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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.***

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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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34 **1. Abstract**

35 36 37 **Introduction**

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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
42 with low specificity leading to unnecessary biopsies and over-diagnosis of low-risk cancers.
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44 The STHLM3 trial has paved the way for improved specificity in early detection of prostate
45 cancer using the blood-based STHLM3 test for identifying men at increased risk of
46 harbouring significant prostate cancer. Targeted prostate biopsies based on MRI images
47 have been shown non-inferior sensitivity to detect significant prostate cancer and decrease
48 the number of biopsies and non-significant cancers among men referred for prostate biopsy
49 in clinical practice.
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55 The overarching strategy of the STHLM3-MRI projects is to study an improved diagnostic
56 pathway including an improved blood-based test for identification of men with increased
57 risk of prostate cancer and use of MRI to select men for diagnostic workup with targeted
58 prostate biopsies.
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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 ≥ 7) and simultaneously decreasing the number of low-grade tumors (Gleason Score ≤ 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 ≥ 2) and reduces the number of performed biopsy procedures compared to a diagnostic pathway using systematic biopsies in men with PSA ≥ 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 ≥ 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 ≥ 2) and reduces the number of performed biopsy procedures compared to a diagnostic pathway using systematic biopsies in men with PSA ≥ 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 ≥ 2) and reduces the number of MRI examinations and performed biopsies compared to a diagnostic pathway using PSA ≥ 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 ≥ 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 ≥ 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 **5.3. Study design**

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

53 54 55 **5.4. Participants, interventions and outcomes**

56 57 58 **5.4.1. Study setting**

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This is a screening-by-invitation study including one study administrative center, two
radiological sites and three urological sites where data will be collected.

99 100 **Participating urological centres**

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

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.
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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**

32 Men randomized to the control arm undergoes systematic biopsies as defined below.
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35 36 **Technology**

37 38 **Cut-offs for performing the STHLM3 test**

39 The STHLM3 test will be performed for men with a PSA ≥ 1.5 ng/ml
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44 45 **Cut-offs for entering randomization**

46 Participants with PSA ≥ 3.0 ng/ml or STHLM3-test $\geq 11\%$ risk of Gleason Score ≥ 7 cancer
47 will be randomized and offered to undergo either MR or systematic biopsies (See Process
48 description).
49
50

51 52 **MRI technology**

53 54 **Location and MRI equipment**

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

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

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

prophylaxis, lesions are according to below. Targeted biopsies are always combined with systematic biopsies.

Biopsy procedure for targeted biopsies

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

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

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

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

Definition of systematic biopsies

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

Pathology

Pathology is centralized to Unilabs/Capio St Görans hospital. Dr Axel Glaessgen is responsible for the integrity of analyzes of pathological specimen. 2-3 uro-pathologists at dr Glaessgens department assesses all pathological specimen with intermittent cross-validation between them. Pathology preparation and reporting follow ISUP 2014 guidelines.

The pathology preparation is done by Unilabs as part of the normal clinical routine. Biopsy specimens are analyzed according to local practice.

Localisation of biopsies in the prostate are described using Swedish National Guideline nomenclature (A1-4; B1-4; C1-4; anterior/posterior). Gleason Score, mm cancer and % Gleason 4 is reported on each needle specimen.

Pathologist notes results in the usual way in the laboratory system. The result of the pathological analysis is submitted in accordance to existing clinical routines to the referring urologist. A copy of the result is delivered to the study administration.

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 ≥ 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:***

20
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***

29
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 ≥ 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 ≥ 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 ≥ 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 ≥ 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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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.
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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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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**

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

34 We thank participants, study organizers, participating researchers and clinicians, and
35 patient advisers for their contributions to the STHLM3MRI project.
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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**

