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## A study protocol for the randomized diagnostic study STHLM3MRI Main Study.

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**Title:**

***A study protocol for the randomized diagnostic study STHLM3MRI  
Main Study.***

**Authors:**

Tobias Nordström<sup>a,b</sup>, MD PhD

Fredrik Jäderling<sup>e,f</sup>, MD PhD

Stefan Carlsson<sup>d,f</sup>, MD PhD

Markus Aly<sup>a,d,f</sup>, MD PhD

Henrik Grönberg<sup>a</sup>, MD PhD, Professor

Martin Eklund<sup>a</sup>, PhD

<sup>a</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet,  
Sweden

<sup>b</sup>Department of Clinical Sciences at Danderyd Hospital, Karolinska Institutet,  
Sweden

<sup>d</sup>Department of Urology, Karolinska University Hospital Solna, Stockholm,  
Sweden

<sup>e</sup>Department of Diagnostic Radiology, Karolinska University Hospital, Stockholm,  
Sweden

<sup>f</sup>Department of Molecular Medicine and Surgery, Karolinska Institutet,  
Stockholm, Sweden

1  
2  
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5  
6 Correspondence to:  
7

8  
9 Tobias Nordström

10  
11 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

12  
13  
14  
15 S-171 77 Stockholm, Sweden

16  
17  
18 Email: tobias.nordstrom@ki.se

19  
20  
21 Phone: + 46 70 539 17 91  
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27 Keywords: Prostate cancer, Prostate neoplasm, biomarker, STHLM3, prostate  
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29 biopsy, magnetic resonance imaging  
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## 31 32 33 34 **1. Abstract**

### 35 36 37 **Introduction**

38  
39 Prostate cancer is a leading cause of cancer death among men in the Western world.  
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41 Early detection of prostate cancer has been shown to decrease mortality, but has limitations  
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43 with low specificity leading to unnecessary biopsies and over-diagnosis of low-risk cancers.  
44  
45 The STHLM3 trial has paved the way for improved specificity in early detection of prostate  
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47 cancer using the blood-based STHLM3 test for identifying men at increased risk of  
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49 harbouring significant prostate cancer. Targeted prostate biopsies based on MRI images  
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51 have been shown non-inferior sensitivity to detect significant prostate cancer and decrease  
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53 the number of biopsies and non-significant cancers among men referred for prostate biopsy  
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55 in clinical practice.

56  
57 The overarching strategy of the STHLM3-MRI projects is to study an improved diagnostic  
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59 pathway including an improved blood-based test for identification of men with increased  
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61 risk of prostate cancer and use of MRI to select men for diagnostic workup with targeted  
62  
63 prostate biopsies.

## Methods

This is a study comparing traditional prostate cancer detection using PSA and systematic biopsies with the improved pathway for prostate cancer detection using the STHLM3 test and targeted biopsies in a screening context. The study will recruit 10,000 participants during 2018-2019 combining a paired and randomized design. This protocol follows SPIRIT guidelines. Endpoints include the number of detected prostate cancers, number of performed biopsy procedures and number of performed MRIs. Additional aims include to assess the health economic consequences and development of automated image-analysis.

## Ethics and dissemination

The study has approval from the regional ethical board in Stockholm (2017-1280/31). Study findings will be published in peer-review journals. Findings will be also disseminated by conference/departmental presentations and by social and traditional media.

## Registration details

ClinicalTrials.gov Identifier: NCT03377881

## 2. Strengths and limitations of this study

- This is the first randomized study to examine the role of improved blood-based risk stratification used in sequence with MRI and targeted prostate biopsies in a screening-by-invitation context.
- The study examines the performance of the Stockholm3 test used together with MRI/Fusion technique compared with traditional PSA screening and will provide important data also on the performance of the Stockholm3 test or MRI/Fusion when used as standalone strategies.
- The study is performed at three study sites and uses centralized radiology and pathology.

### 3. Trial identifier

ClinicalTrials.gov Identifier: NCT03377881

## 4. Introduction

### 4.1. Public health significance of prostate cancer

Prostate cancer is the most common cancer and the leading cause of cancer death among men in Sweden. In year 2011 over 10,000 men were diagnosed with prostate cancer and more than 2,500 died due to the disease, approximately 20% of these in the Stockholm region. Prostate cancer incidence rates in Sweden are now comparable to rates in countries that had an early introduction of PSA testing, while prostate cancer mortality rates in Sweden are higher than in most other countries[1]. With over 90,000 prevalent cases, the health burden and the costs on the health care system are substantial. While a number of risk factors have been proposed for prevention of prostate cancer, including diet and occupational exposures, the only factors conclusively shown to increase risk of the disease are age, ethnicity and family history. Given the high prevalence of the cancer and limited opportunities for primary prevention, improved detection would reduce both procedure-related harm to men and economical cost in the healthcare system.

### 4.2. Early detection and treatment of prostate cancer: benefits and harms

The PSA test was first used to monitor disease progression in prostate cancer patients. The PSA test was taken up as a *de facto* screening test for prostate cancer in many countries, leading to rapid rises in prostate cancer incidence. The test characteristics for the PSA test in detecting prostate cancer are comparable to those for mammography for breast cancer screening, with a sensitivity of 72% and a specificity of 30-35% at a test threshold of 4 ng/ml[2]. However, a lower threshold of 3 ng/ml adopted in Sweden recently has led to increased sensitivity at the expense of reduced specificity. Recent analyses of PSA testing in the Stockholm area confirms these results showing that 46%, 68% and 77% of men 50-59, 60-69 and 70-79 years respectively have had at least one PSA test during a 9 years period[3].

Recent results from the large European Randomized Study of Screening for Prostate Cancer (ERSPC) including over 180,000 men provide increasing evidence that PSA screening has led to reduced mortality[4]. This report showed that PSA screening without digital rectal

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3 examination was associated with a 21% relative reduction in the death rate from prostate  
4 cancer at a median follow-up of 11 years, with an absolute reduction of about 7 prostate  
5 cancer deaths per 10,000 men screened. Estimations from the ERSPC trial (men aged 55-69)  
6 show that 1,048 men would need to be offered screening and an additional 37 would need  
7 to be managed to prevent one prostate-cancer death during a 10-year period, leading to a  
8 significant overtreatment of indolent disease. The effectiveness of PSA testing was more  
9 marked at the Göteborg site of the ERSPC trial, with a risk reduction of 44% over 14 years in  
10 men aged 50-64[5]. This effect size is larger than that observed for mammographic  
11 screening for breast cancer and fecal occult blood testing for colorectal cancer.  
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19 However, using traditional systematic biopsies for diagnosis, approximately half of  
20 diagnosed cancers are low-risk tumors using the same main cutoff for biopsy as the ERSPC  
21 trial (PSA=3ng/ml) [6,7]. It has been shown that men with low-risk tumors treated without  
22 curative intent have the same survival as men in the background population[8], illustrating  
23 the large proportion of over-diagnosed cancers[9].  
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28 The STHLM3 study has shown a way to improve identification of men at increased risk of  
29 significant prostate cancer. Using the STHLM3 test, 32% of the prostate biopsies may be  
30 saved while not decreasing the sensitivity to high-grade disease (defined as Gleason Score  
31  $\geq 7$ ) and simultaneously decreasing the number of low-grade tumors (Gleason Score  $\leq 6$ ) by  
32 17%, thus decreasing overdiagnosis[7].  
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### 38 **4.3. Traditional evaluation of men with increased risk of** 39 **prostate cancer** 40

41 Men at increased risk of prostate cancer - commonly estimated using PSA and palpatory  
42 findings - are traditionally assessed using systematic prostate biopsies. The procedure is  
43 performed under local anesthesia using antibiotic prophylaxis and includes 10-12 cores  
44 taken from predefined areas of the peripheral zone of the gland as visualized by endorectal  
45 ultrasound. While the biopsies systematically covers the prostatic gland rather than  
46 targeting a lesion, and non-lethal tumors are common, the risk of over-diagnosis (i.e.  
47 detection of non-significant tumors) is high [9]. The risk of non-representative biopsy  
48 findings result in underestimation of tumor grade compared with subsequent prostatectomy  
49 in up to 40% of men undergoing surgery[10]. The risk of severe post-biopsy infection has  
50 increased to 1-2% with increasing frequency of antibiotic resistance, further illustrating the  
51 need both to increase precision and decrease the number of performed biopsies[11].  
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#### **4.4. Multi-parametric Magnetic Resonance Imaging (mpMRI) for detection of prostate cancer**

Multi-parametric magnetic resonance imaging (mpMRI) incorporating anatomical and functional imaging has now been validated as a means of detecting and characterizing prostate tumors and can aid in risk stratification and treatment selection. The European Society of Urogenital Radiology (ESUR) in 2012 established the Prostate Imaging Reporting and Data System (PI-RADS) guidelines aimed at standardizing the acquisition, interpretation and reporting of prostate mpMRI. Consensus on an updated version (PI-RADS v2) have recently been published, outlining aspects of both interpretation and the technical execution[12-14]. Use of the revised PI-RADS provides moderately reproducible MR imaging scores for detection of clinically relevant disease[15]. Using MP-MRI to triage men might allow 27% of patients avoid a primary biopsy and diagnosis fewer clinically insignificant cancers. If subsequent TRUS-biopsies were directed by MP-MRI findings, up to 18% more cases of clinically significant cancer might be detected compared with the standard pathway of TRUS-biopsy for all[16].

In summary, PI-RADS recommends to use 3T or 1.5T machines, including T2- and T1-weighted sequences together with diffusion weighted images (DWI). Currently, the added value of dynamic contrast is not firmly established regarding tumor detection. At this time, there is no consensus among experts concerning the potential benefits of the use of endorectal coils for cancer detection. It has been suggested that the prevalence of suspicious lesions on MRI in men with clinical suspicion of prostate cancer is approximately 60% [17].

#### **4.5. Targeted prostate biopsies guided by fusion technology**

Targeted biopsies of the prostate consist of imaging (MRI) detecting significant tumors and a biopsy procedure where biopsies are targeted to the tumor using various devices for guidance[18]. While traditional endorectal ultrasound poorly identifies tumors, direction of biopsy needles can be performed in various ways. Cognitive or soft fusion is based on skilled urologists/radiologists interpreting the MRI images and directing needles solely based on the ultrasound images. The disadvantages of cognitive fusion lie in the potential for human error when attempting to mentally fuse the MRI with TRUS while aiming for cancers that are often <1 cm in diameter and the inability to track the location of each biopsy site. Hard fusion enables proper fusion of MRI information on the ultrasound image, possibly increasing precision.



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Despite methodological flaws, a number of studies have investigated the value of fusion biopsies, primarily using non-randomized designs and non-screening populations[19]. In 2018, Kasi et al provided high quality evidence for men referred for prostate biopsy and showed that MRI/target biopsies are non-inferior for detection of significant cancer and decreases the number of in-significant cancers and number of biopsies as compared with systematic biopsies[20].

The proportion of men upgraded when comparing specimen from targeted biopsies and subsequent prostatectomy have been shown to be very low (<5%) when using targeted biopsies[21], increasing the proportion of men where treatment decisions are based on valid risk estimations.

#### **4.6. Improving the diagnostic pathway for prostate cancer detection**

The current diagnostic pathway for prostate cancer detection is characterized by several challenging hallmarks. First, testing with PSA is frequent also in men not benefitting from testing due to low PSA levels or high age[3]. Second, the currently used test for detection (PSA) lacks in specificity, resulting in frequent over-diagnosis[22,23]. Third, systematic biopsies shows high frequencies of benign tests, over-diagnosis, up-grading at prostatectomy, and risk of infectious complications[7,24]. Further, PSA testing increases with educational length and men with long education are more likely to have a prostate biopsy after an increased PSA value. These differences may contribute to the worse prostate cancer outcomes observed among men with lower socioeconomic status[25].

The STHLM3 test offers improved disease detection[7]. To further decrease over-detection, improve disease classification and spare men of test-related harm, prostate biopsy practice need to be improved. We hypothesize that an improved pathway for prostate cancer detection including a better blood-based screening test, improved selection to biopsy based on MRI findings and targeted biopsies guided by MRI/ultrasound fusion would dramatically decrease the number of biopsy procedures, overdiagnosis and improve treatment decisions.

## **5. Methods**

## 5.1. Hypotheses

### 5.1.1. Primary hypotheses

The below hypothesis is posed for men in screening-by-invitation context:

A diagnostic pathway using the Stockholm3 test to select men for further workup using MRI followed by targeted biopsies and systematic biopsies (S3M-MR-TBx/SBx) has non-inferior sensitivity for detecting clinically significant cancer (ISUP grade group  $\geq 2$ ) and reduces the number of performed biopsy procedures compared to a diagnostic pathway using systematic biopsies in men with PSA  $\geq 3$  ng/ml (PSA-SBx).

### 5.1.2. Additional hypotheses

1. As compared with performing systematic biopsies for men with elevated risk of prostate cancer in prostate cancer screening, targeted prostate biopsies performed with MRI/Fusion technique with or without addition of systematic biopsies has non-inferior sensitivity for detecting clinically significant cancer (ISUP grade group  $\geq 2$ ) and reduces the number of performed biopsy procedures.
2. A diagnostic pathway using the Stockholm3 test to select men for further workup using MRI followed by ONLY targeted biopsies (S3M-MR-TBx) has non-inferior sensitivity for detecting clinically significant cancer (ISUP grade group  $\geq 2$ ) and reduces the number of performed biopsy procedures compared to a diagnostic pathway using systematic biopsies in men with PSA  $\geq 3$  ng/ml (PSA-SBx).
3. Adding prostate volume as parameter in the diagnostic pathway with Stockholm3 test and MRI/Fusion biopsies improves model precision.
4. A diagnostic pathway with Stockholm3 followed by MRI and targeted biopsies has non-inferior sensitivity for detecting clinically significant cancer (ISUP grade group  $\geq 2$ ) and reduces the number of MRI examinations and performed biopsies compared to a diagnostic pathway using PSA  $\geq 3$  ng/ml followed by MRI and targeted biopsies.
5. SBx in the MRI arm has superior sensitive than SBx in the non-MRI arm (due to cognitive fusion).
6. Biopsy compliance is higher after biopsy is recommended based on MRI compared to recommended without MRI.

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3 7. A diagnostic pathway using the Stockholm3 test to select men for further workup  
4 using MRI and targeted biopsies (S3M+TBx) shows better health economy (positive  
5 ICER) compared to a diagnostic pathway using systematic biopsies in men with PSA  
6  $\geq 3$  ng/ml (PSA+SBx).  
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## 10 11 12 **5.2. Aims**

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15 To compare a diagnostic pathway using the Stockholm3 test ( $S3M \geq 11\%$ ) to select men  
16 for further workup using MRI ( $PI-RADS \geq 3$ ) and targeted biopsies (S3M+TBx) to a diagnostic  
17 pathway using systematic biopsies in men with  $PSA \geq 3$  ng/ml (PSA+SBx) with respect to  
18 number of diagnosed clinically significant cancer (ISUP grade group  $\geq 2$ ) and number of  
19 performed biopsies. Additional aims corresponding to hypotheses 2-8 above will be  
20 assessed.  
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## 25 26 27 **5.3. Study design**

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30 STHLM3-MR Phase 2 is a study combining a paired and a randomized design (Figure 1).  
31 The study will follow the following outline: Participants will be invited by mail. All  
32 participants will undergo a blood-test, including PSA and the STHLM3 test. Men with an  
33 elevated PSA  $\geq 3$  ng/ml or PSA  $\geq 1.5$  ng/ml and  $S3M > 11\%$  will be randomized to either  
34 traditional prostate biopsies or MR with targeted biopsies on MR lesions.  
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## 44 45 46 **5.4. Participants, interventions and outcomes**

### 47 48 **5.4.1. Study setting**

49 This is a screening-by-invitation study including one study administrative center, two  
50 radiological sites and three urological sites where data will be collected.  
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#### 54 **Participating urological centres**

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56 Department of Urology, Capio St Görans Hospital: dr Henrik Grönberg  
57 Uroclinic, Sophiahemmet, Stockholm; dr Olof Jansson  
58  
59 Odenplans läkarhus; dr Magnus Annerstedt  
60

## 5.4.2. Eligibility criteria

### *Inclusion criterias*

Men age 50-74 years without prior diagnosis of prostate cancer (ICD-9 C61).

Permanent postal address in Stockholm

Not a previous participant in the Stockholm3 study (2012-2014)

### *Exclusion criterias*

Severe illnesses such as metastatic cancers, severe cardio-vascular disease or dementia

Contraindications for magnetic resonance imaging (MRI) eg pacemaker, magnetic cerebral clips, cochlear implants or severe claustrophobia.

Men with a previous prostate biopsy the preceding 60 days before invitation.

## 5.4.3. Randomization

Randomization is performed 2:3 between control arm and experimental arm. Randomization will be performed will be performed using stratification on disease risk [6 stratas]. Disease risk is assessed using the Stockholm3 test. Test are discordant if PSA is negative and Stockholm3 positive or vice versa.

Four allocation lists [high/low risk vs discordant/concordant tests] have been created with the sequence [control arm, control arm, experimental arm, experimental arm, experimental arm]. Participants are first allocated to corresponding list, and then allocated to study arm according to the order in which they participate. The allocation sequence is blinded for the study investigators and handled by the study database administrator (A Björklund).

In order to enhance resource usage, men are allocated to the study sites according to local availability of biopsy procedure slots.

