools. A parallel dilemma with the current biopsy protocol is the difficulty hitting the tumor with the needle. Especially tumors located anteriorly in the prostate are often missed with standard biopsies; the rate of false negative results is in the range of 5%, i.e. about one of 20 biopsied men with negative result still has an undetected relevant cancer.

The effect of regular PSA-screening on morbidity and prostate cancer mortality is robust and substantial; the *European Randomized Study of Screening for Prostate Cancer* (ERSPC) as well as the *Göteborg Randomized Population-based Prostate Cancer Screening Trial ("The Göteborg-1 trial")* have shown that regular PSA-screening of men 50-70 years of age with PSA-screening, significantly reduces the risk of developing metastasized disease (*Schröder 2012*) and reduces prostate cancer mortality by 21-44% after 11-14 years of follow-up.(*Schröder 2009, Schröder 2012, Schröder 2014, Hugosson 2010*)

2.2 Rationale

Current screening strategies, solely relying on the blood test PSA, are far from optimal. PSA screening is associated with both benefits—early detection and treatment, prevention of metastatic disease, morbidity, and disease- specific death—and harms—anxiety, over-diagnosis, side-effects from biopsies and treatment, impact on quality of life, and costs. (*Carlsson, 2010*) To circumvent the problems with low specificity of the PSA-test, too frequent biopsies and risk of over-diagnosis, we need a better screening strategy that involves the latest technology in this field. During the past few years, magnetic resonance imaging (MRI) has been suggested as a triage test for men with elevated PSA levels, to be used in combination with transrectal ultrasound (TRUS)-MRI-fusion imaging to better guide the biopsies(*Ahmed 2009)*. MRI has also been suggested to have potential to aid in the discrimination of insignificant cancers from harmful ones.*(Akin 2012, Moore 2013)* The recent technological development of so called multi-parametric MRI (mpMRI) has evolved as a promising method to increase specificity and avoid over-diagnosis, by having potential to image only clinically significant tumors and allowing targeted biopsies against these lesions. We now propose a completely novel and world-unique screening design using PSA followed by imaging of the prostate using MRI. To the best of our knowledge, this has never been tested in a prospective, randomized trial. Imaging to find tumors has long been used in other cancer forms, e.g. mammography (x-ray) to screen for breast cancer or computer tomography (CT) to screen for lung cancer. In the field of prostate, MRI is used in clinical practice to guide biopsies or for pre-operative planning before surgery, but not as a screening method in conjunction with PSA for screening and diagnostic purposes. The conceptual idea of our trial is to prescreen men with PSA, and for men with a PSA over a threshold perform MRI, and then only biopsy men with abnormal findings (hot spots) on MRI – so called targeted biopsies. By adding mpMRI, the chance of proper direction of the biopsy cores could be optimized and thereby increasing the sensitivity for clinically relevant cancers. At the same time, excessive standard biopsies could possibly be avoided. A third dilemma is that some cancers, especially in small prostates, are too advanced already at the current PSA threshold of 3 ng/mL, which means that some tumors are detected too late. To improve the effectiveness of prostate cancer screening there is a need to detect these cancers earlier i.e. in perhaps also in the PSA range below 3.0 ng/mL. Our study implies a completely unique study design and is the first trial of its kind by also evaluating a lower PSA cut-off.

3.0 STUDY DESIGN

This is a three-arm randomized controlled screening trial, following the schema on page 10. The proposed design is appropriate for prostate cancer screening since it will 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 to compare cancers detected by standard biopsy alone and those detected by targeted biopsies.

3.1 Study Enrollment Procedures

3.1.1 Identification of random study sample

The extraction of the initial random study population will be carried out stratified on:

1. year of birth, with respect to the age distribution in the underlying population

and

2. county, with respect to the number of inhabitants in that county.

3.1.2 Randomization to Control Group and Screening Group

The Ethical committee at Göteborg University, 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. The control group will be followed for prostate cancer incidence and prostate cancer mortality by cross-linking to the Swedish 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 PSA-testing (but some degree of opportunistic screening). A mailed letter will inform men in the control group that they are part of a control group and that their participation is voluntarily.