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

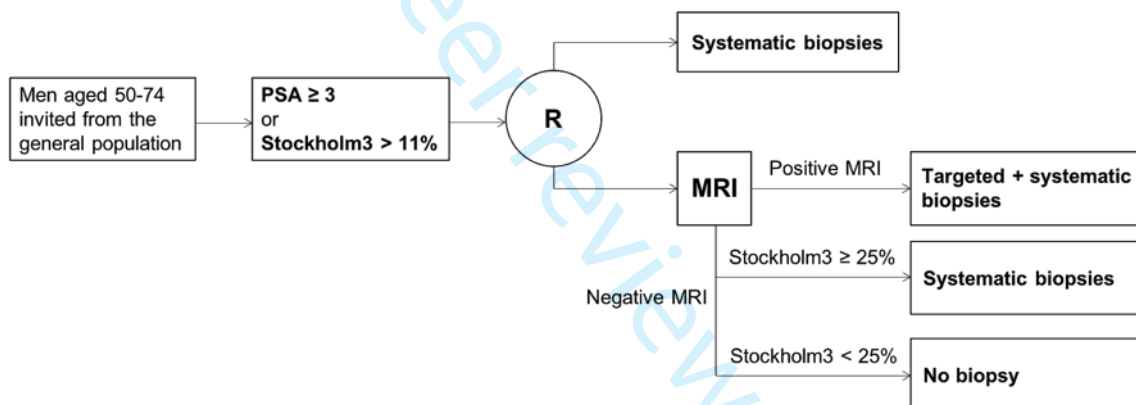
11. References

- 1 Ferlay J, Soerjomataram I, Dikshit R, *et al.* Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2014;:n/a–n/a. doi:10.1002/ijc.29210
- 2 Mistry K, Cable G. Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma. *J Am Board Fam Pract* 2003;**16**:95–101.
- 3 Nordström T, Aly M, Clements MS, *et al.* Prostate-specific antigen (PSA) testing is prevalent and increasing in Stockholm County, Sweden, Despite no recommendations for PSA screening: results from a population-based study, 2003-2011. *Eur Urol* 2013;**63**:419–25. doi:10.1016/j.eururo.2012.10.001
- 4 Schröder FH, Hugosson J, Roobol MJ, *et al.* Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med* 2012;**366**:981–90. doi:10.1056/NEJMoa1113135
- 5 Hugosson J, Carlsson S, Aus G, *et al.* Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol* 2010;**11**:725–32. doi:10.1016/S1470-2045(10)70146-7
- 6 Nationell kvalitetsrapport för diagnosår 2012. Regionala Cancercentrum i Samverkan 2013. <http://npcr.se/wp-content/uploads/2013/04/20131121-NPCR-Rapport-2012.pdf>
- 7 Grönberg H, Adolfsson J, Aly M, *et al.* Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. *Lancet Oncol* 2015;**16**:1667–76.
- 8 Rider JR, Sandin F, Andrén O, *et al.* Long-term outcomes among noncuratively treated men according to prostate cancer risk category in a nationwide, population-based study. *Eur Urol* 2013;**63**:88–96. doi:10.1016/j.eururo.2012.08.001
- 9 Loeb S, Bjurlin MA, Nicholson J, *et al.* Overdiagnosis and overtreatment of prostate cancer. *Eur Urol* 2014;**65**:1046–55. doi:10.1016/j.eururo.2013.12.062
- 10 Soares R, Di Benedetto A, Dovey Z, *et al.* Minimum 5-year follow-up of 1138 consecutive laparoscopic radical prostatectomies. *BJU Int* 2015;**115**:546–53. doi:10.1111/bju.12887
- 11 Aly M, Dyrdak R, Nordström T, *et al.* Rapid increase in multidrug-resistant enteric bacilli blood stream infection after prostate biopsy-A 10-year population-based cohort study. *Prostate* 2015;**75**:947–56. doi:10.1002/pros.22979