## 5.4.4. Interventions

### *Blood sampling*

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3 Participating men undergo blood-sampling with analysis of PSA and the Stockholm3 test  
4 at Karolinska University Laboratory.  
5

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7 For the main analysis, the Stockholm3 test include clinical data as answered when  
8 consenting participation (previous biopsy, age, finasteride medication, relatives with  
9 prostate cancer); single nucleotide polymorphisms and measurements of protein levels  
10 (MSMB, MIC1, PSA, fPSA, hK2). For secondary analyses, clinical information on DRE and  
11 prostate volume is included. The algorithm for calculation of the Stockholm3 test result has  
12 been described (Ström et al, European Urology 2018).  
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### 17 18 **Definition of EXPERIMENTAL ARM**

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20 Men randomized to the experimental arm undergoes MRI. If suspicious lesions are  
21 found, the participant undergoes targeted biopsies using Fusion technology *followed by*  
22 *systematic biopsies*.  
23

24 Men without lesions are exempted from further intervention and receives notification on  
25 recommendation for follow-up. Technology and process are described below.  
26

27 Men with a Stockholm3 risk  $\geq 25\%$  and no suspicious lesion on MRI will undergo  
28 systematic biopsies.  
29

### 30 31 **Definition of CONTROL ARM**

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33 Men randomized to the control arm undergoes systematic biopsies as defined below.  
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35

### 36 37 **Technology**

#### 38 39 **Cut-offs for performing the STHLM3 test**

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41 The STHLM3 test will be performed for men with a PSA  $\geq 1.5$  ng/ml  
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#### 44 45 **Cut-offs for entering randomization**

46 Participants with PSA  $\geq 3.0$  ng/ml or STHLM3-test  $\geq 11\%$  risk of Gleason Score  $\geq 7$  cancer  
47 will be randomized and offered to undergo either MR or systematic biopsies (See Process  
48 description).  
49  
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### 51 52 **MRI technology**

#### 53 54 **Location and MRI equipment**

55  
56  
57 Capio St Görans Hospital: General Electric, Architect, 3T

58  
59 Globen Unilabs Healthcare: Siemens Magnetom Aera 1.5T  
60

### ***Patient preparations***

Refraining from sexual activity with ejaculation 3 days prior to examination

Fasting patient 6 h

Minimal preparation enema prior to examination

Antispasmodic agent (Glucagon) just before the examination

### ***MRI Protocol***

A short (14 minutes) MRI protocol will be used. A detailed description is available. Briefly, the protocol includes: T2w images axial, sagittal, coronal; Diffusion weighted imaging b0 and b1000 with ADC and a synthetic b1500 limited to the prostate location; No endorectal coil will be used.

### ***MRI Interpretation***

MRI interpretation is centralized to Capio St Görans hospital and is performed according to PIRAD v2.0 for examinations without adequate perfusion studies. Dr Fredrik Jäderling is responsible for MRI interpretation. Dr Jäderling or 1-2 other, experienced radiologists at his department performs all MRI interpretations.

PI-RADS v2 ("Assessment without adequate dynamic contrast enhanced imaging") will be used, with a 1-5 grade scale of suspicious lesions (1= clinically significant cancer is highly unlikely to be present, 5= clinically significant cancer is highly likely to be present).

During the study period participating radiologist will have access to updated histology results of fusion biopsies to be able to adjust their MRI reading according to tumor detection rates for different PIRAD diagnoses as defined above.

### ***Fusion biopsy technology***

#### ***Brand/models***

#### ***BK Medical (BK Ultrasound ; [www.bkultrasound.com/bk-medical/fusion](http://www.bkultrasound.com/bk-medical/fusion))***

The BK Medical fusion system is the only fusion device compatible with BK Medicals ultrasound devices, used by the urology departments participating in the study. The system represents a second generation ultrasound system with integrated MRI Fusion. MRI data is imported through HIPAA-compliant PACS connection with the local radiology department.

#### ***Definition of targeted biopsies***

Using MRI data with pre-marked borders of the prostate and tumor, fusion of MRI images and ultrasound images are performed bedside. Using local anesthetic and antibiotic

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3 prophylaxis, lesions are according to below. Targeted biopsies are always combined with  
4 systematic biopsies.  
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### 6 ***Biopsy procedure for targeted biopsies***

8 **PI-RADS $\geq$ 3:** 3-4 targeted biopsies on marked lesions + systematic biopsies

10 **Large diffuse lesions or poor image quality:** Systematic biopsies including lesion

12 **No PI-RADS $\geq$ 3, diffuse lesions and at least acceptable image quality:** No biopsies are  
13 performed.  
14

16 In larger lesions in PI-RADS category 3 and 5, areas within the lesion with the lowest ADC  
17 value ("Target-within-target") will be targeted with the first biopsy taken from the lesion, to  
18 evaluate the additional value regarding tumor staging.  
19

### 21 ***Definition of systematic biopsies***

23 10-12 systematic biopsies are taken from the peripheral zone as previously described in  
24 STLHLM3 and the National Guidelines. Extra biopsies are allowed from additional sites  
25 visible on ultrasound or according to palpatory findings. In summary, systematic biopsies are  
26 performed in the peripheral zone as 4 lateral and para-median biopsies on the left and right  
27 side, in the base and mid part of the gland. In the apical third of the gland one lateral left  
28 and right biopsy is performed.  
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### 34 ***Pathology***

36 Pathology is centralized to Unilabs/Capio St Görans hospital. Dr Axel Glaessgen is  
37 responsible for the integrity of analyzes of pathological specimen. 2-3 uro-pathologists at dr  
38 Glaessgens department assesses all pathological specimen with intermittent cross-validation  
39 between them. Pathology preparation and reporting follow ISUP 2014 guidelines.  
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44 The pathology preparation is done by Unilabs as part of the normal clinical routine.  
45 Biopsy specimens are analyzed according to local practice.  
46  
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48 Localisation of biopsies in the prostate are described using Swedish National Guideline  
49 nomenclature (A1-4; B1-4; C1-4; anterior/posterior). Gleason Score, mm cancer and %  
50 Gleason 4 is reported on each needle specimen.  
51  
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53 Pathologist notes results in the usual way in the laboratory system. The result of the  
54 pathological analysis is submitted in accordance to existing clinical routines to the referring  
55 urologist. A copy of the result is delivered to the study administration.  
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## 60 ***5.4.5. Outcomes***

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3 There are three co-primary endpoints in this trial:

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5 Number of diagnosed ISUP grade group  $\geq 2$  cancers

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7 Number of diagnosed ISUP grade group 1 cancers

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10 Number of performed biopsies

### 11 12 13 **5.4.6. Follow-up**

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15 Main study outcomes are assessed after prostate biopsy procedures. Additional  
16 participant data will be secured in the following circumstances:

#### 17 18 19 ***No suspicious lesion on MRI:***

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21 Men in the experimental arm without suspicious lesions on MRI will be informed and  
22 recommended follow-up by the responsible, local urologist. After additional ethical  
23 application, the co-investigators might initiate retrospective follow-up of these participants.

#### 24 25 26 27 28 ***Men with diagnosed prostate cancer***

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30 Participants with prostate cancer diagnosed on biopsy within the study will be followed  
31 up after the biopsy to secure data on the following: Treatment modality (Active Surveillance,  
32 Surgery, Radiation); Treatment lead-time and site; Pathological report after surgery (positive  
33 margins, T-stage, etc). Data will be assessed through medical records intermittently.

### 34 35 36 37 38 39 40 41 **5.5. Serious adverse events**

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43 Study nurse will monitor serious adverse events after the prostate biopsy procedures. To  
44 ensure this, the study nurse will follow this check medical journals for hospitalization within  
45 1 week after the biopsy procedure in the journal systems Take Care and Cosmic (covering  
46 the main part of hospitals in Stockholm region). This will be initiated as individual biopsy  
47 results are registered at the study administration. Results will be provided to the Data Safety  
48 and Monitoring Board.

### 49 50 51 52 53 54 55 **5.6. Participant timeline**

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57 Figure 2 illustrates the approximate timeline for participating men in STHLM3MRI Main  
58 Study.  
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## 5.7. Sample size

STHLM3-MR/Fusion Phase 2 will invite 25,000 men and aim to include 10,000 participants (see **Error! Reference source not found.**). We anticipate to perform 1,039 biopsy procedures altogether. Inclusion will continue until complete data on 415 men in the control arm (SBx) and 623 men in the experimental arm (MR-TBx-SBx).

### **Basic data and assumptions used in the sample size calculations**

We used data from the STHLM3 trial [REF Grönberg et al. Lancet Oncology 2015] for sample size calculations. In this data, 18% of men with PSA  $\geq 3$  had a clinically significant prostate cancer when biopsied with SBx. We further noted that rTPR=1.45 for clinically significant prostate cancer comparing MRI+TBx with SBx based on the results from the PRECISION randomized trial [REF Kasivisvanathan et al. NEJM 2018]. However, we will for sample size calculations use rTPR=1.25 for MRI+TBx vs. SBx as a more conservative estimate. We set the noninferiority delta to 4 percentage points for demonstrating noninferiority with respect to sensitivity of clinically significant prostate cancer. We set the alpha to 5%.

### **Primary contrast**

Simulating 1000 trials (by bootstrapping from the STHLM3 data) under the assumptions outlined in the preceding section 303 men need to be biopsied in the SBx arm based on PSA  $\geq 3$  to have 80% power to demonstrate non-inferior sensitivity of S3M+MRI+TBx compared with PSA+SBx. This means that at least **415** men need to be biopsied in the SBx arm (since some men are not randomized based on PSA  $\geq 3$  but on S3M  $\geq 11\%$ ) and, consequently, **623** to the MRI arm (because of the 2:3 randomization). Total number of men undergoing workup according to protocol (SBx in the no MRI arm and MRI and TBx if Pi-RADS  $\geq 3$  in the MRI arm) is thus 1038. Assuming 20% dropout, 1300 men need to be randomized. These numbers give 80% power to detect a modest 17% reduction in biopsies between the two strategies.

## 5.8. Recruitment and Process Description

The STHLM3-MR Phase 2 will use existing solutions developed and optimized in the previous studies STHLM3 and STHLM3-MR Phase 1 where all major components of the process have been tested. First, participants will follow the *paired design study process* where inclusion, blood-test and delivery of recommendation letter is performed. Men with increased risk of high-grade prostate cancer then enter the *randomized study process*, where extended work-up including biopsies are performed.

## **5.9. Data Collection, management, analysis**

### **5.9.1. Data collection**

Primary data sources are

- i. clinical variables collected from laboratory referral
- ii. biopsy referrals and reports
- iii. pathology reports
- iv. MRI reports
- v. blood concentrations of kallikreins, MSMB, MIC1, SNPs

Collection of i. – iv. is performed by study nurses (C Cavalli-Björkman) on a weekly basis from participating urology sites, participating radiologists. For v., this is digitally transferred from Karolinska University Laboratory.

### **5.9.2. Data management**

Data is collected, entered, coded and stored at Department of Medical Epidemiology and Biostatistics, Karolinska Institutet. Data is entered by Study Nurse using predefined database sheets developed in STHLM3MRI Phase 1. This is blinded from study co-investigators and data is stored at the department under supervision by the study database administrator (SDA, Astrid Björklund). Any extraction of study data is performed by the SDA after approval of PI Tobias Nordström.

### **5.9.3. Data analysis**

Analysis of data is described in the Statistical Analysis Plan (SAP).

### **5.9.4. Auditing and Monitoring**

A Data Safety and Monitoring Board (DSMB) is assembled and consist of dr Hans Garmo (Statistician), prof Ola Bratt (Urology) and prof Holmberg (Urology/Study Design). The DSMB audits protocol and process descriptions and one interim data extraction performed by the study database administrator after 10% (100 men) have completed the control or experimental arms. The co-investigators are blinded to the interim data and analysis results. The work of the DSMB is regulated in the DSMB Charter.

## **5.10. Patient and Public Involvement**

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2  
3 The research question and outcome measures were designed to improve prostate  
4 cancer diagnostics. This includes optimizing prostate biopsies and decreasing over-detection,  
5 both associated with morbidity. Patient organisations were informed on the results from the  
6 STHLM3MRI Phase 1 study. Patients were not involved in recruitment of the study. Results  
7 will be disseminated to participants through common and scientific channels.  
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## 14 **6. Ethics and dissemination**

### 17 **6.1. Research ethics approval**

18 The study has approval from the regional ethical board in Stockholm (2017-  
19 1280/31).  
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### 23 **6.2. Consent**

24 Participant consent is secured when the participant is included to the study at  
25 www.kliniskastudier.se. This includes secure identification using Mobilt BankID. Additional  
26 approval on use of biological specimen data is collected on the biopsy referral.  
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### 33 **6.3. Confidentiality**

34 Study data is collected and stored at Department of Medical Epidemiology and  
35 Biostatistics, Karolinska Institutet using secure Oracle servers. All data extractions are made  
36 by database administrator and are anonymized (personal id number is removed) before  
37 dissemination to researchers.  
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### 44 **6.4. Dissemination**

45 Analyses results on the posed aims will be submitted for peer-reviewed publication and  
46 submitted for presentation at scientific congress. Communication of the results will be made  
47 to patient organisations (Prostatacancerförbundet) and non-scientific channels. No use of  
48 professional writers are planned.  
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53 The study protocol is made publicly available through [clinicaltrials.gov](http://clinicaltrials.gov).  
54  
55

### 56 **6.5. Data Sharing Statement**

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2  
3 Anonymized, individual participant data that underlie the results reported in this  
4 article, after deidentification (text, tables, figures and appendices) will be available for data  
5 sharing. Proposals may be submitted up to 36 months following article publication. Data will  
6 be shared with investigators whose proposed use of the data has been approved by an  
7 independent review committee identified for this purpose.  
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13

## 14 **7. Declarations of interest**

17 Henrik Grönberg has five prostate cancer diagnostic related patents pending, has patent  
18 applications licensed to Thermo Fisher Scientific, and might receive royalties from sales  
19 related to these patents. Martin Eklund is named on four of these five patent applications.  
20 Karolinska Institutet collaborates with Thermo Fisher Scientific in developing the technology  
21 for the Stockholm3 test.  
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## 28 **8. Contributions**

31 TN was the Principal Investigator. TN, HG, ME, SC and MA designed the study. ME and  
32 TN interpreted preliminary data. FJ designed MRI protocols and collected data.  
33  
34

35 We thank participants, study organizers, participating researchers and clinicians, and  
36 patient advisers for their contributions to the STHLM3MRI project.  
37  
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## 41 **9. Funding statement**

42 Funding was provided by the Swedish Cancer Society, (Cancerfonden), the Swedish  
43 Research Council (Vetenskapsrådet), Swedish Research Council for Health Working Life and  
44 Welfare (FORTE), The Strategic Research Programme on Cancer (StratCan), Karolinska  
45 Institutet, Swedish e-Science Research Center (SeRC) and Stockholm City Council (SLL). The  
46 STHLM3 study is a part of the Linnaeus Center CRISP "Predication and prevention of breast  
47 and prostate cancer" funded by the Swedish Research Council.  
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## 55 **10. Figure legends**

58 Figure 1: Study design overview STHLM3MRI Main Study  
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Figure 2: Timeline overview for study participants in STHLM3MRI Main Study

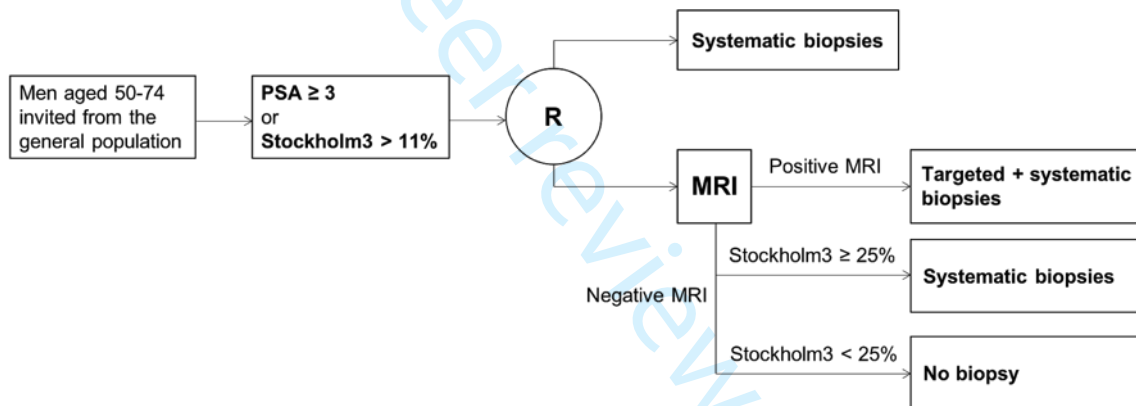
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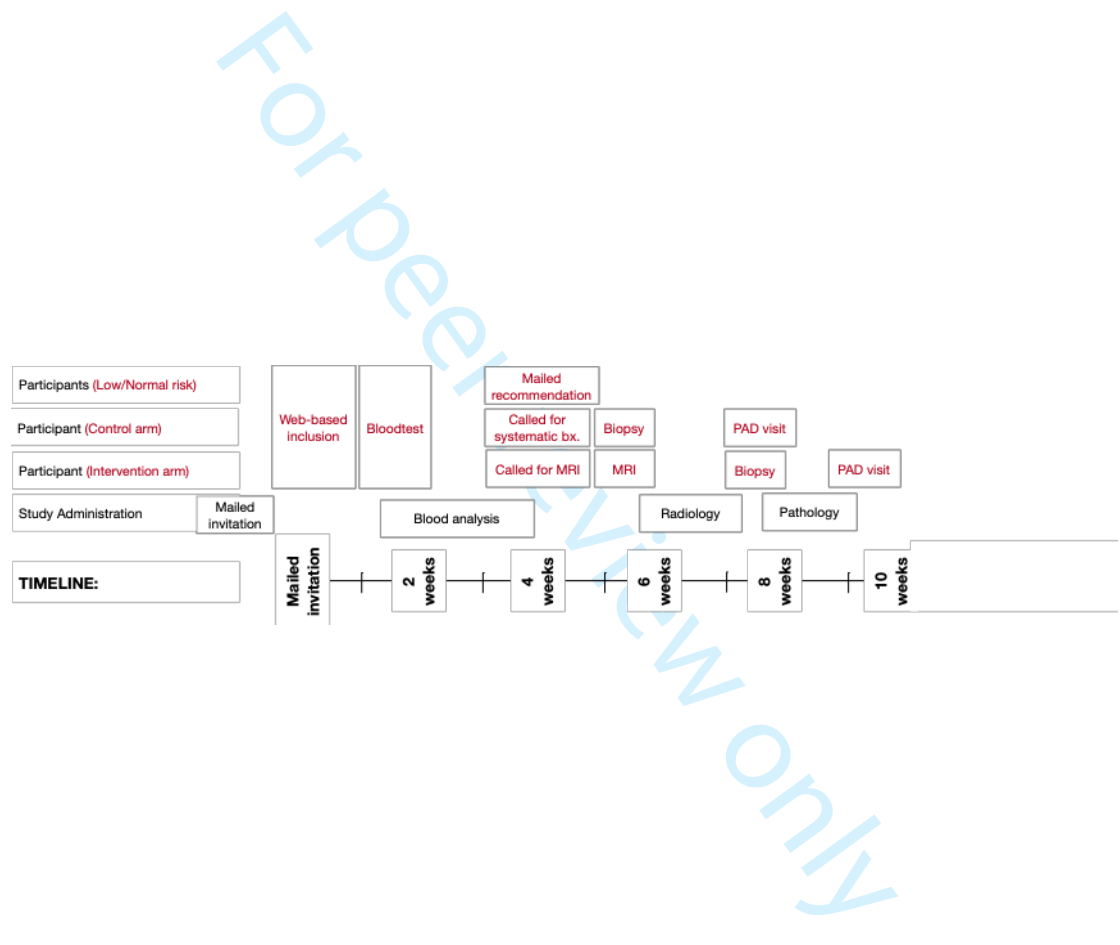
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## CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	4-7
	2b	Specific objectives or hypotheses	8-9
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	10
Participants	4a	Eligibility criteria for participants	10
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10-13
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	14
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	15
	7b	When applicable, explanation of any interim analyses and stopping guidelines	16
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	-
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	-