3.1.3 Sub-randomization of Screening Group to three study arms

Thereafter, men randomized to the screening group will be randomized 1:1:1 into one of the three study arms. This randomization will also be carried out stratified by year of birth, to the greatest possible extent.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

The study population will be identified from a random sample from the population register of men in the age group 50-60.99 years in the county of Göteborg and 6 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 more accurately estimate this effect if population-based screening were introduced. This, in contrast to had the study 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 are Caucasians, the results of the study may not be generalizable to other races.

4.1 Inclusion Criteria

At date of randomization:

4.1.1 Alive

4.1.2. A registered address in the county of Gothenburg, Sweden or any of 6 specified surrounding municipalities

4.1.3. Age 50 to 60.99 years

4.2 Exclusion Criteria

At date of randomization:

4.2.1 Prevalent prostate cancer

4.2.2 Emigration during the period between randomization and update of the Population register, to which the study participants' unique personal identification numbers are linked.

4.2.3 Death during the period between randomization and update of the Population register, to which the study participants' unique personal identification numbers are linked.

5.0 STUDY INTERVENTION

5.1 *Intervention*

Arm (1) (reference 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 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 a mpMRI.

First, all men will be recommended standard biopsy, i.e. digital rectal exam followed by TRUS-guided 10-core standard prostate biopsy according to the screening protocol (as is also clinical practice). These standard biopsies will be taken with both the urologist and subject blinded to the MRI result. After the standard biopsies, the study nurse will show the urologist the result from MRI, and in case of a suspicious lesion at MRI 3-4 targeted* biopsies will be performed at the same séance; 3 if one of the systematic biopsies already hit the area, and 4 if otherwise.

Arm (2) (experimental arm I)

- 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 mpMRI.
  - If the mpMRI is positive, only targeted* biopsies will be performed, i.e. 4 biopsy cores targeted against each suspicious lesion, but no systematic biopsies.
  - If the mpMRI is negative, no biopsies will be performed.

Arm (3) (experimental arm II)
Identical to arm (2) except that the PSA-cut off is lower, 1.8 ng/mL.

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

5.2 *Re-invitation intervals*

Re-invitation intervals will follow these algorithms:

Re-invitation intervals	
Arm 1+2	
PSA (ng/mL)	Interval (years)
< 0.59	8
0.6 – 1.19	4
1.2 – 2.39	2
2.4 – 2.99	1
Arm 3	
< 0.59	8
0.6 – 1.19	4
1.2 – 1.79	2

Special re-invitation intervals	
Non-responder in round 1	3 months, 9 months, then never again
Non-responder in following rounds	3 months, 9 months, then two years
No cancer after biopsy twice in a row	4 years
Negative MRI twice in a row	2 years
PSA ≥3, no MRI	2 years
PSA ≥3, positive MRI, no biopsies	2 years

5.3 *Upper age limit*

The upper age limit for termination of screening, will depend on the total PSA-value in the preceding screening round.

Upper age limit (no more screening)	
All arms	
PSA (ng/mL)	Age (years)
< 0.59	> 65
0.6 – 1.19	> 70
1.2 – 2.39	> 75
irrespective	80

5.4 *Special circumstances*

Due to high risk of lethal prostate cancer, all men with PSA ≥ 20.0 ng/mL***)***, irrespective of arm, will, for ethical reasons, be recommended 10 standard TRUS-biopsies plus additional targeted biopsies if positive MRI.

6.0 SCHEDULE OF EVENTS

(for the initial 4 years)

	Study period						
	Enrollment	Allocation	Post-allocation				Closeout
Time point	-t1	0	t1	t2	t3	t4	
Eligibility screen	x						
Informed Consent			x				
Allocation		x					
Interventions			x	x	x	x	
Assessments			x	x	x	x	
Baseline variables			x				
Outcome variables					x	x	x
Other variables			x	x	x	x	x

6.1 *Outcome Ascertainment*

The project is planned to run for an initial 4 years with an evaluation of the secondary endpoints during year 4, and the main endpoint at year 12.

Prostate cancer diagnosis

Reporting of cancer to the National Prostate Cancer Register and 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

Only one pathologist (Dr. Carl-Gustaf Pihl) at the department of Pathology will review the prostate biopsies in the study.