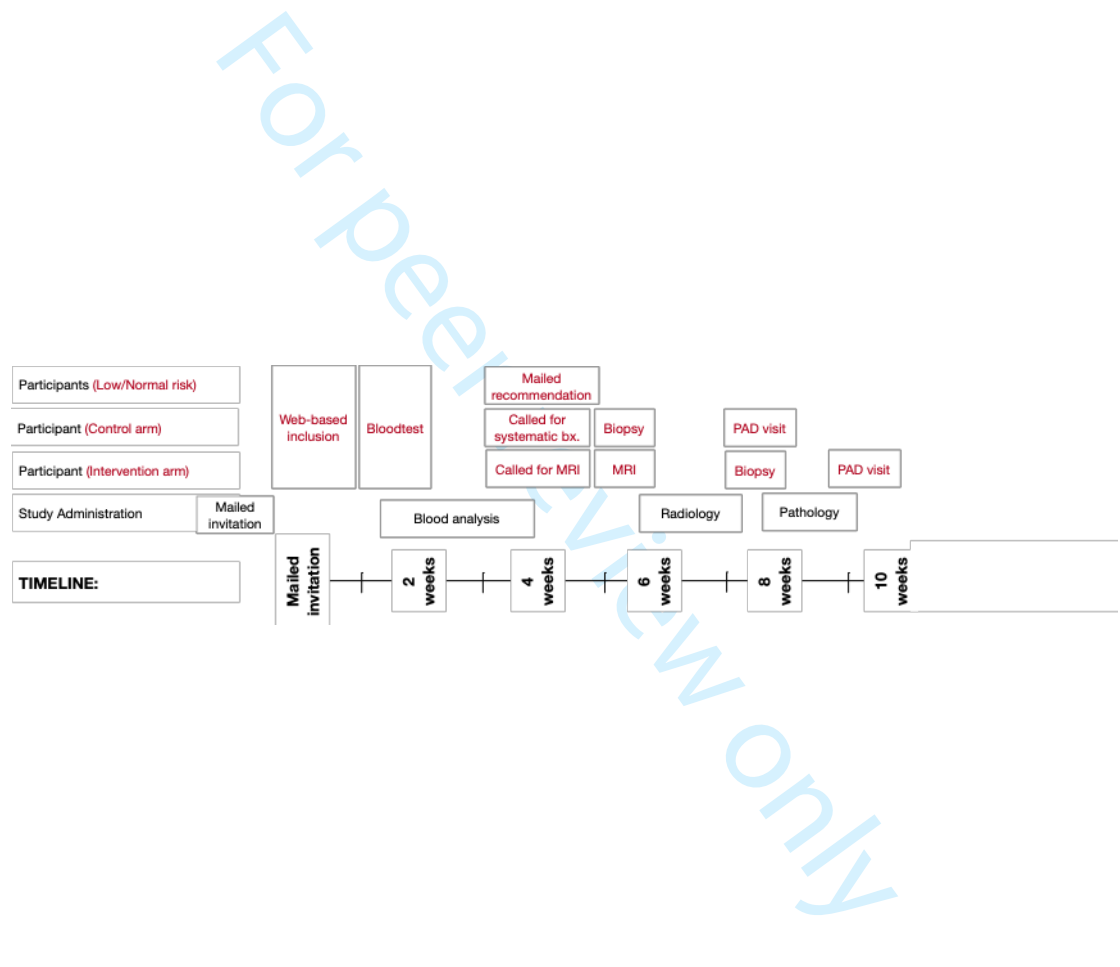
- 1
2
3 12 Barrett T, Turkbey B, Choyke PL. PI-RADS version 2: what you need to know.
4 *Clin Radiol* 2015;**70**:1165–76. doi:10.1016/j.crad.2015.06.093
5
- 6
7 13 Barentsz JO, Weinreb JC, Verma S, *et al.* Synopsis of the PI-RADS v2
8 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging and
9 Recommendations for Use. *Eur Urol* 2015;**69**:41–9.
10 doi:10.1016/j.eururo.2015.08.038
11
- 12
13 14 Weinreb JC, Barentsz JO, Choyke PL, *et al.* PI-RADS Prostate Imaging -
14 Reporting and Data System: 2015, Version 2. *Eur Urol* 2015;**69**:16–40.
15 doi:10.1016/j.eururo.2015.08.052
16
- 17
18 15 Muller BG, Shih JH, Sankineni S, *et al.* Prostate Cancer: Interobserver
19 Agreement and Accuracy with the Revised Prostate Imaging Reporting and Data
20 System at Multiparametric MR Imaging. *Radiology* 2015;**277**:741–50.
21 doi:10.1148/radiol.2015142818
22
- 23
24 16 Ahmed HU, El-Shater Bosaily A, Brown LC, *et al.* Diagnostic accuracy of
25 multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired
26 validating confirmatory study. *Lancet* Published Online First: 19 January 2017.
27 doi:10.1016/S0140-6736(16)32401-1
28
- 29
30 17 Moore CM, Robertson NL, Arsanious N, *et al.* Image-guided prostate biopsy
31 using magnetic resonance imaging-derived targets: a systematic review. *Eur*
32 *Urol* 2013;**63**:125–40. doi:10.1016/j.eururo.2012.06.004
33
- 34
35 18 Sonn GA, Margolis DJ, Marks LS. Target detection: magnetic resonance
36 imaging-ultrasound fusion-guided prostate biopsy. *Urol Oncol* 2014;**32**:903–11.
37 doi:10.1016/j.urolonc.2013.08.006
38
- 39
40 19 Schoots IG, Roobol MJ, Nieboer D, *et al.* Magnetic Resonance Imaging-targeted
41 Biopsy May Enhance the Diagnostic Accuracy of Significant Prostate Cancer
42 Detection Compared to Standard Transrectal Ultrasound-guided Biopsy: A
43 Systematic Review and Meta-analysis. *Eur Urol* 2014;**68**:438–50.
44 doi:10.1016/j.eururo.2014.11.037
45
- 46
47 20 Kasivisvanathan V, Rannikko AS, Borghi M, *et al.* MRI-Targeted or Standard
48 Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med* 2018;:NEJMoa1801993.
49 doi:10.1056/NEJMoa1801993
50
- 51
52 21 Baco E, Ukimura O, Rud E, *et al.* Magnetic resonance imaging-transectal
53 ultrasound image-fusion biopsies accurately characterize the index tumor:
54 correlation with step-sectioned radical prostatectomy specimens in 135 patients.
55 *Eur Urol* 2015;**67**:787–94. doi:10.1016/j.eururo.2014.08.077
56
- 57
58 22 Arnsrud Godtman R, Holmberg E, Lilja H, *et al.* Opportunistic Testing Versus
59 Organized Prostate-specific Antigen Screening: Outcome After 18 Years in the
60 Göteborg Randomized Population-based Prostate Cancer Screening Trial. *Eur*
Urol 2014;**68**:354–60. doi:10.1016/j.eururo.2014.12.006