1		assessing outcomes) and how	
2		11b If relevant, description of the similarity of interventions	
3	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	Separate doc
4		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	Separate doc
5			
6	<b>Results</b>		
7	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	
8	diagram is strongly	were analysed for the primary outcome	
9	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	
10	Recruitment	14a Dates defining the periods of recruitment and follow-up	
11		14b Why the trial ended or was stopped	
12	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	
13	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	
14		by original assigned groups	
15	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	
16	estimation	precision (such as 95% confidence interval)	
17		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
18	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	
19		pre-specified from exploratory	
20	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
21			
22	<b>Discussion</b>		
23	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
24	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	
25	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
26			
27	<b>Other information</b>		
28	Registration	23 Registration number and name of trial registry	2
29	Protocol	24 Where the full trial protocol can be accessed, if available	1
30	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	18
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36  
37 \*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also  
38 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.  
39 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).  
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# BMJ Open

**Do a novel diagnostic pathway including blood-based risk-prediction and MRI-targeted biopsies outperform prostate cancer screening using prostate-specific antigen and systematic prostate biopsies? - The randomized, diagnostic study STHLM3MRI.**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027816.R1
Article Type:	Protocol
Date Submitted by the Author:	20-Feb-2019
Complete List of Authors:	Nordstrom, Tobias; Karolinska Inst, Dpt Medical Epidemiology and Biostatistics Jäderling, Fredrik; Karolinska Institutet, Molecular Medicine and Surgery Carlsson, Stefan; Karolinska Institutet Aly, Markus; Karolinska Institutet, Grönberg, H; Karolinska Institutet, Eklund, Martin; Karolinska Institutet,
<b>Primary Subject Heading</b>:	Urology
Secondary Subject Heading:	Diagnostics
Keywords:	Prostate disease < UROLOGY, Magnetic resonance imaging < RADIOTHERAPY, Urological tumours < UROLOGY

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1 **Title:**

2 Do a novel diagnostic pathway including blood-based risk-prediction and MRI-  
3 targeted biopsies outperform prostate cancer screening using prostate-  
4 specific antigen and systematic prostate biopsies? - The randomized,  
5 diagnostic study STHLM3MRI.

6 **Authors:**

7 Tobias Nordström<sup>a,b</sup>, MD PhD

8 Fredrik Jäderling<sup>e,f</sup>, MD PhD

9 Stefan Carlsson<sup>d,f</sup>, MD PhD

10 Markus Aly<sup>a,d,f</sup>, MD PhD

11 Henrik Grönberg<sup>a</sup>, MD PhD, Professor

12 Martin Eklund<sup>a</sup>, PhD

13 <sup>a</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden

14 <sup>b</sup>Department of Clinical Sciences at Danderyd Hospital, Karolinska Institutet, Sweden

15 <sup>d</sup>Department of Urology, Karolinska University Hospital Solna, Stockholm, Sweden

16 <sup>e</sup>Department of Diagnostic Radiology, Karolinska University Hospital, Stockholm, Sweden

17 <sup>f</sup>Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm,  
18 Sweden

19  
20 **Correspondence to:**

21 Tobias Nordström

22 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

23 S-171 77 Stockholm, Sweden

24 Email: tobias.nordstrom@ki.se

25 Phone: + 46 70 539 17 91

26  
27 **Keywords:** Prostate cancer, Prostate neoplasm, biomarker, STHLM3, prostate biopsy,  
28 magnetic resonance imaging

## 1. Abstract

### Introduction

Prostate cancer is a leading cause of cancer death among men in the Western world. Early detection of prostate cancer has been shown to decrease mortality, but has limitations with low specificity leading to unnecessary biopsies and over-diagnosis of low-risk cancers. The STHLM3 trial has paved the way for improved specificity in early detection of prostate cancer using the blood-based STHLM3 test for identifying men at increased risk of harbouring significant prostate cancer. Targeted prostate biopsies based on MRI images have been shown non-inferior sensitivity to detect significant prostate cancer and decrease the number of biopsies and non-significant cancers among men referred for prostate biopsy in clinical practice.

The strategy of the STHLM3-MRI projects is to study a diagnostic pathway including an improved blood-based test for identification of men with increased risk of prostate cancer and use of MRI to select men for diagnostic workup with targeted prostate biopsies.

### Methods

This study compares prostate cancer detection using PSA and systematic biopsies with the improved pathway for prostate cancer detection using the STHLM3 test and targeted biopsies in a screening context. The study will recruit 10,000 participants during 1 June 2018- 1 June 2020 combining a paired and randomized design. Participants are grouped by PSA and Stockholm3 test level and men with Stockholm3 $\geq$ 11% or PSA  $\geq$ 3ng/ml are randomized to systematic or MRI-targeted biopsies. This protocol follows SPIRIT guidelines. Endpoints include the number of detected prostate cancers, number of performed biopsy procedures and number of performed MRIs. Additional aims include to assess the health economic consequences and development of automated image-analysis.

### Ethics and dissemination

The study has approval from the Regional Ethical Review Board in Stockholm (2017-1280/31). Study findings will be published in peer-review journals. Findings will also be disseminated by conference/departmental

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3 61 presentations and by social/traditional media.  
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5 62 **Registration details**

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7 63 ClinicalTrials.gov: NCT03377881  
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12 64 **2. Strengths and limitations of this study**

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  - This is the first randomized study to examine the role of improved  
15 66 blood-based risk stratification used in sequence with MRI and  
16 67 targeted prostate biopsies in a screening-by-invitation context.
  - The study examines the performance of the Stockholm3 test used  
17 68 together with MRI/Fusion technique compared with traditional PSA  
18 69 screening and will provide important data also on the performance  
19 70 of the Stockholm3 test or MRI/Fusion when used as standalone  
20 71 strategies.
  - The study is performed at three study sites and uses centralized  
21 72 radiology and pathology.
  - The study is limited to a Swedish screening population, the use of  
22 73 the Stockholm3 test as blood-based risk prediction and the used  
23 74 technology for MRI-targeted biopsies.

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78 60 **3. Trial identifier**

79 61 ClinicalTrials.gov Identifier: NCT03377881

80 62 **4. Introduction**

81 63 **4.1. Public health significance of prostate cancer**

82 64 Prostate cancer is the most common cancer and the leading cause of  
83 65 cancer death among men in Sweden. In year 2011 over 10,000 men were  
84 66 diagnosed with prostate cancer and more than 2,500 died due to the disease,  
85 67 approximately 20% of these in the Stockholm region. Prostate cancer  
86 68 incidence rates in Sweden are now comparable to rates in countries that had  
87 69 an early introduction of PSA testing, while prostate cancer mortality rates in

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3 88 Sweden are higher than in most other countries[1]. With over 90,000  
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5 89 prevalent cases, the health burden and the costs on the health care system  
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7 90 are substantial. While a number of risk factors have been proposed for  
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9 91 prevention of prostate cancer, including diet and occupational exposures, the  
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11 92 only factors conclusively shown to increase risk of the disease are age,  
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13 93 ethnicity and family history. Given the high prevalence of the cancer and  
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15 94 limited opportunities for primary prevention, improved detection would reduce  
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17 95 both procedure-related harm to men and economical cost in the healthcare  
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19 96 system.

#### 20 97 **4.2. Early detection and treatment of prostate cancer: benefits and** 21 98 **harms**

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23 99 The PSA test was first used to monitor disease progression in prostate  
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25 100 cancer patients. The PSA test was taken up as a *de facto* screening test for  
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27 101 prostate cancer in many countries, leading to rapid rises in prostate cancer  
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29 102 incidence. The test characteristics for the PSA test in detecting prostate  
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31 103 cancer are comparable to those for mammography for breast cancer  
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33 104 screening, with a sensitivity of 72% and a specificity of 30-35% at a test  
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35 105 threshold of 4 ng/ml[2]. However, a lower threshold of 3 ng/ml adopted in  
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37 106 Sweden recently has led to increased sensitivity at the expense of reduced  
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39 107 specificity. Recent analyses of PSA testing in the Stockholm area confirms  
40  
41 108 these results showing that 46%, 68% and 77% of men 50-59, 60-69 and 70-  
42  
43 109 79 years respectively have had at least one PSA test during a 9 years  
44  
45 110 period[3].

46  
47 111 Recent results from the large European Randomized Study of Screening  
48  
49 112 for Prostate Cancer (ERSPC) including over 180,000 men provide increasing  
50  
51 113 evidence that PSA screening has led to reduced mortality[4]. This report  
52  
53 114 showed that PSA screening without digital rectal examination was associated  
54  
55 115 with a 21% relative reduction in the death rate from prostate cancer at a  
56  
57 116 median follow-up of 11 years, with an absolute reduction of about 7 prostate  
58  
59 117 cancer deaths per 10,000 men screened. Estimations from the ERSPC trial  
60  
118 (men aged 55-69) show that 1,048 men would need to be offered screening  
119  
120 and an additional 37 would need to be managed to prevent one prostate-  
cancer death during a 10-year period, leading to a significant overtreatment of



1  
2  
3 121 indolent disease. The effectiveness of PSA testing was more marked at the  
4  
5 122 Göteborg site of the ERSPC trial, with a risk reduction of 44% over 14 years in  
6  
7 123 men aged 50-64[5]. This effect size is larger than that observed for  
8  
9 124 mammographic screening for breast cancer and faecal occult blood testing for  
10  
11 125 colorectal cancer.

12  
13 126 However, using traditional systematic biopsies for diagnosis,  
14  
15 127 approximately half of diagnosed cancers are low-risk tumours using the same  
16  
17 128 main cut-off for biopsy as the ERSPC trial (PSA=3ng/ml) [6,7]. It has been  
18  
19 129 shown that men with low-risk tumours treated without curative intent have the  
20  
21 130 same survival as men in the background population[8], illustrating the large  
22  
23 131 proportion of over-diagnosed cancers[9].

24  
25 132 The STHLM3 study has shown a way to improve identification of men at  
26  
27 133 increased risk of significant prostate cancer. Using the STHLM3 test, 32% of  
28  
29 134 the prostate biopsies may be saved while not decreasing the sensitivity to  
30  
31 135 high-grade disease (defined as Gleason Score  $\geq 7$ ) and simultaneously  
32  
33 136 decreasing the number of low-grade tumours (Gleason Score  $\leq 6$ ) by 17%,  
34  
35 137 thus decreasing overdiagnosis[7].

### 35 138 **4.3. Traditional evaluation of men with increased risk of prostate** 36 139 **cancer**

37  
38 140 Men at increased risk of prostate cancer - commonly estimated using PSA  
39  
40 141 and palpatory findings - are traditionally assessed using systematic prostate  
41  
42 142 biopsies. The procedure is performed under local anaesthesia using antibiotic  
43  
44 143 prophylaxis and includes 10-12 cores taken from predefined areas of the  
45  
46 144 peripheral zone of the gland as visualized by endorectal ultrasound. While the  
47  
48 145 biopsies systematically covers the prostatic gland rather than targeting a  
49  
50 146 lesion, and non-lethal tumours are common, the risk of over-diagnosis (i.e.  
51  
52 147 detection of non-significant tumours) is high [9]. The risk of non-representative  
53  
54 148 biopsy findings result in underestimation of tumour grade compared with  
55  
56 149 subsequent prostatectomy in up to 40% of men undergoing surgery[10]. The  
57  
58 150 risk of severe post-biopsy infection has increased to 1-2% with increasing  
59  
60 151 frequency of antibiotic resistance, further illustrating the need both to increase  
152  
153 152 precision and decrease the number of performed biopsies[11]. Since  
153  
154 153 screening using PSA and systematic prostate biopsies have been shown to

1  
2  
3 154 decrease prostate cancer mortality, it is reasonable to use this strategy as  
4  
5 155 comparator for novel diagnostic strategies[4-5].  
6  
7

#### 8 156 **4.4. Multi-parametric Magnetic Resonance Imaging (mpMRI) for** 9 157 **detection of prostate cancer**

10 158 Multi-parametric magnetic resonance imaging (mpMRI) incorporating  
11 159 anatomical and functional imaging has now been validated as a means of  
12 160 detecting and characterizing prostate tumours and can aid in risk stratification  
13 161 and treatment selection. The European Society of Urogenital Radiology  
14 162 (ESUR) in 2012 established the Prostate Imaging Reporting and Data System  
15 163 (PI-RADS) guidelines aimed at standardizing the acquisition, interpretation  
16 164 and reporting of prostate mpMRI. Consensus on an updated version (PI-  
17 165 RADS v2) have recently been published, outlining aspects of both  
18 166 interpretation and the technical execution[12-14]. Use of the revised PI-RADS  
19 167 provides moderately reproducible MR imaging scores for detection of clinically  
20 168 relevant disease[15]. Using MP-MRI to triage men might allow 27% of patients  
21 169 avoid a primary biopsy and diagnosis fewer clinically insignificant cancers. If  
22 170 subsequent TRUS-biopsies were directed by MP-MRI findings, up to 18%  
23 171 more cases of clinically significant cancer might be detected compared with  
24 172 the standard pathway of TRUS-biopsy for all[16].  
25  
26  
27  
28  
29  
30  
31  
32  
33  
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36

37 173 In summary, PI-RADS recommends to use 3T or 1.5T machines, including  
38 174 T2- and T1-weighted sequences together with diffusion weighted images  
39 175 (DWI). Currently, the added value of dynamic contrast is not firmly established  
40 176 regarding tumour detection. At this time, there is no consensus among  
41 177 experts concerning the potential benefits of the use of endorectal coils for  
42 178 cancer detection. It has been suggested that the prevalence of suspicious  
43 179 lesions on MRI in men with clinical suspicion of prostate cancer is  
44 180 approximately 60% [17].  
45  
46  
47  
48  
49  
50  
51

#### 52 181 **4.5. Targeted prostate biopsies guided by fusion technology**

53 182 Targeted biopsies of the prostate consist of imaging (MRI) detecting  
54 183 significant tumours and a biopsy procedure where biopsies are targeted to the  
55 184 tumour using various devices for guidance[18]. While traditional endorectal  
56 185 ultrasound poorly identifies tumours, direction of biopsy needles can be  
57  
58  
59  
60

1  
2  
3 186 performed in various ways. Cognitive or soft fusion is based on skilled  
4 187 urologists/radiologists interpreting the MRI images and directing needles  
5 188 solely based on the ultrasound images. The disadvantages of cognitive fusion  
6 189 lie in the potential for human error when attempting to mentally fuse the MRI  
7 190 with TRUS while aiming for cancers that are often <1 cm in diameter and the  
8 191 inability to track the location of each biopsy site. Hard fusion enables proper  
9 192 fusion of MRI information on the ultrasound image, possibly increasing  
10 193 precision.

11  
12  
13 194 Despite methodological flaws, a number of studies have investigated the  
14 195 value of fusion biopsies, primarily using non-randomized designs and non-  
15 196 screening populations[19]. In 2018, Kasivisvanathan et al provided high  
16 197 quality evidence for men referred for prostate biopsy and showed that  
17 198 MRI/target biopsies are non-inferior for detection of significant cancer and  
18 199 decreases the number of in-significant cancers and number of biopsies as  
19 200 compared with systematic biopsies[20].

20 201 The proportion of men upgraded when comparing specimen from targeted  
21 202 biopsies and subsequent prostatectomy have been shown to be very low  
22 203 (<5%) when using targeted biopsies[21], increasing the proportion of men  
23 204 where treatment decisions are based on valid risk estimations.