Prostate cancer mortality

The project is planned to continue for evaluating long-term effects on prostate cancer mortality. In the Göteborg-1 trial (*Hugosson, Carlsson 2010*), 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.

6.2 *Equipment and infrastructure*

Laboratory evaluations (blood draw)

Blood sampling will be offered at blood draw units and primary care facilities in Göteborg. Analyses of PSA and creatinin (for MRI) will be performed by a central laboratory in Göteborg, UniLabs.

Imaging (MRI)

A 3 Tesla MRI equipment is available for this study at the Dept. of Radiology, Sahlgrenska University Hospital. A mpMRI with 3 sequences will be used with a lower abdomen coil. The 3 sequences are: one T2-weighted sequence, another sequence with dynamic contrast-enhanced MRI and the third with diffusion-weighted MRI. A "positive MRI" or abnormal / suspicious lesion, will be defined by means of a centralized evaluation at the radiology department, using the European Society of Urogenital Radiology (ESUR) criteria's Prostate Image-Reporting and Data system (PIRAD) score. A score of 3-5 will be considered "positive".

Histopathological specimens (prostate biopsies)

TRUS-biopsy of the prostate will be carried out by urologists and urology residents, with assistance from the study nurse, using existing equipment at the Dept. of Urology, Sahlgrenska University Hospital.

7.0 MANAGEMENT ISSUES

Study secretariat

With 20-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.

Advisory committee

An advisory committee with 4-5 members will meet with the study board once/year. This committee will advise the study board in recommending possible extensions of the study and changes/amendments in the protocol. The advisory Committee will also be asked for advise in other questions brought up by the study board. The Advisory committee will be recruited from national and international experts in the field.

8.0 STATISTICAL CONSIDERATIONS

8.1 *General Design Issues*

Because of sample size, this practically implies that the study will be carried out in the city of Göteborg and 6 surrounding municipalities.

8.2 *Outcome Measures*

8.2.1 Primary Outcome Measures

Between arm difference in prostate cancer mortality between the screening and control group.

8.2.2 Secondary Outcome Measures

Between arm differences in overall prostate cancer (detection rate) and biopsy frequency.

Between arm differences in proportions of clinically insignificant and significant prostate cancer in terms of absolute and relative risk reductions in arm 3 vs arm 1, and in arm 2 vs arm 1, with 95% confidence intervals (CI's). Clinically insignificant will be defined as no Gleason grade 4 or 5. Clinically significant cancers are all cancers not defined as insignificant.

8.2.3 Substudy Outcome Measures

Additional endpoints from side-studies embedded in the trial: Technical aspects of mpMRI, feasibility and logistic, costs and cost-effectiveness, quality of life, biomarkers, equitable care and health care disparities.

8.3 *Sample Size Calculation*

8.3.1 Sample Size Calculation

Analysis of prostate cancer mortality will be carried out according to the intention to screen (ITS) principle, comparing men randomized to the screening group to men randomized to the control group, regardless of whether they attend screening or not. Based on findings from the Göteborg-1 trial (Hugosson, Carlsson 2010), we expect prostate cancer specific mortality to be 0.5% in the control group and 0.25% in the screening group at 12 years, corresponding to a 50% relative risk reduction in prostate cancer mortality.

With an anticipated 50% participation rate, a randomization rate of 1:1 to screening and control groups, a power of 80% and alpha 0.05, a one-sided test, an accrual period of 2 years and a total study duration of 12 years, a total sample size of N=40,952 (20,476 x 2 due to 50% participation rate) is needed to detect a difference in prostate-cancer specific mortality from 0.5% in the control group to 0.25% in the screening group,

```
Sample size calculation:

 stpower exponential 0.995 0.9975, t(12) fperiod(10) aperiod(2)
 Note: Input parameters are survival probabilities.

 Estimated sample sizes for two-sample comparison of survivor functions
 Exponential test, hazard difference, conditional
 Ho: h2-h1 = 0
```

```
Input parameters:

       alpha =    0.0500  (two sided)
          s1 =    0.9950
          s2 =    0.9975
           t =   12.0000
       h2-h1 =   -0.0002
       power =    0.8000
          p1 =    0.5000

 Accrual and follow-up information:

    duration =   12.0000
   follow-up =   10.0000
     accrual =    2.0000  (uniform)

Estimated sample sizes:

           N =     20476
          N1 =     10238
          N2 =     10238
```

8.4 *Monitoring*

Data will be prospectively and continuously recorded in the screening database.