- 1
2
3 23 Thompson IM, Pauler DK, Goodman PJ, *et al*. Prevalence of prostate cancer
4 among men with a prostate-specific antigen level. *N Engl J Med* 2004;**350**:2239–
5 46. doi:10.1056/NEJMoa031918
6
7
8 24 Loeb S, Vellekoop A, Ahmed HU, *et al*. Systematic review of complications of
9 prostate biopsy. *Eur Urol* 2013;**64**:876–92. doi:10.1016/j.eururo.2013.05.049
10
11 25 Nordström T, Bratt O, Örtengren J, *et al*. A population-based study on the
12 association between educational length, prostate-specific antigen testing and use
13 of prostate biopsies. *Scand J Urol* 2016;**50**:104–9.
14 doi:10.3109/21681805.2015.1113200
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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
Title and abstract			
	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
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-7
	2b	Specific objectives or hypotheses	8-9
Methods			
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
Randomisation:			
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	Results		
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	Discussion		
22	Limitations	20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
23	Generalisability	21 Generalisability (external validity, applicability) of the trial findings	
24	Interpretation	22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
25	Other information		
26	Registration	23 Registration number and name of trial registry	2
27	Protocol	24 Where the full trial protocol can be accessed, if available	1
28	Funding	25 Sources of funding and other support (such as supply of drugs), role of funders	18
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*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.

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,
Primary Subject Heading:	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:**

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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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14 65
 - 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.
 - 17 68 • The study examines the performance of the Stockholm3 test used
 - 18 69 together with MRI/Fusion technique compared with traditional PSA
 - 19 70 screening and will provide important data also on the performance
 - 20 71 of the Stockholm3 test or MRI/Fusion when used as standalone
 - 21 72 strategies.
 - 22 73 • The study is performed at three study sites and uses centralized
 - 23 74 radiology and pathology.
 - 24 75 • The study is limited to a Swedish screening population, the use of
 - 25 76 the Stockholm3 test as blood-based risk prediction and the used
 - 26 77 technology for MRI-targeted biopsies.

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39 78 **3. Trial identifier**

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41 79 ClinicalTrials.gov Identifier: NCT03377881
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46 80 **4. Introduction**

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48 81 **4.1. Public health significance of prostate cancer**

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50 82 Prostate cancer is the most common cancer and the leading cause of
51 83 cancer death among men in Sweden. In year 2011 over 10,000 men were
52 84 diagnosed with prostate cancer and more than 2,500 died due to the disease,
53 85 approximately 20% of these in the Stockholm region. Prostate cancer
54 86 incidence rates in Sweden are now comparable to rates in countries that had
55 87 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
14
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
28
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
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41 108 these results showing that 46%, 68% and 77% of men 50-59, 60-69 and 70-
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43 109 79 years respectively have had at least one PSA test during a 9 years
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45 110 period[3].