#### 24 205 ***4.6. Improving the diagnostic pathway for prostate cancer detection***

25 206 The current diagnostic pathway for prostate cancer detection is  
26 207 characterized by several challenging hallmarks. First, testing with PSA is  
27 208 frequent also in men not benefitting from testing due to low PSA levels or high  
28 209 age[3]. Second, the currently used test for detection (PSA) lacks in specificity,  
29 210 resulting in frequent over-diagnosis[22,23]. Third, systematic biopsies shows  
30 211 high frequencies of benign tests, over-diagnosis, up-grading at prostatectomy,  
31 212 and risk of infectious complications[7,24]. Further, PSA testing increases with  
32 213 educational length and men with long education are more likely to have a  
33 214 prostate biopsy after an increased PSA value. These differences may  
34 215 contribute to the worse prostate cancer outcomes observed among men with  
35 216 lower socioeconomic status[25].

1  
2  
3 217 The STHLM3 test offers improved disease detection[7]. To further  
4  
5 218 decrease over-detection, improve disease classification and spare men of  
6  
7 219 test-related harm, prostate biopsy practices need to be improved. We  
8  
9 220 hypothesize that an improved pathway for prostate cancer detection including  
10  
11 221 a better blood-based screening test, improved selection to biopsy based on  
12  
13 222 MRI findings and targeted biopsies guided by MRI/ultrasound fusion would  
14  
15 223 dramatically decrease the number of biopsy procedures, overdiagnosis and  
16  
17 224 improve treatment decisions.

## 225 **5. Methods**

### 226 **5.1. Hypotheses**

#### 227 **5.1.1. Primary hypotheses**

228 The below hypothesis is posed for men in screening-by-invitation context:

229 A diagnostic pathway using the Stockholm3 test to select men for further  
230 workup using MRI followed by targeted biopsies and systematic biopsies  
231 (S3M-MR-TBx/SBx) has non-inferior sensitivity for detecting clinically  
232 significant cancer (ISUP grade group  $\geq 2$ ) and shows superior specificity  
233 (reduction in number of performed biopsy procedures and detected ISUP 1  
234 tumours) compared to a diagnostic pathway using systematic biopsies in men  
235 with PSA  $\geq 3$  ng/ml (PSA-SBx).

#### 236 **5.1.2. Additional hypotheses**

237

- 238 1. As compared with performing systematic biopsies for men with  
239 elevated risk of prostate cancer in prostate cancer screening, targeted  
240 prostate biopsies performed with MRI/Fusion technique with or without  
241 addition of systematic biopsies has non-inferior sensitivity for detecting  
242 clinically significant cancer (ISUP grade group  $\geq 2$ ) and reduces the  
243 number of performed biopsy procedures.
- 244 2. A diagnostic pathway using the Stockholm3 test to select men for  
245 further workup using MRI followed by ONLY targeted biopsies (S3M-

- 1  
2  
3 246 MR-TBx) has non-inferior sensitivity for detecting clinically significant  
4  
5 247 cancer (ISUP grade group  $\geq 2$ ) and reduces the number of performed  
6  
7 248 biopsy procedures compared to a diagnostic pathway using systematic  
8  
9 249 biopsies in men with PSA  $\geq 3$  ng/ml (PSA-SBx).  
10 250 3. Adding prostate volume as parameter in the diagnostic pathway with  
11  
12 251 Stockholm3 test and MRI/Fusion biopsies improves model precision.  
13  
14 252 4. A diagnostic pathway with Stockholm3 followed by MRI and targeted  
15  
16 253 biopsies has non-inferior sensitivity for detecting clinically significant  
17  
18 254 cancer (ISUP grade group  $\geq 2$ ) and reduces the number of MRI  
19  
20 255 examinations and performed biopsies compared to a diagnostic  
21  
22 256 pathway using PSA  $\geq 3$  ng/ml followed by MRI and targeted biopsies.  
23  
24 257 5. SBx in the MRI arm has superior sensitive than SBx in the non-MRI  
25  
26 258 arm (due to cognitive fusion).  
27  
28 259 6. Biopsy compliance is higher after biopsy is recommended based on  
29  
30 260 MRI compared to recommended without MRI.  
31  
32 261 7. A diagnostic pathway using the Stockholm3 test to select men for  
33  
34 262 further workup using MRI and targeted biopsies (S3M+TBx) shows  
35  
36 263 better health economy (positive ICER) compared to a diagnostic  
37  
38 264 pathway using systematic biopsies in men with PSA  $\geq 3$  ng/ml  
39  
40 265 (PSA+SBx).  
41  
42 266

## 40 267 **5.2. Aims**

42 268 To compare a diagnostic pathway using the Stockholm3 test (S3M  $\geq 11\%$ )  
43  
44 269 to select men for further workup using MRI (PI-RADS  $\geq 3$ ) and targeted  
45  
46 270 biopsies (S3M+TBx) to a diagnostic pathway using systematic biopsies in  
47  
48 271 men with PSA  $\geq 3$  ng/ml (PSA+SBx) with respect to number of diagnosed  
49  
50 272 clinically significant cancer (ISUP grade group  $\geq 2$ ) and number of performed  
51  
52 273 biopsies. Additional aims corresponding to hypotheses 2-8 above will be  
53  
54 274 assessed.

## 55 275 **5.3. Study design**

56 276  
57  
58  
59  
60

1  
2  
3 277       STHLM3-MR Phase 2 is a study combining a paired and a randomized  
4  
5 278       design (Figure 1). The study will follow the following outline: Participants will  
6  
7 279       be invited by mail. All participants will undergo a blood-test, including PSA  
8  
9 280       and the STHLM3 test. Men with an elevated PSA  $\geq 3$  ng/ml or PSA  $\geq 1.5$  ng/ml  
10  
11 281       and S3M  $> 11\%$  will be randomized to either traditional prostate biopsies or MR  
12  
13 282       with targeted biopsies on MR lesions.

#### 14 15 283       **5.4. Participants, interventions and outcomes**

##### 16 17 18 284       **5.4.1. Study setting**

19 285       This is a screening-by-invitation study including one study administrative  
20  
21 286       centre, two radiological sites and three urological sites where data will be  
22  
23 287       collected.

##### 24 25 26 288       **Participating urological centres**

27  
28 289       Department of Urology, Capio St Görans Hospital: dr Henrik Grönberg  
29  
30 290       Uroclinic, Sophiahemmet, Stockholm; dr Olof Jansson  
31  
32 291       Odenplans läkarhus; dr Magnus Annerstedt

##### 33 34 292       **5.4.2. Eligibility criteria**

##### 35 36 37 293       **Inclusion criteria**

38  
39 294       Men age 50-74 years without prior diagnosis of prostate cancer (ICD-9  
40  
41 295       C61).

42  
43 296       Permanent postal address in Stockholm

44  
45 297       Not a previous participant in the Stockholm3 study (2012-2014)

##### 46 47 48 298       **Exclusion criterias**

49  
50 299       Severe illnesses such as metastatic cancers, severe cardio-vascular  
51  
52 300       disease or dementia

53  
54 301       Contraindications for magnetic resonance imaging (MRI) eg pacemaker,  
55  
56 302       magnetic cerebral clips, cochlear implants or severe claustrophobia.

57  
58 303       Men with a previous prostate biopsy the preceding 60 days before  
59  
60 304       invitation.

### 305 **5.4.3. Randomization**

306 Randomization is performed 2:3 between control arm and experimental  
307 arm. Randomization will be performed will be performed using stratification on  
308 disease risk [6 strata]. Disease risk is assessed using the Stockholm3 test.  
309 Test are discordant if PSA is negative and Stockholm3 positive or vice versa.

310 Four allocation lists [high/low risk vs discordant/concordant tests] have  
311 been created with the sequence [control arm, control arm, experimental arm,  
312 experimental arm, experimental arm]. Participants are first allocated to  
313 corresponding list, and then allocated to study arm according to the order in  
314 which they participate. The allocation sequence is blinded for the study  
315 investigators and handled by the study database administrator (A Björklund).

316 In order to enhance resource usage, men are allocated to the study sites  
317 according to local availability of biopsy procedure slots.

### 318 **5.4.4 Interventions**

#### 319 ***Blood sampling***

320 Participating men undergo blood-sampling with analysis of PSA and the  
321 Stockholm3 test at Karolinska University Laboratory.

322 For the main analysis, the Stockholm3 test include clinical data as  
323 answered when consenting participation (previous biopsy, age, finasteride  
324 medication, relatives with prostate cancer); single nucleotide polymorphisms  
325 and measurements of protein levels (MSMB, MIC1, PSA, fPSA, hK2)[7]. For  
326 secondary analyses, clinical information on DRE and prostate volume is  
327 included.

#### 328 ***Definition of EXPERIMENTAL ARM***

329 Men randomized to the experimental arm undergoes MRI. If suspicious  
330 lesions are found, the participant undergoes targeted biopsies using Fusion  
331 technology *followed by systematic biopsies*.



1  
2  
3 332 Men without lesions are excepted from further intervention and receives  
4 333 notification on recommendation for follow-up. Technology and process are  
5 334 described below.

6  
7  
8  
9 335 Men with a Stockholm3 risk  $\geq 25\%$  and no suspicious lesion on MRI will  
10 336 undergo systematic biopsies.

### 11 12 13 337 **Definition of CONTROL ARM**

14  
15  
16 338 Men randomized to the control arm undergoes systematic biopsies as  
17 339 defined below.

### 18 19 20 340 **5.4.5 Technology**

#### 21 22 23 341 **Cut-offs for performing the STHLM3 test**

24  
25 342 The STHLM3 test will be performed for men with a PSA  $\geq 1.5$  ng/ml

#### 26 27 28 343 **Cut-offs for entering randomization**

29  
30 344 Participants with PSA  $\geq 3.0$  ng/ml or STHLM3-test  $\geq 11\%$  risk of Gleason  
31 345 Score  $\geq 7$  cancer will be randomized and offered to undergo either MR or  
32 346 systematic biopsies (See Process description).

#### 33 34 35 347 **MRI technology**

##### 36 37 38 348 *Location and MRI equipment*

39  
40  
41 349 Capio St Görans Hospital: General Electric, Architect, 3T  
42 350 Globen Unilabs Healthcare: Siemens Magnetom Aera 1.5T

##### 43 44 45 351 *Patient preparations*

46  
47  
48 352 Refraining from sexual activity with ejaculation 3 days prior to examination  
49 353 Fasting patient 6 h  
50 354 Minimal preparation enema prior to examination  
51 355 Antispasmodic agent (Glucagon) just before the examination

##### 52 53 54 356 *MRI Protocol*

55  
56  
57 357 A short (14 minutes) MRI protocol will be used. A detailed description is  
58 358 available. Briefly, the protocol includes: T2w images axial, sagittal, coronal;



1  
2  
3 359 Diffusion weighted imaging b0 and b1000 with ADC and a synthetic b1500  
4 360 limited to the prostate location; No endorectal coil will be used.

5  
6  
7  
8 361 *MRI Interpretation*

9  
10 362 MRI interpretation is centralized to Capio St Görans hospital and is  
11 363 performed according to PIRAD v2.0 for examinations without adequate  
12 364 perfusion studies. Dr Fredrik Jäderling is responsible for MRI interpretation. Dr  
13 365 Jäderling or 1-2 other, experienced radiologists at his department performs all  
14 366 MRI interpretations.

15 367 PI-RADS v2 (“Assessment without adequate dynamic contrast enhanced  
16 368 imaging”) will be used, with a 1-5 grade scale of suspicious lesions (1=  
17 369 clinically significant cancer is highly unlikely to be present, 5= clinically  
18 370 significant cancer is highly likely to be present).

19 371 During the study period participating radiologist will have access to  
20 372 updated histology results of fusion biopsies to be able to adjust their MRI  
21 373 reading according to tumour detection rates for different PIRAD diagnoses as  
22 374 defined above.

23 375 *Fusion biopsy technology*

24 376 *Brand/models*

25 377 BK Medical (BK Ultrasound ; [www.bkultrasound.com/bk-medical/fusion](http://www.bkultrasound.com/bk-medical/fusion))

26 378 The BK Medical fusion system is the only fusion device compatible with BK  
27 379 Medicals ultrasound devices, used by the urology departments participating in  
28 380 the study. The system represents a second generation ultrasound system  
29 381 with integrated MRI Fusion. MRI data is imported through HIPAA-compliant  
30 382 PACS connection with the local radiology department.

31 383 *Definition of targeted biopsies*

32 384 Using MRI data with pre-marked borders of the prostate and tumor, fusion of  
33 385 MRI images and ultrasound images are performed bedside. Using local  
34 386 anesthetic and antibiotic prophylaxis, lesions are according to below.  
35 387 Targeted biopsies are always combined with systematic biopsies.

1  
2  
3 388 *Biopsy procedure for targeted biopsies*

4  
5 389 **PI-RADS $\geq$ 3:** 3-4 targeted biopsies on marked lesions + systematic  
6  
7 390 biopsies.

8  
9 391 **Large diffuse lesions or poor image quality:** Systematic biopsies  
10  
11 392 including lesion.

12  
13 393 **No PI-RADS $\geq$ 3, diffuse lesions and at least acceptable image quality:**  
14  
15 394 No biopsies are performed.

16  
17 395 In larger lesions in PI-RADS category 3 and 5, areas within the lesion with the  
18  
19 396 lowest ADC value ("Target-within-target") will be targeted with the first biopsy  
20  
21 397 taken from the lesion, to evaluate the additional value regarding tumor  
22  
23 398 staging.

24  
25 399 *Definition of systematic biopsies*

26  
27 400 10-12 systematic biopsies are taken from the peripheral zone as previously  
28  
29 401 described in STLHLM3 and the National Guidelines. Extra biopsies are  
30  
31 402 allowed from additional sites visible on ultrasound or according to palpatory  
32  
33 403 findings. In summary, systematic biopsies are performed in the peripheral  
34  
35 404 zone as 4 lateral and para-median biopsies on the left and right side, in the  
36  
37 405 base and mid part of the gland. In the apical third of the gland one lateral left  
38  
39 406 and right biopsy is performed.

40  
41 407 ***Pathology***

42  
43 408 Pathology is centralized to Unilabs/Capio St Görans hospital. Dr Axel  
44  
45 409 Glaessgen is responsible for the integrity of analyzes of pathological  
46  
47 410 specimen. 2-3 uro-pathologists at dr Glaessgens department assesses all  
48  
49 411 pathological specimen with intermittent cross-validation between them.  
50  
51 412 Pathology preparation and reporting follow ISUP 2014 guidelines.

52  
53 413 The pathology preparation is done by Unilabs as part of the normal clinical  
54  
55 414 routine. Biopsy specimens are analyzed according to local practice.

56  
57 415 Localisation of biopsies in the prostate are described using Swedish  
58  
59 416 National Guideline nomenclature (A1-4; B1-4; C1-4; anterior/posterior).  
60

1  
2  
3 417 Gleason Score, mm cancer and % Gleason 4 is reported on each needle  
4  
5 418 specimen.  
6

7 419 Pathologist notes results in the usual way in the laboratory system. The  
8  
9 420 result of the pathological analysis is submitted in accordance to existing  
10  
11 421 clinical routines to the referring urologist. A copy of the result is delivered to  
12  
13 422 the study administration.  
14

#### 15 423 **5.4.4. Outcomes**

16  
17 424 There are three co-primary endpoints in this trial: (i) Number of diagnosed  
18  
19 425 ISUP grade group  $\geq 2$  cancers; (ii) Number of diagnosed ISUP grade group 1  
20  
21 426 cancers; (iii) Number of performed biopsies.  
22

#### 23 24 427 **5.4.5. Follow-up**

25  
26 428 Main study outcomes are assessed after prostate biopsy procedures.  
27  
28 429 Additional participant data will be secured in the following circumstances:  
29

##### 30 31 430 *No suspicious lesion on MRI*

32  
33 431 Men in the experimental arm without suspicious lesions on MRI will be  
34  
35 432 informed and recommended follow-up by the responsible, local urologist. After  
36  
37 433 additional ethical application, the co-investigators might initiate retrospective  
38  
39 434 follow-up of these participants.  
40

##### 41 435 *Men with diagnosed prostate cancer*

42  
43 436 Participants with prostate cancer diagnosed on biopsy within the study will  
44  
45 437 be followed up after the biopsy to secure data on the following: Treatment  
46  
47 438 modality (Active Surveillance, Surgery, Radiation); Treatment lead-time and  
48  
49 439 site; Pathological report after surgery (positive margins, T-stage, etc). Data  
50  
51 440 will be assessed through medical records intermittently.  
52

#### 53 441 **5.5. Serious adverse events**

54  
55 442 Study nurse will monitor serious adverse events after the prostate biopsy  
56  
57 443 procedures. To ensure this, the study nurse will follow this check medical  
58  
59 444 journals for hospitalization within 1 week after the biopsy procedure in the  
60

1  
2  
3 445 journal systems Take Care and Cosmic (covering the main part of hospitals in  
4 446 Stockholm region). This will be initiated as individual biopsy results are  
5 447 registered at the study administration. Results will be provided to the Data  
6 448 Safety and Monitoring Board.

### 449 **5.6. Participant timeline**

450 Figure 2 illustrates the approximate timeline for participating men in  
451 STHLM3MRI Main Study.

### 452 **5.7. Sample size**

453 STHLM3-MR/Fusion Phase 2 will invite 25,000 men and aim to include  
454 10,000 participants. We anticipate to perform 1,039 biopsy procedures  
455 altogether. Inclusion will continue until complete data on 415 men in the  
456 control arm (SBx) and 623 men in the experimental arm (MR-TBx-SBx).

#### 457 *Basic data and assumptions used in the sample size calculations*

458 We used data from the STHLM3 trial for sample size calculations [7]. In  
459 this data, 18% of men with PSA  $\geq 3$  had a clinically significant prostate cancer  
460 when biopsied with SBx. We further noted that rTPR=1.45 for clinically  
461 significant prostate cancer comparing MRI+TBx with SBx based on the results  
462 from the PRECISION randomized trial [20]. However, we will for sample size  
463 calculations use rTPR=1.25 for MRI+TBx vs. SBx as a more conservative  
464 estimate. We set the non-inferiority delta to 4 percentage points for  
465 demonstrating noninferiority with respect to sensitivity of clinically significant  
466 prostate cancer. We set the alpha to 5%.