8.5 *Analyses*

The main endpoint, prostate cancer mortality will be evaluated at 12 years from study initiation. Data will be analyzed according to the intention to screen (ITS) principle, i.e. men randomized to the three arms will be analyzed with respect to their study arm, regardless of whether the individuals did or did not attend screening. No interim analysis will be performed.

The secondary endpoints, prostate cancer detection, will be evaluated at 4 years from study initiation.

9.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

9.1 *Records to Be Kept*

The study database will be kept at a server at Gothenburg University for 30 years.

9.2 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.

10.0 HUMAN SUBJECTS

10.1 *Ethical Committee Approval and Informed Consent*

The Ethics Review Committee at the University of Göteborg approved the pilot study (Diarie nr 13-138).

Application for the main study was sent to The Ethics Review Committee as of 14 Nov 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. Having 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." Men who undergo biopsy will sign an informed consent form (consenting to having received information about risks with prostate biopsy, agreeing to store blood and tissue samples for 30 years and agreeing to obtain information from hospital records for the purpose of the study) and receive a copy of the consent. The consent is scanned and recorded in the database.

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

10.2 *Subject Confidentiality*

Data integration will ensure privacy of human subjects. Data will be completely de-identified. No data will be linked to any individual. Data are analyzed and reported on a group level.

10.3 *Harms, benefits and equipoise*

This study aims at evaluating whether the current screening algorithm can improve on the ratio of harms to benefits and achieving equipoise.

10.3.1. *Potential risks for study participants*

Potential risks associated with the screening procedures will be mailed to the participants with the invitation letter.

Screening for prostate cancer

Potential risks include anxiety, over-diagnosis, side-effects from biopsies and treatment and negative impact on quality of life.

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.

Blood test

Potential risks include anxiety, bruise, and fainting.

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-allergy.

Low risk 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 contra indication to MRI.

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 contact information who to call in the event of an adverse event.

Survey

May cause some degree of distress in certain subjects. To fill out 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, can be completed in a short time and without stress.

10.3.2. *Potential benefits for study participants*

Screening for prostate cancer

Potential benefits include early detection and treatment 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 this 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.

10.4 *Benefit: Risk Endpoints*

11.4.1 *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 allergy requiring medication
- Serious side-effects from MRI: Any major side-effect from MRI requiring hospitalization or 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 death.

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

10.4.2 *Number Needed to Invite to Screening and Number Needed to Diagnose*

Numbers needed to invite to screening (NNI) and numbers needed to diagnose (NND) will be calculated, following the methods previously applied in the Göteborg-1 trial (*Hugosson, Carlsson 2010*).

NNI = number needed to invite to screening (as opposed to screen, since not all men participate) to avert one prostate cancer death: inverse of the absolute risk reduction (incidence rate difference) between the screened and unscreened groups. 95% confidence interval will be calculated.

NND = number needed to diagnose (since not all men with prostate cancer are treated but managed expectantly, as opposed to calling it treat) to avert one prostate cancer death: inverse of the absolute risk reduction multiplied by the excess prostate cancer incidence in the screened group. A credible interval will be calculated.

10.5 *Retention Plan*

The invitation letter is comprehensive and describes the number of screening visits, length of visits, tasks involved at each visits (PSA-testing, MRI, biopsies), duration of the overall study and that participation is free of costs. Study participation is completely voluntary and participants can withdraw from the study at any time. PSA-testing will be possible to carry out at not only one clinic, but

several, to ease participation.

There will be flexibility regarding opening hours and scheduling of clinic visits to accommodate the busy schedules of participants. To ensure a high participation rate to screening, non-attendees to the first invitation will be sent 2 reminders: one at 3 months and one at 9 months from invitation. Men who do not fill out the surveys will also be sent automatic reminders. A study nurse will call patients who have not completed their surveys, despite reminders.

Since every Swedish resident has a unique personal identification number, this allows almost complete follow-up for cancer status, vital status and cause of death. The registries have about 95% coverage.

11.0 PUBLICATION OF RESEARCH FINDINGS

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

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