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

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

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

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

36 138 **4.3. Traditional evaluation of men with increased risk of prostate** 37 139 **cancer**

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

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3 154 decrease prostate cancer mortality, it is reasonable to use this strategy as
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5 155 comparator for novel diagnostic strategies[4-5].
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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].
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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].
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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
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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 ≥ 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 ≥ 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 ≥ 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 cancer (ISUP grade group ≥ 2) and reduces the number of performed
5 247 biopsy procedures compared to a diagnostic pathway using systematic
6 248 biopsies in men with PSA ≥ 3 ng/ml (PSA-SBx).
7 249
8 250 3. Adding prostate volume as parameter in the diagnostic pathway with
9 251 Stockholm3 test and MRI/Fusion biopsies improves model precision.
10 252 4. A diagnostic pathway with Stockholm3 followed by MRI and targeted
11 253 biopsies has non-inferior sensitivity for detecting clinically significant
12 254 cancer (ISUP grade group ≥ 2) and reduces the number of MRI
13 255 examinations and performed biopsies compared to a diagnostic
14 256 pathway using PSA ≥ 3 ng/ml followed by MRI and targeted biopsies.
15 257 5. SBx in the MRI arm has superior sensitive than SBx in the non-MRI
16 258 arm (due to cognitive fusion).
17 259 6. Biopsy compliance is higher after biopsy is recommended based on
18 260 MRI compared to recommended without MRI.
19 261 7. A diagnostic pathway using the Stockholm3 test to select men for
20 262 further workup using MRI and targeted biopsies (S3M+TBx) shows
21 263 better health economy (positive ICER) compared to a diagnostic
22 264 pathway using systematic biopsies in men with PSA ≥ 3 ng/ml
23 265 (PSA+SBx).
24 266

267 **5.2. Aims**

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

275 **5.3. Study design**

276

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 ≥ 3 ng/ml or PSA ≥ 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
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.

25 288 **Participating urological centres**

26
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

33 292 **5.4.2. Eligibility criteria**

35 293 **Inclusion criteria**

36
37
38 294 Men age 50-74 years without prior diagnosis of prostate cancer (ICD-9
39
40 295 C61).

41
42
43 296 Permanent postal address in Stockholm

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

47 298 **Exclusion criterias**

48
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 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
10 336 undergo systematic biopsies.

13 337 **Definition of CONTROL ARM**

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

20 340 **5.4.5 Technology**

23 341 **Cut-offs for performing the STHLM3 test**

25 342 The STHLM3 test will be performed for men with a PSA ≥ 1.5 ng/ml

28 343 **Cut-offs for entering randomization**

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

36 347 **MRI technology**

39 348 *Location and MRI equipment*

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

45 351 *Patient preparations*

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

53 356 *MRI Protocol*

55 357 A short (14 minutes) MRI protocol will be used. A detailed description is
56 358 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)

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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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.
42
43

44 523 **6. Ethics and dissemination**

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

48
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. This includes secure identification using Mobilt
59
60

1
2
3 530 BankID. Additional approval on use of biological specimen data is collected on
4
5 531 the biopsy referral.
6
7

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.
26
27
28

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.
56
57
58
59
60

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.

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570 Research Center (SeRC) and Stockholm City Council (SLL). The STHLM3
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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**

- 578 1 Ferlay J, Soerjomataram I, Dikshit R, *et al.* Cancer incidence and
579 mortality worldwide: Sources, methods and major patterns in
580 GLOBOCAN 2012. *Int J Cancer* 2014;:n/a–n/a. doi:10.1002/ijc.29210
- 581 2 Mistry K, Cable G. Meta-analysis of prostate-specific antigen and digital
582 rectal examination as screening tests for prostate carcinoma. *J Am Board
583 Fam Pract* 2003;**16**:95–101.
- 584 3 Nordström T, Aly M, Clements MS, *et al.* Prostate-specific antigen (PSA)
585 testing is prevalent and increasing in Stockholm County, Sweden,
586 Despite no recommendations for PSA screening: results from a