#### 467 **Primary contrast**

468 Simulating 1000 trials (by bootstrapping from the STHLM3 data) under the  
469 assumptions outlined in the preceding section 303 men need to be biopsied in  
470 the SBx arm based on PSA  $\geq 3$  to have 80% power to demonstrate non-  
471 inferior sensitivity of S3M+MRI+TBx compared with PSA+SBx. This means  
472 that at least **415** men need to be biopsied in the SBx arm (since some men  
473 are not randomized based on PSA  $\geq 3$  but on S3M  $\geq 11\%$ ) and, consequently,

1  
2  
3 474 **623** to the MRI arm (because of the 2:3 randomization). Total number of men  
4  
5 475 undergoing workup according to protocol (SBx in the no MRI arm and MRI  
6  
7 476 and TBx if Pi-RADS  $\geq 3$  in the MRI arm) is thus 1038. Assuming 20% dropout,  
8  
9 477 1300 men need to be randomized. These numbers give 80% power to detect  
10  
11 478 a modest 17% reduction in biopsies between the two strategies.

## 12 13 479 **5.8. Recruitment and Process Description**

14  
15 480 The STHLM3-MR Phase 2 will use existing solutions developed and  
16  
17 481 optimized in the previous studies STHLM3 and STHLM3-MR Phase 1 where  
18  
19 482 all major components of the process have been tested. First, participants will  
20  
21 483 follow the *paired design study process* where inclusion, blood-test and  
22  
23 484 delivery of recommendation letter is performed. Men with increased risk of  
24  
25 485 high-grade prostate cancer then enter the *randomized study process*, where  
26  
27 486 extended work-up including biopsies are performed.

## 28 29 487 **5.9. Data Collection, management, analysis**

### 30 31 32 488 **5.9.1. Data collection**

33  
34 489 Primary data sources are

- 35 490 i. clinical variables collected from laboratory referral
- 36 491 ii. biopsy referrals and reports
- 37 492 iii. pathology reports
- 38 493 iv. MRI reports
- 39 494 v. blood concentrations of kallikreins, MSMB, MIC1, SNPs

40  
41 495 Collection of i. – iv. is performed by study nurses (C Cavalli-Björkman) on  
42  
43 496 a weekly basis from participating urology sites, participating radiologists. For  
44  
45 497 v., this is digitally transferred from Karolinska University Laboratory.

### 46 47 48 498 **5.9.2. Data management**

49  
50 499 Data is collected, entered, coded and stored at Department of Medical  
51  
52 500 Epidemiology and Biostatistics, Karolinska Institutet. Data is entered by Study  
53  
54 501 Nurse using predefined database sheets developed in STHLM3MRI Phase 1.  
55  
56 502 This is blinded from study co-investigators and data is stored at the  
57  
58 503 department under supervision by the study database administrator (SDA,

1  
2  
3 504 Astrid Björklund). Any extraction of study data is performed by the SDA after  
4  
5 505 approval of PI Tobias Nordström.  
6  
7

### 8 506 **5.9.3. Data analysis**

9  
10 507 Analysis of data is described in the Statistical Analysis Plan (SAP).  
11  
12

### 13 508 **5.9.4. Auditing and Monitoring**

14  
15 509 A Data Safety and Monitoring Board (DSMB) is assembled and consist of  
16  
17 510 dr Hans Garmo (Statistician), prof Ola Bratt (Urology) and prof Holmberg  
18  
19 511 (Urology/Study Design). The DSMB audits protocol and process descriptions  
20  
21 512 and one interim data extraction performed by the study database  
22  
23 513 administrator after 10% (100 men) have completed the control or  
24  
25 514 experimental arms. The co-investigators are blinded to the interim data and  
26  
27 515 analysis results. The work of the DSMB is regulated in the DSMB Charter.  
28

### 29 516 **5.10. Patient and Public Involvement**

30  
31 517 The research question and outcome measures were designed to improve  
32  
33 518 prostate cancer diagnostics. This includes optimizing prostate biopsies and  
34  
35 519 decreasing over-detection, both associated with morbidity. Patient  
36  
37 520 organisations were informed on the results from the STHLM3MRI Phase 1  
38  
39 521 study. Patients were not involved in recruitment of the study. Results will be  
40  
41 522 disseminated to participants through common and scientific channels.  
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## 44 523 **6. Ethics and dissemination**

### 45 46 47 524 **6.1. Research ethics approval**

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49  
50 525 The study has approval from the Regional Ethical Review Board in  
51  
52 526 Stockholm (2017-1280/31).  
53

### 53 527 **6.2. Consent**

54  
55  
56 528 Participant consent is secured when the participant is included to the study  
57  
58 529 at [www.kliniskastudier.se](http://www.kliniskastudier.se). This includes secure identification using Mobilt  
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3 530 BankID. Additional approval on use of biological specimen data is collected on  
4  
5 531 the biopsy referral.  
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### 8 532 **6.3. Confidentiality**

9  
10 533 Study data is collected and stored at Department of Medical Epidemiology  
11 534 and Biostatistics, Karolinska Institutet using secure Oracle servers. All data  
12 535 extractions are made by database administrator and are anonymized  
13  
14 536 (personal id number is removed) before dissemination to researchers.  
15  
16  
17

### 18 537 **6.4. Dissemination**

19  
20 538 Analyses results on the posed aims will be submitted for peer-reviewed  
21 539 publication and submitted for presentation at scientific congress.  
22  
23 540 Communication of the results will be made to patient organizations  
24 541 (Prostatacancerförbundet) and non-scientific channels. No use of professional  
25 542 writers is planned.  
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29  
30 543 The study protocol is made publicly available through clinicaltrials.gov.  
31  
32

### 33 544 **6.5. Data Sharing Statement**

34  
35 545 Anonymized, individual participant data that underlie the results reported in  
36 546 this article, after deidentification (text, tables, figures and appendices) will be  
37 547 available for data sharing. Proposals may be submitted up to 36 months  
38 548 following article publication. Data will be shared with investigators whose  
39 549 proposed use of the data has been approved by an independent review  
40 550 committee identified for this purpose.  
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## 48 551 **7. Declarations of interest**

49  
50 552 Henrik Grönberg has five prostate cancer diagnostic related patents  
51 553 pending, has patent applications licensed to Thermo Fisher Scientific, and  
52 554 might receive royalties from sales related to these patents. Martin Eklund is  
53 555 named on four of these five patent applications. Karolinska Institutet  
54 556 collaborates with Thermo Fisher Scientific in developing the technology for the  
55 557 Stockholm3 test.  
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## 558 **8. Contributions**

559 TN was the Principal investigator. TN, HG, ME, SC and MA designed the  
560 study. ME and TN interpreted preliminary data. FJ designed MRI protocols  
561 and collected data.

562 We thank participants, study organizers, participating researchers and  
563 clinicians, and patient advisers for their contributions to the STHLM3MRI  
564 project.

## 565 **9. Funding statement**

566 Funding was provided by the Swedish Cancer Society, (Cancerfonden),  
567 the Swedish Research Council (Vetenskapsrådet), Swedish Research Council  
568 for Health Working Life and Welfare (FORTE), The Strategic Research  
569 Programme on Cancer (StratCan), Karolinska Institutet, Swedish e-Science  
570 Research Center (SeRC) and Stockholm City Council (SLL). The STHLM3  
571 study is a part of the Linnaeus Center CRISP “Predication and prevention of  
572 breast and prostate cancer” funded by the Swedish Research Council.

## 573 **10. Figure legends**

574 Figure 1: Study design overview STHLM3MRI Main Study

575 Figure 2: Timeline overview for study participants in STHLM3MRI Main  
576 Study

## 577 **11. References**

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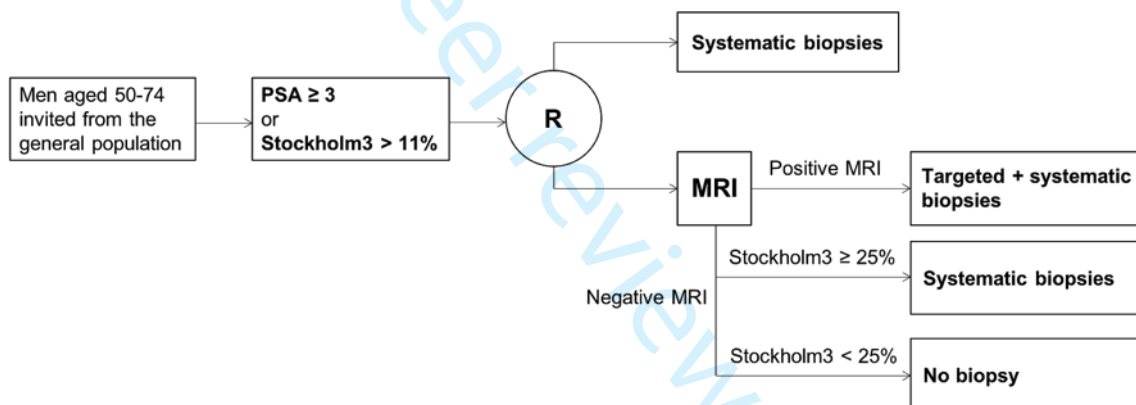
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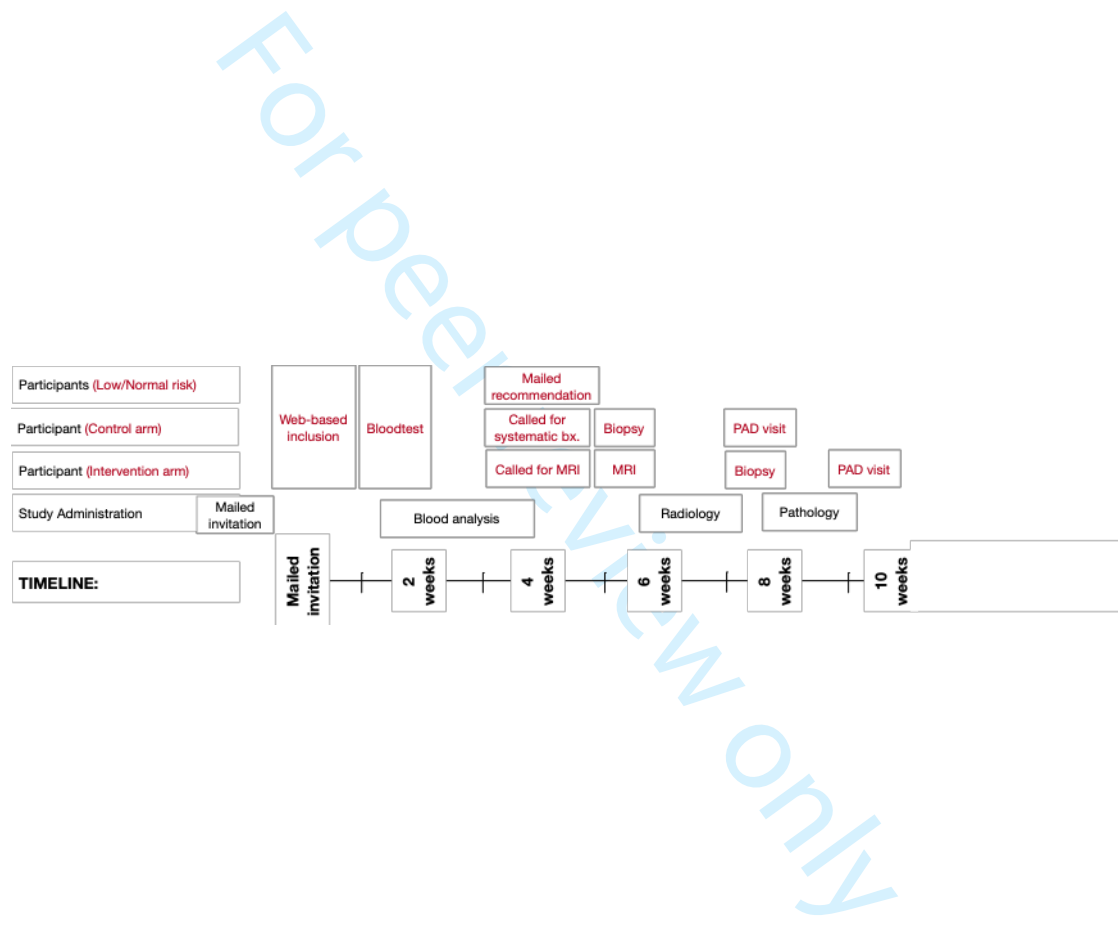
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## CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	4-7
	2b	Specific objectives or hypotheses	8-9
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	10
Participants	4a	Eligibility criteria for participants	10
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10-13
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	14
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	15
	7b	When applicable, explanation of any interim analyses and stopping guidelines	16
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	-
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	-

1		assessing outcomes) and how	
2		11b If relevant, description of the similarity of interventions	
3	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	Separate doc
4		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	Separate doc
5			
6	<b>Results</b>		
7	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	
8	diagram is strongly	were analysed for the primary outcome	
9	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	
10	Recruitment	14a Dates defining the periods of recruitment and follow-up	
11		14b Why the trial ended or was stopped	
12	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	
13	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	
14		by original assigned groups	
15	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	
16	estimation	precision (such as 95% confidence interval)	
17		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
18	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	
19		pre-specified from exploratory	
20	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
21			
22	<b>Discussion</b>		
23	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
24	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	
25	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
26			
27	<b>Other information</b>		
28	Registration	23 Registration number and name of trial registry	2
29	Protocol	24 Where the full trial protocol can be accessed, if available	1
30	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	18

36  
37 \*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also  
38 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.  
39 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).  
40  
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## SPIRIT CHECKLIST STHLM3MRI Study, BMJ Open

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

Section/item	ROW NUMBER	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	62	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	Full protocol	Date and version identifier
Funding	566	Sources and types of financial, material, and other support
Roles and responsibilities	7+559	Names, affiliations, and roles of protocol contributors
	20	Name and contact information for the trial sponsor
	Full protocol	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	Full protocol	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
<b>Introduction</b>		
Background and rationale	80, 267	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	152	Explanation for choice of comparators



1			
2	Objectives	225	Specific objectives or hypotheses
3			
4	Trial design	275	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
5			
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7			
8			
9			
10	<b>Methods: Participants, interventions, and outcomes</b>		
11			
12	Study setting	284	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
13			
14			
15			
16	Eligibility criteria	293	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
17			
18			
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20			
21	Interventions	319	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
22			
23			
24		N/A	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
25			
26			
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28		N/A	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
29			
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33		N/A	Relevant concomitant care and interventions that are permitted or prohibited during the trial
34			
35			
36	Outcomes	424	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
37			
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44	Participant timeline	450	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
45			
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49	Sample size	453	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
50			
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52			
53	Recruitment	480	Strategies for achieving adequate participant enrolment to reach target sample size
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### Methods: Assignment of interventions (for controlled trials)

Allocation:

1			
2	Sequence	305	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions
8			
9			
10	Allocation	305	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned
14			
15	Implementation	315	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions
17			
18	Blinding	N/A	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20			how
21			
22			
23		N/A	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
26			
27			

### Methods: Data collection, management, and analysis

28			
29			
30	Data collection	488	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol
36			
37			
38		N/A	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols
41			
42	Data	498	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol
46			
47			
48	Statistical	506	Statistical methods for analysing primary and secondary outcomes.
49	methods	Full	Reference to where other details of the statistical analysis plan can be
50		proto	found, if not in the protocol
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54		Full	Methods for any additional analyses (eg, subgroup and adjusted
55		proto	analyses)
56		col	
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2 Full Definition of analysis population relating to protocol non-adherence  
3 Proto (eg, as randomised analysis), and any statistical methods to handle  
4 col missing data (eg, multiple imputation)  
5

## 6 **Methods: Monitoring**

7  
8 Data monitoring 508 Composition of data monitoring committee (DMC); summary of its role  
9 and reporting structure; statement of whether it is independent from  
10 the sponsor and competing interests; and reference to where further  
11 details about its charter can be found, if not in the protocol.  
12 Alternatively, an explanation of why a DMC is not needed  
13  
14  
15 508 Description of any interim analyses and stopping guidelines, including  
16 who will have access to these interim results and make the final  
17 decision to terminate the trial  
18  
19 Harms 441 Plans for collecting, assessing, reporting, and managing solicited and  
20 spontaneously reported adverse events and other unintended effects  
21 of trial interventions or trial conduct  
22  
23  
24 Auditing 508 Frequency and procedures for auditing trial conduct, if any, and  
25 whether the process will be independent from investigators and the  
26 sponsor  
27  
28

## 29 **Ethics and dissemination**

30 Research ethics 524 Plans for seeking research ethics committee/institutional review board  
31 approval (REC/IRB) approval  
32  
33  
34 Protocol Full Plans for communicating important protocol modifications (eg,  
35 amendments proto changes to eligibility criteria, outcomes, analyses) to relevant parties  
36 col (eg, investigators, REC/IRBs, trial participants, trial registries, journals,  
37 regulators)  
38  
39  
40 Consent or assent Full Who will obtain informed consent or assent from potential trial  
41 proto participants or authorised surrogates, and how (see Item 32)  
42 col  
43  
44 Full Additional consent provisions for collection and use of participant data  
45 proto and biological specimens in ancillary studies, if applicable  
46 col  
47  
48 Confidentiality 532 How personal information about potential and enrolled participants will  
49 be collected, shared, and maintained in order to protect confidentiality  
50 before, during, and after the trial  
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52  
53 Declaration of 551 Financial and other competing interests for principal investigators for  
54 interests the overall trial and each study site  
55  
56 Access to data 544 Statement of who will have access to the final trial dataset, and  
57 disclosure of contractual agreements that limit such access for  
58 investigators  
59  
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1			
2	Ancillary and	N/A	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			
5	Dissemination	537	Plans for investigators and sponsor to communicate trial results to
6	policy		participants, healthcare professionals, the public, and other relevant
7			groups (eg, via publication, reporting in results databases, or other
8			data sharing arrangements), including any publication restrictions
9			
10		537	Authorship eligibility guidelines and any intended use of professional
11			writers
12			
13		537	Plans, if any, for granting public access to the full protocol, participant-
14			level dataset, and statistical code
15			
16			
17	<b>Appendices</b>		
18			
19	Informed consent	Appe	Model consent form and other related documentation given to
20	materials	nxd	participants and authorised surrogates
21			
22	Biological	N/A	Plans for collection, laboratory evaluation, and storage of biological
23	specimens		specimens for genetic or molecular analysis in the current trial and for
24			future use in ancillary studies, if applicable
25			

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26  
27 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013  
28 Explanation & Elaboration for important clarification on the items. Amendments to the  
29 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT  
30 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"  
31 license.  
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# BMJ Open

**Does a novel diagnostic pathway including blood-based risk-prediction and MRI-targeted biopsies outperform prostate cancer screening using prostate-specific antigen and systematic prostate biopsies? – Protocol of the randomized study STHLM3MRI.**

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<b>Primary Subject Heading</b>:	Urology
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Keywords:	Prostate disease < UROLOGY, Magnetic resonance imaging < RADIOTHERAPY, Urological tumours < UROLOGY

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1 **Title:**

2 Does a novel diagnostic pathway including blood-based risk-prediction and  
3 MRI-targeted biopsies outperform prostate cancer screening using prostate-  
4 specific antigen and systematic prostate biopsies? – Protocol of the  
5 randomized study STHLM3MRI.

6 **Authors:**

7 Tobias Nordström<sup>a,b</sup>, MD PhD

8 Fredrik Jäderling<sup>e,f</sup>, MD PhD

9 Stefan Carlsson<sup>d,f</sup>, MD PhD

10 Markus Aly<sup>a,d,f</sup>, MD PhD

11 Henrik Grönberg<sup>a</sup>, MD PhD, Professor

12 Martin Eklund<sup>a</sup>, PhD

13 <sup>a</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden

14 <sup>b</sup>Department of Clinical Sciences at Danderyd Hospital, Karolinska Institutet, Sweden

15 <sup>d</sup>Patient area Pelvic Cancer, Theme Cance Karolinska University Hospital Solna,  
16 Stockholm, Sweden

17 <sup>e</sup>Department of Diagnostic Radiology, Karolinska University Hospital, Stockholm,Sweden

18 <sup>f</sup>Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm,  
19 Sweden

20  
21 **Correspondence to:**

22 Tobias Nordström

23 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

24 S-171 77 Stockholm, Sweden

25 Email: tobias.nordstrom@ki.se

26 Phone: + 46 70 539 17 91

27  
28 **Keywords:** Prostate cancer, Prostate neoplasm, biomarker, STHLM3, prostate biopsy,  
29 magnetic resonance imaging

## 1. Abstract

### Introduction

Prostate cancer is a leading cause of cancer death among men in the Western world. Early detection of prostate cancer has been shown to decrease mortality, but has limitations with low specificity leading to unnecessary biopsies and over-diagnosis of low-risk cancers. The STHLM3 trial has paved way for improved specificity in early detection of prostate cancer using the blood-based STHLM3 test for identifying men at increased risk of harbouring significant prostate cancer. Targeted prostate biopsies based on MRI images have been shown non-inferior sensitivity to detect significant prostate cancer and decrease the number of biopsies and non-significant cancers among men referred for prostate biopsy in clinical practice.

The strategy of the STHLM3-MRI projects is to study an improved diagnostic pathway including an improved blood-based test for identification of men with increased risk of prostate cancer and use of MRI to select men for diagnostic workup with targeted prostate biopsies.

### Methods

This study compares prostate cancer detection using PSA and systematic biopsies to the improved pathway for prostate cancer detection using the STHLM3 test and targeted biopsies in a screening context. The study will recruit 10,000 participants during June 1<sup>st</sup> 2018 to June 1<sup>st</sup> 2020 combining a paired and randomized design. Participants are grouped by PSA and Stockholm3 test level. Men with Stockholm3  $\geq 11\%$  or PSA  $\geq 3\text{ng/ml}$  are randomized to systematic or MRI-targeted biopsies. This protocol follows SPIRIT guidelines. Endpoints include the number of detected prostate cancers, number of performed biopsy procedures and number of performed MRIs. Additional aims include to assess the health economic consequences and development of automated image-analysis.

### Ethics and dissemination

The study is approved by the regional ethical review board in Stockholm (2017-1280/31). Study findings will be published in peer-review journals. Findings will also be disseminated by conference/departmental presentations

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3 62 and by media.

4  
5 63 **Registration details**

6  
7 64 ClinicalTrials.gov: NCT03377881

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12 65 **2. Strengths and limitations of this study**

- 13  
14 66
  - This is the first randomized study to examine the role of improved
  - 15 67 blood-based risk stratification used in sequence with MRI and
  - 16 68 targeted prostate biopsies in a screening-by-invitation context.
  - 17 69
  - 18 69 • The study examines the performance of the Stockholm3 test used
  - 19 70 together with MRI/Fusion technique compared to traditional PSA
  - 20 71 screening and will provide important data also on the performance
  - 21 72 of the Stockholm3 test or MRI/Fusion when used as standalone
  - 22 73 strategies.
  - 23 74
  - 24 74 • The study is performed at three study sites and uses centralized
  - 25 75 radiology and pathology.
  - 26 76
  - 27 76 • The study is limited to a Swedish screening population, the use of
  - 28 77 the Stockholm3 test as blood-based risk prediction test and the
  - 29 78 technology used for MRI-targeted biopsies.
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39 79 **3. Trial identifier**

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41 80 ClinicalTrials.gov Identifier: NCT03377881

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45 81 **4. Introduction**

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48 82 **4.1. Public health significance of prostate cancer**

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50 83 Prostate cancer is the most common cancer and the leading cause of

51  
52 84 cancer death among men in Sweden. In year 2011 over 10,000 men were

53  
54 85 diagnosed with prostate cancer and more than 2,500 died due to the disease,

55  
56 86 approximately 20% of these in the Stockholm region. Prostate cancer

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58 87 incidence rates in Sweden are now comparable to rates in countries that had

59  
60 88 an early introduction of PSA testing, while prostate cancer mortality rates are



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3 89 higher than in most other countries[1]. With over 90,000 prevalent cases, the  
4 90 health burden and the costs on the health care system are substantial. While  
5 91 a number of risk factors have been proposed for prevention of prostate  
6 92 cancer, including diet and occupational exposures, the only factors  
7 93 conclusively shown to increase risk of the disease are age, ethnicity and  
8 94 family history. Given the high prevalence of the cancer and limited  
9 95 opportunities for primary prevention, improved detection would reduce both  
10 96 procedure-related harm to men and economical cost in the healthcare system.

#### 97 **4.2. Early detection and treatment of prostate cancer: benefits and** 98 **harms**

99 The PSA test was first used to monitor disease progression in prostate  
100 cancer patients. The PSA test was taken up as a *de facto* screening test for  
101 prostate cancer in many countries, leading to a rapid rise in prostate cancer  
102 incidence. The test characteristics for the PSA test in detecting prostate  
103 cancer are comparable to those for mammography for breast cancer  
104 screening, with a sensitivity of 72% and a specificity of 30-35% at a test  
105 threshold of 4 ng/ml[2]. However, a lower threshold of 3 ng/ml adopted in  
106 Sweden recently has led to increased sensitivity at the expense of reduced  
107 specificity. Recent analyses of PSA testing in the Stockholm area confirms  
108 these results showing that 46%, 68% and 77% of men 50-59, 60-69 and 70-  
109 79 years respectively have had at least one PSA test during a 9 years  
110 period[3].

111 Recent results from the large European Randomized Study of Screening  
112 for Prostate Cancer (ERSPC) including over 180,000 men provide increasing  
113 evidence that PSA screening has led to reduced mortality[4]. This report  
114 showed that PSA screening without digital rectal examination was associated  
115 with a 21% relative reduction in the death rate from prostate cancer at a  
116 median follow-up of 11 years, with an absolute reduction of about 7 prostate  
117 cancer deaths per 10,000 men screened. Estimations from the ERSPC trial  
118 (men aged 55-69) show that 1,048 men would need to be offered screening  
119 and an additional 37 would need to be managed to prevent one prostate-  
120 cancer death during a 10-year period, leading to a significant overtreatment of  
121 indolent disease. The effectiveness of PSA testing was more marked at the

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2  
3 122 Göteborg site of the ERSPC trial, with a risk reduction of 44% over 14 years in  
4 123 men aged 50-64[5]. This effect size is larger than that observed for  
5 124 mammographic screening for breast cancer and faecal occult blood testing for  
6 125 colorectal cancer.

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10 126 However, using traditional systematic biopsies for diagnosis,  
11 127 approximately half of diagnosed cancers are low-risk tumours using the same  
12 128 main cut-off for biopsy as the ERSPC trial (PSA=3ng/ml) [6,7]. It has been  
13 129 shown that men with low-risk tumours treated without curative intent have the  
14 130 same survival as men in the background population[8], illustrating the large  
15 131 proportion of over-diagnosed cancers[9].

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21 132 The STHLM3 study has shown one way to improve identification of men at  
22 133 increased risk of significant prostate cancer. Using the STHLM3 test, 32% of  
23 134 the prostate biopsies may be saved while not decreasing the sensitivity to  
24 135 high-grade disease (defined as Gleason Score  $\geq 7$ ) and simultaneously  
25 136 decreasing the number of low-grade tumours (Gleason Score  $\leq 6$ ) by 17%,  
26 137 thus decreasing overdiagnosis[7].

### 27 28 29 30 31 32 33 138 **4.3. Traditional evaluation of men with increased risk of prostate** 34 139 **cancer**

35  
36 140 Men at increased risk of prostate cancer - commonly estimated using PSA  
37 141 and palpatory findings - are traditionally assessed using systematic prostate  
38 142 biopsies. The procedure is performed under local anaesthesia using antibiotic  
39 143 prophylaxis and includes 10-12 cores taken from predefined areas of the  
40 144 peripheral zone of the gland as visualized by endorectal ultrasound. While the  
41 145 biopsies systematically covers the prostatic gland rather than targeting a  
42 146 specific lesion, and non-lethal tumours are common, the risk of over-diagnosis  
43 147 (i.e. detection of non-significant tumours) is high [9]. The risk of non-  
44 148 representative biopsy findings result in underestimation of tumour grade  
45 149 compared with subsequent prostatectomy in up to 40% of men undergoing  
46 150 surgery[10]. The risk of severe post-biopsy infection has increased to 1-2%  
47 151 with increasing frequency of antibiotic resistance, further illustrating the need  
48 152 both to increase precision and decrease the number of performed  
49 153 biopsies[11]. Since screening using PSA and systematic prostate biopsies  
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3 154 have been shown to decrease prostate cancer mortality, it is reasonable to  
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5 155 use this strategy as comparator for novel diagnostic strategies[4-5].  
6  
7

#### 8 156 **4.4. Multi-parametric Magnetic Resonance Imaging (mpMRI) for** 9 157 **detection of prostate cancer**

10 158 Multi-parametric magnetic resonance imaging (mpMRI) incorporating  
11 159 anatomical and functional imaging has now been validated as a means of  
12 160 detecting and characterizing prostate tumours and can aid in risk stratification  
13 161 and treatment selection. The European Society of Urogenital Radiology  
14 162 (ESUR) in 2012 established the Prostate Imaging Reporting and Data System  
15 163 (PI-RADS) guidelines aimed at standardizing the acquisition, interpretation  
16 164 and reporting of prostate mpMRI. Consensus on an updated version (PI-  
17 165 RADS v2) have recently been published, outlining aspects of both  
18 166 interpretation and the technical execution[12-14]. Use of the revised PI-RADS  
19 167 provides moderately reproducible MR imaging scores for detection of clinically  
20 168 relevant disease[15]. Using MP-MRI to triage men might allow 27% of patients  
21 169 avoid a primary biopsy and diagnosis fewer clinically insignificant cancers. If  
22 170 subsequent TRUS-biopsies were directed by MP-MRI findings, up to 18%  
23 171 more cases of clinically significant cancer might be detected compared with  
24 172 the standard pathway of TRUS-biopsy for all[16].

25 173 In summary, PI-RADS recommends to use 3T or 1.5T machines, including  
26 174 T2- and T1-weighted sequences together with diffusion weighted images  
27 175 (DWI). Currently, the added value of dynamic contrast is not firmly established  
28 176 regarding tumour detection. At this time, there is no consensus among  
29 177 experts concerning the potential benefits of the use of endorectal coils for  
30 178 cancer detection. It has been suggested that the prevalence of suspicious  
31 179 lesions on MRI in men with clinical suspicion of prostate cancer is  
32 180 approximately 60% [17].  
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#### 37 181 **4.5. Targeted prostate biopsies guided by fusion technology**

38 182 Targeted biopsies of the prostate consist of imaging (MRI) detecting  
39 183 significant tumours and a biopsy procedure where biopsies are targeted to the  
40 184 tumour using various devices for guidance[18]. While traditional endorectal  
41 185 ultrasound poorly identifies tumours, direction of biopsy needles can be  
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3 186 performed in various ways. Cognitive or soft fusion is based on skilled  
4 187 urologists/radiologists interpreting the MRI images and directing needles  
5 188 solely based on the ultrasound images. The disadvantages of cognitive fusion  
6 189 lie in the potential for human error when attempting to mentally fuse the MRI  
7 190 with TRUS while aiming for cancers that are often <1 cm in diameter and the  
8 191 inability to track the location of each biopsy site. Hard fusion enables proper  
9 192 fusion of MRI information on the ultrasound image, possibly increasing  
10 193 precision.

11  
12  
13 194 Despite methodological flaws, a number of studies have investigated the  
14 195 value of fusion biopsies, primarily using non-randomized designs and non-  
15 196 screening populations[19]. In 2018, Kasivisvanathan et al provided high  
16 197 quality evidence for men referred for prostate biopsy and showed that  
17 198 MRI/target biopsies are non-inferior for detection of significant cancer and  
18 199 decreases the number of in-significant cancers and number of biopsies as  
19 200 compared with systematic biopsies[20].

20 201 The proportion of men upgraded when comparing specimen from targeted  
21 202 biopsies and subsequent prostatectomy have been shown to be very low  
22 203 (<5%) when using targeted biopsies[21], increasing the proportion of men  
23 204 where treatment decisions are based on valid risk estimations.

#### 24 205 ***4.6. Improving the diagnostic pathway for prostate cancer detection***

25 206 The current diagnostic pathway for prostate cancer detection is  
26 207 characterized by several challenging hallmarks. First, testing with PSA is  
27 208 frequent also in men not benefitting from testing due to low PSA levels or high  
28 209 age[3]. Second, the currently used test for detection (PSA) lacks in specificity,  
29 210 resulting in frequent over-diagnosis[22,23]. Third, systematic biopsies shows  
30 211 high frequencies of benign tests, over-diagnosis, up-grading at prostatectomy,  
31 212 and risk of infectious complications[7,24]. Further, PSA testing increases with  
32 213 educational length and men with long education are more likely to have a  
33 214 prostate biopsy after an increased PSA value. These differences may  
34 215 contribute to the worse prostate cancer outcomes observed among men with  
35 216 lower socioeconomic status[25].

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3 217 The STHLM3 test offers improved disease detection[7]. To further  
4  
5 218 decrease over-detection, improve disease classification and spare men of  
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7 219 test-related harm, prostate biopsy practices need to be improved. We  
8  
9 220 hypothesize that an improved pathway for prostate cancer detection including  
10  
11 221 a better blood-based screening test, improved selection to biopsy based on  
12  
13 222 MRI findings and targeted biopsies guided by MRI/ultrasound fusion would  
14  
15 223 dramatically decrease the number of biopsy procedures, overdiagnosis and  
16  
17 224 improve treatment decisions.

## 225 **5. Methods**

### 226 **5.1. Hypotheses**

#### 227 **5.1.1. Primary hypotheses**

228 The hypothesis below is posed for men in screening-by-invitation context:

229 A diagnostic pathway using the Stockholm3 test to select men for further  
230 workup using MRI followed by targeted biopsies and systematic biopsies  
231 (S3M-MR-TBx/SBx) has non-inferior sensitivity for detecting clinically  
232 significant cancer (ISUP grade group  $\geq 2$ ) and shows superior specificity  
233 (reduction in number of performed biopsy procedures and detected ISUP 1  
234 tumours) compared to the diagnostic pathway using systematic biopsies in  
235 men with PSA  $\geq 3$  ng/ml (PSA-SBx).