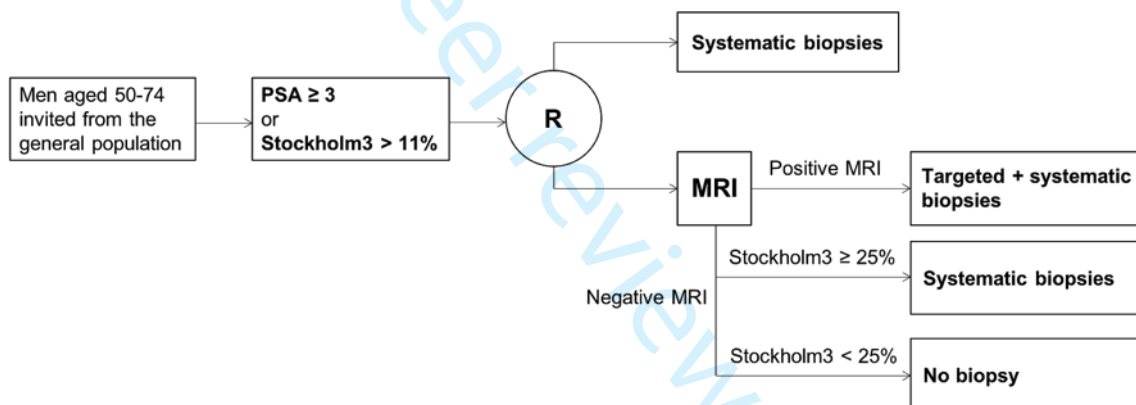
- 1
2
3 587 population-based study, 2003-2011. *Eur Urol* 2013;**63**:419–25.
4 588 doi:10.1016/j.eururo.2012.10.001
5
6
7 589 4 Schröder FH, Hugosson J, Roobol MJ, *et al*. Prostate-cancer mortality at
8 590 11 years of follow-up. *N Engl J Med* 2012;**366**:981–90.
9 591 doi:10.1056/NEJMoa1113135
10
11 592 5 Hugosson J, Carlsson S, Aus G, *et al*. Mortality results from the Göteborg
12 593 randomised population-based prostate-cancer screening trial. *Lancet*
13 594 *Oncol* 2010;**11**:725–32. doi:10.1016/S1470-2045(10)70146-7
14
15 595 6 Nationell kvalitetsrapport för diagnosår 2012. Regionala Cancercentrum i
16 596 Samverkan 2013. [http://npcr.se/wp-content/uploads/2013/04/20131121-](http://npcr.se/wp-content/uploads/2013/04/20131121-NPCR-Rapport-2012.pdf)
17 597 [NPCR-Rapport-2012.pdf](http://npcr.se/wp-content/uploads/2013/04/20131121-NPCR-Rapport-2012.pdf)
18
19
20 598 7 Grönberg H, Adolfsson J, Aly M, *et al*. Prostate cancer screening in men
21 599 aged 50-69 years (STHLM3): a prospective population-based diagnostic
22 600 study. *Lancet Oncol* 2015;**16**:1667–76.
23
24 601 8 Rider JR, Sandin F, Andrén O, *et al*. Long-term outcomes among
25 602 noncuratively treated men according to prostate cancer risk category in a
26 603 nationwide, population-based study. *Eur Urol* 2013;**63**:88–96.
27 604 doi:10.1016/j.eururo.2012.08.001
28
29
30 605 9 Loeb S, Bjurlin MA, Nicholson J, *et al*. Overdiagnosis and overtreatment
31 606 of prostate cancer. *Eur Urol* 2014;**65**:1046–55.
32 607 doi:10.1016/j.eururo.2013.12.062
33
34 608 10 Soares R, Di Benedetto A, Dovey Z, *et al*. Minimum 5-year follow-up of
35 609 1138 consecutive laparoscopic radical prostatectomies. *BJU Int*
36 610 2015;**115**:546–53. doi:10.1111/bju.12887
37
38
39 611 11 Aly M, Dyrdak R, Nordström T, *et al*. Rapid increase in multidrug-resistant
40 612 enteric bacilli blood stream infection after prostate biopsy-A 10-year
41 613 population-based cohort study. *Prostate* 2015;**75**:947–56.
42 614 doi:10.1002/pros.22979
43
44 615 12 Barrett T, Turkbey B, Choyke PL. PI-RADS version 2: what you need to
45 616 know. *Clin Radiol* 2015;**70**:1165–76. doi:10.1016/j.crad.2015.06.093
46
47 617 13 Barentsz JO, Weinreb JC, Verma S, *et al*. Synopsis of the PI-RADS v2
48 618 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging
49 619 and Recommendations for Use. *Eur Urol* 2015;**69**:41–9.
50 620 doi:10.1016/j.eururo.2015.08.038
51
52
53 621 14 Weinreb JC, Barentsz JO, Choyke PL, *et al*. PI-RADS Prostate Imaging -
54 622 Reporting and Data System: 2015, Version 2. *Eur Urol* 2015;**69**:16–40.
55 623 doi:10.1016/j.eururo.2015.08.052
56
57
58 624 15 Muller BG, Shih JH, Sankineni S, *et al*. Prostate Cancer: Interobserver
59 625 Agreement and Accuracy with the Revised Prostate Imaging Reporting