#### 236 **5.1.2. Additional hypotheses**

237

- 238 1. As compared with performing systematic biopsies for men with  
239 elevated risk of prostate cancer in prostate cancer screening, targeted  
240 prostate biopsies performed with MRI/Fusion technique with or without  
241 addition of systematic biopsies has non-inferior sensitivity for detecting  
242 clinically significant cancer (ISUP grade group  $\geq 2$ ) and reduces the  
243 number of performed biopsy procedures.
- 244 2. A diagnostic pathway using the Stockholm3 test to select men for  
245 further workup using MRI followed by ONLY targeted biopsies (S3M-

- 1  
2  
3 246 MR-TBx) has non-inferior sensitivity for detecting clinically significant  
4  
5 247 cancer (ISUP grade group  $\geq 2$ ) and reduces the number of performed  
6  
7 248 biopsy procedures compared to a diagnostic pathway using systematic  
8  
9 249 biopsies in men with PSA  $\geq 3$  ng/ml (PSA-SBx).
- 10 250 3. Adding prostate volume as parameter in the diagnostic pathway with  
11  
12 251 Stockholm3 test and MRI/Fusion biopsies improves model precision.
- 13 252 4. A diagnostic pathway with Stockholm3 followed by MRI and targeted  
14  
15 253 biopsies has non-inferior sensitivity for detecting clinically significant  
16  
17 254 cancer (ISUP grade group  $\geq 2$ ) and reduces the number of MRI  
18  
19 255 examinations and performed biopsies compared to a diagnostic  
20  
21 256 pathway using PSA  $\geq 3$  ng/ml followed by MRI and targeted biopsies.
- 22 257 5. SBx in the MRI arm has superior sensitive than SBx in the non-MRI  
23  
24 258 arm (due to cognitive fusion).
- 25 259 6. Biopsy compliance is higher after biopsy is recommended based on  
26  
27 260 MRI compared to recommended without MRI.
- 28  
29 261 7. A diagnostic pathway using the Stockholm3 test to select men for  
30  
31 262 further workup using MRI and targeted biopsies (S3M+TBx) shows  
32  
33 263 better health economy (positive ICER) compared to a diagnostic  
34  
35 264 pathway using systematic biopsies in men with PSA  $\geq 3$  ng/ml  
36  
37 265 (PSA+SBx).  
38  
39 266

## 40 267 **5.2. Aims**

41  
42 268 To compare a diagnostic pathway using the Stockholm3 test (S3M  $\geq 11\%$ )  
43  
44 269 to select men for further workup using MRI (PI-RADS  $\geq 3$ ) and targeted  
45  
46 270 biopsies (S3M+TBx) to a diagnostic pathway using systematic biopsies in  
47  
48 271 men with PSA  $\geq 3$  ng/ml (PSA+SBx) with respect to number of diagnosed  
49  
50 272 clinically significant cancer (ISUP grade group  $\geq 2$ ) and number of performed  
51  
52 273 biopsies. Additional aims corresponding to hypotheses 2-8 above will be  
53  
54 274 assessed.

## 55 56 275 **5.3. Study design**

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3 277       STHLM3-MR Phase 2 is a study combining a paired and a randomized  
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5 278       design (Figure 1). The study will follow the following outline: Participants will  
6  
7 279       be invited by mail. All participants will undergo a blood-test, including PSA  
8  
9 280       and the STHLM3 test. Men with an elevated PSA  $\geq 3$  ng/ml or PSA  $\geq 1.5$  ng/ml  
10  
11 281       and S3M  $> 11\%$  will be randomized to either traditional prostate biopsies or MR  
12  
13 282       with targeted biopsies on MR lesions.

#### 15 283       **5.4. Participants, interventions and outcomes**

##### 17 284       **5.4.1. Study setting**

18 285       This is a screening-by-invitation study including one study administrative  
19  
20 286       centre, two radiological sites and three urological sites where data will be  
21  
22 287       collected.

##### 23 288       **Participating urological centres**

24  
25  
26 289       Department of Urology, Capio St Görans Hospital: dr Henrik Grönberg  
27  
28 290       Uroclinic, Sophiahemmet, Stockholm; dr Olof Jansson  
29  
30 291       Odenplans läkarhus; dr Magnus Annerstedt

##### 31 292       **5.4.2. Eligibility criteria**

##### 32 293       **Inclusion criteria**

33  
34  
35 294       Men age 50-74 years without prior diagnosis of prostate cancer (ICD-9  
36  
37 295       C61).

38  
39 296       Permanent postal address in Stockholm

40  
41 297       Not a previous participant in the Stockholm3 study (2012-2014)

##### 42 298       **Exclusion criteria**

43  
44 299       Severe illnesses such as metastatic cancers, severe cardio-vascular  
45  
46 300       disease or dementia

47  
48 301       Contraindications for magnetic resonance imaging (MRI) e.g. pacemaker,  
49  
50 302       magnetic cerebral clips, cochlear implants or severe claustrophobia.

51  
52 303       Men with a previous prostate biopsy the preceding 60 days before  
53  
54 304       invitation.

### 305 **5.4.3. Randomization**

306 Randomization is performed 2:3 between control arm and experimental  
307 arm. Randomization will be performed will be performed using stratification on  
308 disease risk [6 strata]. Disease risk is assessed using the Stockholm3 test.  
309 Test are discordant if PSA is negative and Stockholm3 positive or vice versa.

310 Four allocation lists [high/low risk vs discordant/concordant tests] have  
311 been created with the sequence [control arm, control arm, experimental arm,  
312 experimental arm, experimental arm]. Participants are first allocated to  
313 corresponding list, and then allocated to study arm according to the order in  
314 which they participate. The allocation sequence is blinded for the study  
315 investigators and handled by the study database administrator (A Björklund).

316 In order to enhance resource usage, men are allocated to the study sites  
317 according to local availability of biopsy procedure slots.

### 318 **5.4.4 Interventions**

#### 319 ***Blood sampling***

320 Participating men undergo blood-sampling with analysis of PSA and the  
321 Stockholm3 test at Karolinska University Laboratory.

322 For the main analysis, the Stockholm3 test include clinical data as  
323 answered when consenting participation (previous biopsy, age, finasteride  
324 medication, relatives with prostate cancer); single nucleotide polymorphisms  
325 and measurements of protein levels (MSMB, MIC1, PSA, fPSA, hK2)[7]. For  
326 secondary analyses, clinical information on DRE and prostate volume is  
327 included.

#### 328 ***Definition of EXPERIMENTAL ARM***

329 Men randomized to the experimental arm undergo MRI. If suspicious  
330 lesions are found, the participant undergoes targeted biopsies using Fusion  
331 technology *followed by systematic biopsies*.



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2  
3 332 Men without lesions are excepted from further intervention and receives  
4 notification on recommendation for follow-up. Technology and process are  
5 333 described below.  
6  
7 334

8  
9 335 Men with a Stockholm3 risk  $\geq 25\%$  and no suspicious lesion on MRI will be  
10 recommended to undergo systematic biopsies.  
11 336

### 12 13 337 **Definition of CONTROL ARM**

14  
15 338 Men randomized to the control arm undergoes systematic biopsies as  
16 defined below.  
17 339

### 18 19 20 340 **5.4.5 Technology**

#### 21 22 341 **Cut-offs for performing the STHLM3 test**

23  
24 342 The STHLM3 test will be performed for men with a PSA  $\geq 1.5$  ng/ml

#### 25 26 343 **Cut-offs for entering randomization**

27  
28 344 Participants with PSA  $\geq 3.0$  ng/ml or STHLM3-test  $\geq 11\%$  risk of Gleason  
29 Score  $\geq 7$  cancer will be randomized and offered to undergo either MR or  
30 systematic biopsies (See Process description).  
31 345  
32 346

#### 33 34 347 **MRI technology**

##### 35 36 348 *Location and MRI equipment*

37  
38 349 Capio St Görans Hospital: General Electric, Architect, 3T  
39  
40 350 Globen Unilabs Healthcare: Siemens Magnetom Aera 1.5T

##### 41 42 351 *Patient preparations*

43  
44 352 Refraining from sexual activity with ejaculation 3 days prior to examination  
45  
46 353 Fasting patient 6 h  
47  
48 354 Minimal preparation enema prior to examination  
49  
50 355 Antispasmodic agent (Glucagon) just before the examination

##### 51 52 356 *MRI Protocol*

53  
54 357 A short (14 minutes) MRI protocol will be used. A detailed description is  
55  
56 358 available. Briefly, the protocol includes: T2w images axial, sagittal, coronal;

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2  
3 359 Diffusion weighted imaging b0 and b1000 with ADC and a synthetic b1500  
4 360 limited to the prostate location; Endorectal coil will not be used.  
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### 8 361 *MRI Interpretation*

9  
10 362 MRI interpretation is centralized to Capio St Görans hospital and is  
11 363 performed according to PIRAD v2.0 for examinations without adequate  
12 364 perfusion studies. Dr Fredrik Jäderling is responsible for MRI interpretation. Dr  
13 365 Jäderling or one to two other, experienced radiologists at his department  
14 366 performs all MRI interpretations.  
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19 367 PI-RADS v2 (“Assessment without adequate dynamic contrast enhanced  
20 368 imaging”) will be used, with a 1-5 grade scale of suspicious lesions (1=  
21 369 clinically significant cancer is highly unlikely to be present, 5= clinically  
22 370 significant cancer is highly likely to be present).  
23  
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25

26 371 During the study period participating radiologist will have access to  
27 372 updated histology results of fusion biopsies to be able to adjust their MRI  
28 373 reading according to tumour detection rates for different PIRAD scores as  
29 374 defined above.  
30  
31  
32  
33

### 34 375 *Fusion biopsy technology*

#### 35 376 *Brand/models*

36  
37 377 BK Medical (BK Ultrasound ; [www.bkultrasound.com/bk-medical/fusion](http://www.bkultrasound.com/bk-medical/fusion))  
38 378 The BK Medical fusion system is the only fusion device compatible with BK  
39 379 Medicals ultrasound devices, used by the urology departments participating in  
40 380 the study. The system represents a second-generation ultrasound system  
41 381 with integrated MRI Fusion. MRI data is imported through HIPAA-compliant  
42 382 PACS connection with the local radiology department.  
43  
44  
45  
46  
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50

#### 51 383 *Definition of targeted biopsies*

52 384 Using MRI data with pre-marked borders of the prostate and tumour, fusion of  
53 385 MRI images and ultrasound images are performed bedside. Using local  
54 386 anaesthetics and antibiotic prophylaxis, lesions are taken according to the  
55  
56  
57  
58  
59  
60

1  
2  
3 387 schedule below. Targeted biopsies are always combined with systematic  
4  
5 388 biopsies.  
6  
7

8 389 *Biopsy procedure for targeted biopsies*

9  
10 390 **PI-RADS $\geq$ 3:** 3-4 targeted biopsies on marked lesions + systematic  
11  
12 391 biopsies.

13  
14 392 **Large diffuse lesions or poor image quality:** Systematic biopsies  
15  
16 393 including lesion.

17  
18 394 **No PI-RADS $\geq$ 3, diffuse lesions and at least acceptable image quality:**  
19  
20 395 No biopsies are performed.

21  
22 396 In larger lesions in PI-RADS category 3 and 5, areas within the lesion with the  
23  
24 397 lowest ADC value (“Target-within-target”) will be targeted with the first biopsy  
25  
26 398 taken from the lesion, to evaluate the additional value regarding tumour  
27  
28 399 staging.

29  
30 400 *Definition of systematic biopsies*

31  
32 401 10-12 systematic biopsies are taken from the peripheral zone as  
33  
34 402 previously described in STLHLM3 and the National Guidelines. Extra biopsies  
35  
36 403 are allowed from additional sites visible on ultrasound or according to  
37  
38 404 palpatory findings. In summary, systematic biopsies are performed in the  
39  
40 405 peripheral zone as 4 lateral and para-median biopsies on the left and right  
41  
42 406 side, in the base and mid part of the gland. In the apical third of the gland one  
43  
44 407 lateral left and right biopsy is performed.

45 408 **Pathology**

46  
47 409 Pathology is centralized to Unilabs/Capio St Görans hospital. Dr Axel  
48  
49 410 Glaessgen is responsible for the integrity of analyses of pathological  
50  
51 411 specimen. 2-3 uro-pathologists at dr Glaessgens department assesses all  
52  
53 412 pathological specimen with intermittent cross-validation between them.  
54  
55 413 Pathology preparation and reporting follow ISUP 2014 guidelines.

56  
57 414 The pathology preparation is done by Unilabs as part of the normal clinical  
58  
59 415 routine. Biopsy specimens are analysed according to local practice.  
60

1  
2  
3 416 Localisation of biopsies in the prostate are described using Swedish  
4  
5 417 National Guideline nomenclature (A1-4; B1-4; C1-4; anterior/posterior).  
6  
7 418 Gleason Score, mm cancer and % Gleason 4 is reported on each needle  
8  
9 419 specimen.

10  
11 420 Pathologist notes results in the usual way in the laboratory system. The  
12  
13 421 result of the pathological analysis is submitted in accordance with existing  
14  
15 422 clinical routines to the referring urologist. A copy of the result is delivered to  
16  
17 423 the study administration.

#### 18 19 424 **5.4.4. Outcomes**

20  
21 425 There are three co-primary endpoints in this trial: (i) Number of diagnosed  
22  
23 426 ISUP grade group  $\geq 2$  cancers; (ii) Number of diagnosed ISUP grade group 1  
24  
25 427 cancers; (iii) Number of performed biopsies.

#### 26 27 428 **5.4.5. Follow-up**

28  
29  
30 429 Main study outcomes are assessed after prostate biopsy procedures.  
31  
32 430 Additional participant data will be secured in the following circumstances:

##### 33 34 431 *No suspicious lesion on MRI*

35  
36  
37 432 Men in the experimental arm without suspicious lesions on MRI will be  
38  
39 433 informed and recommended follow-up by the responsible, local urologist. After  
40  
41 434 additional ethical application, the co-investigators may initiate retrospective  
42  
43 435 follow-up of these participants.

##### 44 45 436 *Men with diagnosed prostate cancer*

46  
47 437 Participants with prostate cancer diagnosed on biopsy within the study will  
48  
49 438 be followed up after the biopsy to secure data on the following: Treatment  
50  
51 439 modality (Active Surveillance, Surgery, Radiation); Treatment lead-time and  
52  
53 440 site; Pathological report after surgery (positive margins, T-stage, etc). Data  
54  
55 441 will be assessed through medical records intermittently.

#### 56 57 442 **5.5. Serious adverse events**

1  
2  
3 443 Study nurse will monitor serious adverse events after the prostate biopsy  
4 444 procedures. To ensure this, the study nurse will follow this check medical  
5 445 journals for hospitalization within 1 week after the biopsy procedure in the  
6 446 journal systems Take Care and Cosmic (covering all hospitals in the  
7 447 Stockholm region). This will be initiated as individual biopsy results are  
8 448 registered at the study administration. Results will be provided to the Data  
9 449 Safety and Monitoring Board.

### 16 450 **5.6. Participant timeline**

17 451 Figure 2 illustrates the approximate timeline for participating men in  
18 452 STHLM3MRI Main Study.

### 23 453 **5.7. Sample size**

24 454 STHLM3-MR/Fusion Phase 2 will invite 25,000 men and aim to include  
25 455 10,000 participants. We anticipate to perform 1,039 biopsy procedures  
26 456 altogether. Inclusion will continue until complete data on 415 men in the  
27 457 control arm (SBx) and 623 men in the experimental arm (MR-TBx-SBx).

#### 33 458 *Basic data and assumptions used in the sample size calculations*

34 459 We used data from the STHLM3 trial for sample size calculations [7]. In  
35 460 this data, 18% of men with PSA  $\geq 3$  had a clinically significant prostate cancer  
36 461 when biopsied with SBx. We further noted that  $rTPR=1.45$  for clinically  
37 462 significant prostate cancer comparing MRI+TBx with SBx based on the results  
38 463 from the PRECISION randomized trial [20]. However, we will for sample size  
39 464 calculations use  $rTPR=1.25$  for MRI+TBx vs. SBx as a more conservative  
40 465 estimate. We set the non-inferiority delta to 4 percentage points for  
41 466 demonstrating noninferiority with respect to sensitivity of clinically significant  
42 467 prostate cancer. We set the alpha to 5%.

#### 52 468 **Primary contrast**

53 469 Simulating 1000 trials (by bootstrapping from the STHLM3 data) under the  
54 470 assumptions outlined in the preceding section 303 men need to be biopsied in  
55 471 the SBx arm based on PSA  $\geq 3$  to have 80% power to demonstrate non-

1  
2  
3 472 inferior sensitivity of S3M+MRI+TBx compared with PSA+SBx. This means  
4 473 that at least **415** men need to be biopsied in the SBx arm (since some men  
5 474 are not randomized based on PSA  $\geq$  3 but on S3M  $\geq$  11%) and, consequently,  
6 475 **623** to the MRI arm (because of the 2:3 randomization). Total number of men  
7 476 undergoing workup according to protocol (SBx in the no MRI arm and MRI  
8 477 and TBx if Pi-RADS  $\geq$  3 in the MRI arm) is thus 1038. Assuming 20% dropout,  
9 478 1300 men need to be randomized. These numbers give 80% power to detect  
10 479 a modest 17% reduction in biopsies between the two strategies.

## 480 **5.8. Recruitment and Process Description**

481 The STHLM3-MR Phase 2 will use existing solutions developed and  
482 optimized in the previous studies STHLM3 and STHLM3-MR Phase 1 where  
483 all major components of the process have been tested. First, participants will  
484 follow the *paired design study process* where inclusion, blood-test and  
485 delivery of recommendation letter is performed. Men with increased risk of  
486 high-grade prostate cancer then enter the *randomized study process*, where  
487 extended work-up including biopsies are performed.

## 488 **5.9. Data Collection, management, analysis**

### 489 **5.9.1. Data collection**

490 Primary data sources are

- 491 i. clinical variables collected from laboratory referral
- 492 ii. biopsy referrals and reports
- 493 iii. pathology reports
- 494 iv. MRI reports
- 495 v. blood concentrations of kallikreins, MSMB, MIC1, SNPs

496 Collection of i. – iv. is performed by study nurses (C Cavalli-Björkman) on  
497 a weekly basis from participating urology sites, participating radiologists. For  
498 v., this is digitally transferred from Karolinska University Laboratory.

### 499 **5.9.2. Data management**

500 Data is collected, entered, coded and stored at Department of Medical  
501 Epidemiology and Biostatistics, Karolinska Institutet. Data is entered by Study  
502 Nurse using predefined database sheets developed in STHLM3MRI Phase 1.

1  
2  
3 503 This is blinded from study co-investigators and data is stored at the  
4  
5 504 department under supervision by the study database administrator (SDA,  
6  
7 505 Astrid Björklund). Any extraction of study data is performed by the SDA after  
8  
9 506 approval of PI Tobias Nordström.

### 10 11 507 **5.9.3. Data analysis**

12  
13 508 Analysis of data is described in the Statistical Analysis Plan (SAP).

### 14 15 16 17 509 **5.9.4. Auditing and Monitoring**

18  
19 510 A Data Safety and Monitoring Board (DSMB) is assembled and consist of  
20  
21 511 dr Hans Garmo (Statistician), prof Ola Bratt (Urology) and prof Holmberg  
22  
23 512 (Urology/Study Design). The DSMB audits protocol and process descriptions  
24  
25 513 and one interim data extraction performed by the study database  
26  
27 514 administrator after 10% (100 men) have completed the control or  
28  
29 515 experimental arms. The co-investigators are blinded to the interim data and  
30  
31 516 analysis results. The work of the DSMB is regulated in the DSMB Charter.

### 32 33 517 **5.10. Patient and Public Involvement**

34  
35 518 The research question and outcome measures were designed to improve  
36  
37 519 prostate cancer diagnostics. This includes optimizing prostate biopsies and  
38  
39 520 decreasing over-detection, both associated with morbidity. Patient  
40  
41 521 organisations were informed on the results from the STHLM3MRI Phase 1  
42  
43 522 study. Patients were not involved in recruitment of the study. Results will be  
44  
45 523 disseminated to participants through common and scientific channels.

## 46 47 48 524 **6. Ethics and dissemination**

### 49 50 51 525 **6.1. Research ethics approval**

52  
53 526 The study has approval from the regional ethical review board Regional  
54  
55 527 Ethical Review Board in Stockholm (2017-1280/31).

### 56 57 528 **6.2. Consent**



1  
2  
3 529 Participant consent is secured when the participant is included to the study  
4  
5 530 at [www.kliniskastudier.se](http://www.kliniskastudier.se). This includes secure identification using Mobilt  
6  
7 531 BankID. Additional approval on use of biological specimen data is collected on  
8  
9 532 the biopsy referral.

### 10 11 533 **6.3. Confidentiality**

12  
13 534 Study data is collected and stored at Department of Medical Epidemiology  
14  
15 535 and Biostatistics, Karolinska Institutet using secure Oracle servers. All data  
16  
17 536 extractions are made by database administrator and are anonymized  
18  
19 537 (personal id number is removed) before dissemination to researchers.

### 20 21 22 538 **6.4. Dissemination**

23  
24 539 Analyses results on the posed aims will be submitted for peer-reviewed  
25  
26 540 publication and submitted for presentation at scientific congress.  
27  
28 541 Communication of the results will be made to patient organizations  
29  
30 542 (Prostatacancerförbundet) and non-scientific channels. No use of professional  
31  
32 543 writers is planned.

33 544 The study protocol is made publicly available through [clinicaltrials.gov](http://clinicaltrials.gov).

### 34 35 36 545 **6.5. Data Sharing Statement**

37  
38 546 Anonymized, individual participant data that underlie the results reported in  
39  
40 547 this article, after deidentification (text, tables, figures and appendices) will be  
41  
42 548 available for data sharing. Proposals may be submitted up to 36 months  
43  
44 549 following article publication. Data will be shared with investigators whose  
45  
46 550 proposed use of the data has been approved by an independent review  
47  
48 551 committee identified for this purpose.

## 49 50 51 552 **7. Declarations of interest**

52  
53 553 Henrik Grönberg has five prostate cancer diagnostic related patents  
54  
55 554 pending, has patent applications licensed to Thermo Fisher Scientific, and  
56  
57 555 might receive royalties from sales related to these patents. Martin Eklund is  
58  
59 556 named on four of these five patent applications. Karolinska Institutet



1  
2  
3 557 collaborates with Thermo Fisher Scientific in developing the technology for the  
4  
5 558 Stockholm3 test.  
6  
7  
8

9 559 **8. Contributions**

10  
11 560 TN was the Principal investigator. TN, HG, ME, SC and MA designed the  
12  
13 561 study. ME and TN interpreted preliminary data. FJ designed MRI protocols  
14  
15 562 and collected data.  
16

17 563 We thank participants, study organizers, participating researchers and  
18  
19 564 clinicians, and patient advisers for their contributions to the STHLM3MRI  
20  
21 565 project.  
22

23  
24  
25 566 **9. Funding statement**

26 567 Funding was provided by the Swedish Cancer Society, (Cancerfonden),  
27  
28 568 the Swedish Research Council (Vetenskapsrådet), Swedish Research Council  
29  
30 569 for Health Working Life and Welfare (FORTE), The Strategic Research  
31  
32 570 Programme on Cancer (StratCan), Karolinska Institutet, Swedish e-Science  
33  
34 571 Research Center (SeRC) and Stockholm City Council (SLL). The STHLM3  
35  
36 572 study is a part of the Linnaeus Center CRISP “Predication and prevention of  
37  
38 573 breast and prostate cancer” funded by the Swedish Research Council.  
39

40  
41 574 **10. Figure legends**

42  
43 575 Figure 1: Study design overview STHLM3MRI Main Study

44  
45 576 Figure 2: Timeline overview for study participants in STHLM3MRI Main  
46  
47 577 Study  
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49  
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51 578 **11. References**

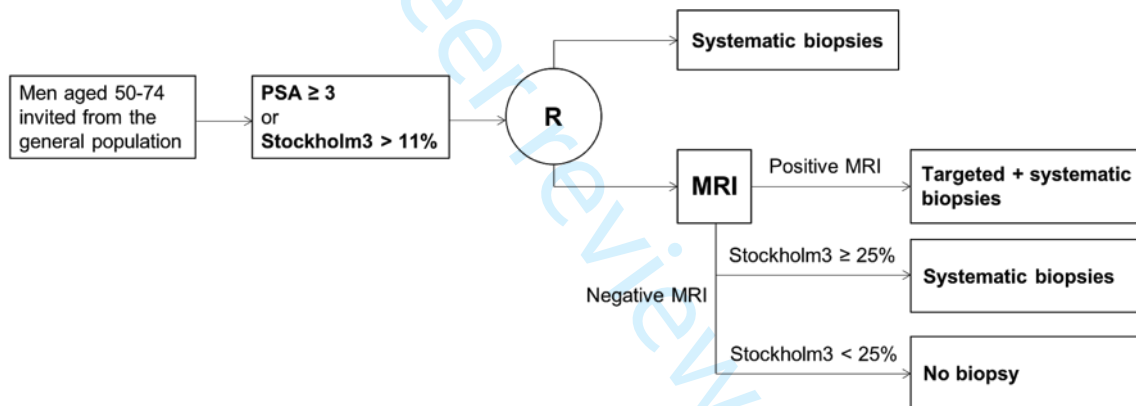
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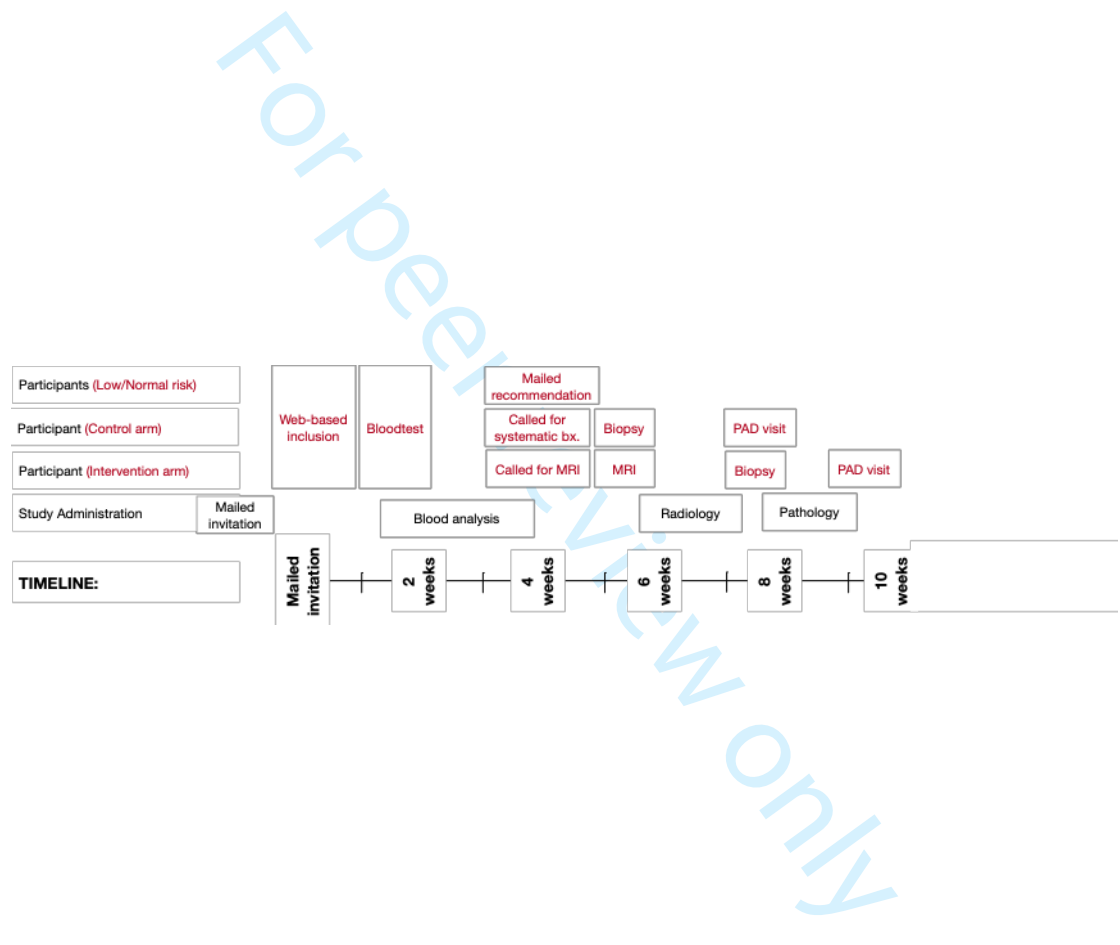
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## CONSORT 2010 checklist of information to include when reporting a randomised trial\*

Section/Topic	Item No	Checklist item	Reported on page No
<b>Title and abstract</b>			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	4-7
	2b	Specific objectives or hypotheses	8-9
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	10
Participants	4a	Eligibility criteria for participants	10
	4b	Settings and locations where the data were collected	9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10-13
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	14
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	15
	7b	When applicable, explanation of any interim analyses and stopping guidelines	16
<b>Randomisation:</b>			
Sequence generation	8a	Method used to generate the random allocation sequence	-
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	-

1		assessing outcomes) and how	
2		11b If relevant, description of the similarity of interventions	
3	Statistical methods	12a Statistical methods used to compare groups for primary and secondary outcomes	Separate doc
4		12b Methods for additional analyses, such as subgroup analyses and adjusted analyses	Separate doc
5			
6	<b>Results</b>		
7	Participant flow (a	13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and	
8	diagram is strongly	were analysed for the primary outcome	
9	recommended)	13b For each group, losses and exclusions after randomisation, together with reasons	
10	Recruitment	14a Dates defining the periods of recruitment and follow-up	
11		14b Why the trial ended or was stopped	
12	Baseline data	15 A table showing baseline demographic and clinical characteristics for each group	
13	Numbers analysed	16 For each group, number of participants (denominator) included in each analysis and whether the analysis was	
14		by original assigned groups	
15	Outcomes and	17a For each primary and secondary outcome, results for each group, and the estimated effect size and its	
16	estimation	precision (such as 95% confidence interval)	
17		17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
18	Ancillary analyses	18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing	
19		pre-specified from exploratory	
20	Harms	19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
21			
22	<b>Discussion</b>		
23	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
24	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	
25	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
26			
27	<b>Other information</b>		
28	Registration	23 Registration number and name of trial registry	2
29	Protocol	24 Where the full trial protocol can be accessed, if available	1
30	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	18

\*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).





STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

## SPIRIT CHECKLIST STHLM3MRI Study, BMJ Open

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

Section/item	ROW NUMBER	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	62	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	Full protocol	Date and version identifier
Funding	566	Sources and types of financial, material, and other support
Roles and responsibilities	7+559	Names, affiliations, and roles of protocol contributors
	20	Name and contact information for the trial sponsor
	Full protocol	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	Full protocol	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
<b>Introduction</b>		
Background and rationale	80, 267	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	152	Explanation for choice of comparators

1			
2	Objectives	225	Specific objectives or hypotheses
3			
4	Trial design	275	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)
5			
6			
7			
8			
9			
10	<b>Methods: Participants, interventions, and outcomes</b>		
11			
12	Study setting	284	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
13			
14			
15			
16	Eligibility criteria	293	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
17			
18			
19			
20			
21	Interventions	319	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
22			
23			
24		N/A	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
25			
26			
27			
28			
29		N/A	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
30			
31			
32			
33		N/A	Relevant concomitant care and interventions that are permitted or prohibited during the trial
34			
35			
36	Outcomes	424	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
37			
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43			
44	Participant timeline	450	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
45			
46			
47			
48			
49	Sample size	453	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
50			
51			
52			
53	Recruitment	480	Strategies for achieving adequate participant enrolment to reach target sample size
54			
55			

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

Allocation:

1			
2	Sequence	305	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions
8			
9			
10	Allocation	305	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned
14			
15	Implementation	315	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions
17			
18	Blinding	N/A	Who will be blinded after assignment to interventions (eg, trial
19	(masking)		participants, care providers, outcome assessors, data analysts), and
20			how
21			
22			
23		N/A	If blinded, circumstances under which unblinding is permissible, and
24			procedure for revealing a participant's allocated intervention during
25			the trial
26			
27			

### Methods: Data collection, management, and analysis

28			
29			
30	Data collection	488	Plans for assessment and collection of outcome, baseline, and other
31	methods		trial data, including any related processes to promote data quality (eg,
32			duplicate measurements, training of assessors) and a description of
33			study instruments (eg, questionnaires, laboratory tests) along with
34			their reliability and validity, if known. Reference to where data
35			collection forms can be found, if not in the protocol
36			
37			
38		N/A	Plans to promote participant retention and complete follow-up,
39			including list of any outcome data to be collected for participants who
40			discontinue or deviate from intervention protocols
41			
42	Data	498	Plans for data entry, coding, security, and storage, including any
43	management		related processes to promote data quality (eg, double data entry;
44			range checks for data values). Reference to where details of data
45			management procedures can be found, if not in the protocol
46			
47			
48	Statistical	506	Statistical methods for analysing primary and secondary outcomes.
49	methods	Full	Reference to where other details of the statistical analysis plan can be
50		proto	found, if not in the protocol
51		col	
52			
53			
54		Full	Methods for any additional analyses (eg, subgroup and adjusted
55		proto	analyses)
56		col	
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1  
2 Full Definition of analysis population relating to protocol non-adherence  
3 Proto (eg, as randomised analysis), and any statistical methods to handle  
4 col missing data (eg, multiple imputation)  
5

## 6 **Methods: Monitoring**

7  
8 Data monitoring 508 Composition of data monitoring committee (DMC); summary of its role  
9 and reporting structure; statement of whether it is independent from  
10 the sponsor and competing interests; and reference to where further  
11 details about its charter can be found, if not in the protocol.  
12 Alternatively, an explanation of why a DMC is not needed  
13  
14  
15 508 Description of any interim analyses and stopping guidelines, including  
16 who will have access to these interim results and make the final  
17 decision to terminate the trial  
18  
19 Harms 441 Plans for collecting, assessing, reporting, and managing solicited and  
20 spontaneously reported adverse events and other unintended effects  
21 of trial interventions or trial conduct  
22  
23  
24 Auditing 508 Frequency and procedures for auditing trial conduct, if any, and  
25 whether the process will be independent from investigators and the  
26 sponsor  
27  
28

## 29 **Ethics and dissemination**

30  
31 Research ethics 524 Plans for seeking research ethics committee/institutional review board  
32 approval (REC/IRB) approval  
33  
34 Protocol Full Plans for communicating important protocol modifications (eg,  
35 amendments proto changes to eligibility criteria, outcomes, analyses) to relevant parties  
36 col (eg, investigators, REC/IRBs, trial participants, trial registries, journals,  
37 regulators)  
38  
39  
40 Consent or assent Full Who will obtain informed consent or assent from potential trial  
41 proto participants or authorised surrogates, and how (see Item 32)  
42 col  
43  
44 Full Additional consent provisions for collection and use of participant data  
45 proto and biological specimens in ancillary studies, if applicable  
46 col  
47  
48 Confidentiality 532 How personal information about potential and enrolled participants will  
49 be collected, shared, and maintained in order to protect confidentiality  
50 before, during, and after the trial  
51  
52  
53 Declaration of 551 Financial and other competing interests for principal investigators for  
54 interests the overall trial and each study site  
55  
56 Access to data 544 Statement of who will have access to the final trial dataset, and  
57 disclosure of contractual agreements that limit such access for  
58 investigators  
59  
60

1			
2	Ancillary and	N/A	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation
4			
5	Dissemination	537	Plans for investigators and sponsor to communicate trial results to
6	policy		participants, healthcare professionals, the public, and other relevant
7			groups (eg, via publication, reporting in results databases, or other
8			data sharing arrangements), including any publication restrictions
9			
10		537	Authorship eligibility guidelines and any intended use of professional
11			writers
12			
13		537	Plans, if any, for granting public access to the full protocol, participant-
14			level dataset, and statistical code
15			
16			
17	<b>Appendices</b>		
18			
19	Informed consent	Apppe	Model consent form and other related documentation given to
20	materials	nxd	participants and authorised surrogates
21			
22	Biological	N/A	Plans for collection, laboratory evaluation, and storage of biological
23	specimens		specimens for genetic or molecular analysis in the current trial and for
24			future use in ancillary studies, if applicable
25			

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27 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013

28 Explanation & Elaboration for important clarification on the items. Amendments to the

29 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT

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