- 1
2
3 626 and Data System at Multiparametric MR Imaging. *Radiology*
4 627 2015;**277**:741–50. doi:10.1148/radiol.2015142818
5
6 628 16 Ahmed HU, El-Shater Bosaily A, Brown LC, *et al.* Diagnostic accuracy of
7 629 multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a
8 630 paired validating confirmatory study. *Lancet* Published Online First: 19
9 631 January 2017. doi:10.1016/S0140-6736(16)32401-1
10
11
12 632 17 Moore CM, Robertson NL, Arsanious N, *et al.* Image-guided prostate
13 633 biopsy using magnetic resonance imaging-derived targets: a systematic
14 634 review. *Eur Urol* 2013;**63**:125–40. doi:10.1016/j.eururo.2012.06.004
15
16 635 18 Sonn GA, Margolis DJ, Marks LS. Target detection: magnetic resonance
17 636 imaging-ultrasound fusion-guided prostate biopsy. *Urol Oncol*
18 637 2014;**32**:903–11. doi:10.1016/j.urolonc.2013.08.006
19
20
21 638 19 Schoots IG, Roobol MJ, Nieboer D, *et al.* Magnetic Resonance Imaging-
22 639 targeted Biopsy May Enhance the Diagnostic Accuracy of Significant
23 640 Prostate Cancer Detection Compared to Standard Transrectal
24 641 Ultrasound-guided Biopsy: A Systematic Review and Meta-analysis. *Eur*
25 642 *Urol* 2014;**68**:438–50. doi:10.1016/j.eururo.2014.11.037
26
27
28 643 20 Kasivisvanathan V, Rannikko AS, Borghi M, *et al.* MRI-Targeted or
29 644 Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med*
30 645 2018;:NEJMoa1801993. doi:10.1056/NEJMoa1801993
31
32 646 21 Baco E, Ukimura O, Rud E, *et al.* Magnetic resonance imaging-transectal
33 647 ultrasound image-fusion biopsies accurately characterize the index
34 648 tumor: correlation with step-sectioned radical prostatectomy specimens in
35 649 135 patients. *Eur Urol* 2015;**67**:787–94. doi:10.1016/j.eururo.2014.08.077
36
37
38 650 22 Arnsrud Godtman R, Holmberg E, Lilja H, *et al.* Opportunistic Testing
39 651 Versus Organized Prostate-specific Antigen Screening: Outcome After 18
40 652 Years in the Göteborg Randomized Population-based Prostate Cancer
41 653 Screening Trial. *Eur Urol* 2014;**68**:354–60.
42 654 doi:10.1016/j.eururo.2014.12.006
43
44
45 655 23 Thompson IM, Pauler DK, Goodman PJ, *et al.* Prevalence of prostate
46 656 cancer among men with a prostate-specific antigen level. *N Engl J Med*
47 657 2004;**350**:2239–46. doi:10.1056/NEJMoa031918
48
49 658 24 Loeb S, Vellekoop A, Ahmed HU, *et al.* Systematic review of
50 659 complications of prostate biopsy. *Eur Urol* 2013;**64**:876–92.
51 660 doi:10.1016/j.eururo.2013.05.049
52
53
54 661 25 Nordström T, Bratt O, Örtengren J, *et al.* A population-based study on the
55 662 association between educational length, prostate-specific antigen testing
56 663 and use of prostate biopsies. *Scand J Urol* 2016;**50**:104–9.
57 664 doi:10.3109/21681805.2015.1113200
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59 665
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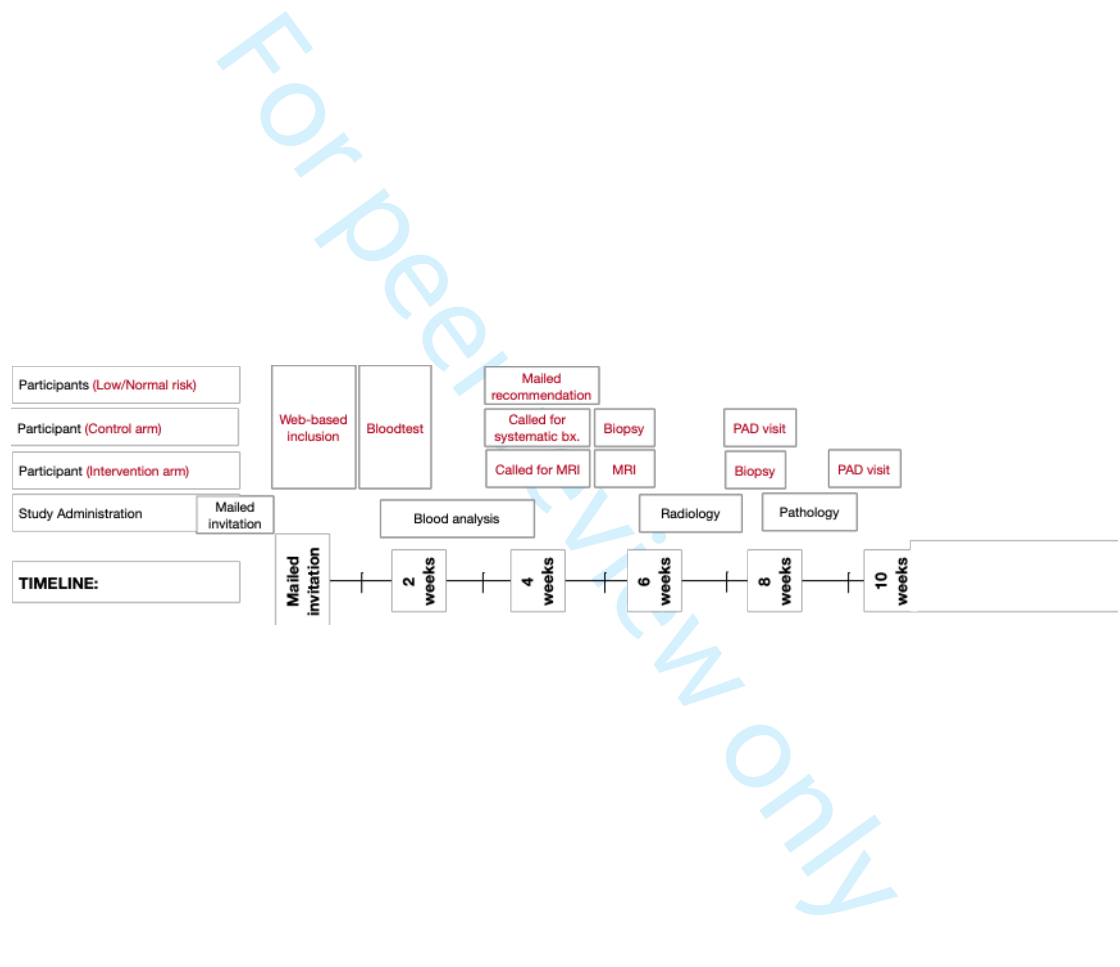
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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	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
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-7
	2b	Specific objectives or hypotheses	8-9
Methods			
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
Randomisation:			
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	-

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



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
Administrative information		
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)
Introduction		
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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9			
10	Methods: Participants, interventions, and outcomes		
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			
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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			
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29		N/A	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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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
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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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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			
19	Blinding	N/A	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how
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	
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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
51
52
53 Declaration of 551 Financial and other competing interests for principal investigators for
54 interests the overall trial and each study site
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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
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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	Appendices		
18			
19	Informed consent	Appendix	Model consent form and other related documentation given to
20	materials	xxix	participants and authorised surrogates
21			
22			
23	Biological	N/A	Plans for collection, laboratory evaluation, and storage of biological
24	specimens		specimens for genetic or molecular analysis in the current trial and for
25			future use in ancillary studies, if applicable
26			

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

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.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-027816.R2
Article Type:	Protocol
Date Submitted by the Author:	13-May-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,
Primary Subject Heading:	Urology
Secondary Subject Heading:	Diagnostics
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.

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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 1st 2018 to June 1st 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

62 and by media.

63 **Registration details**

64 ClinicalTrials.gov: NCT03377881

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

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

79 **3. Trial identifier**

80 ClinicalTrials.gov Identifier: NCT03377881

81 **4. Introduction**

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

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

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2
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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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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11 126 However, using traditional systematic biopsies for diagnosis,
12 127 approximately half of diagnosed cancers are low-risk tumours using the same
13 128 main cut-off for biopsy as the ERSPC trial (PSA=3ng/ml) [6,7]. It has been
14 129 shown that men with low-risk tumours treated without curative intent have the
15 130 same survival as men in the background population[8], illustrating the large
16 131 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 ≥ 7) and simultaneously
25 136 decreasing the number of low-grade tumours (Gleason Score ≤ 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].
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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].

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 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 ≥ 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 ≥ 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 ≥ 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-

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3 246 MR-TBx) has non-inferior sensitivity for detecting clinically significant
4
5 247 cancer (ISUP grade group ≥ 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 ≥ 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 ≥ 2) and reduces the number of MRI
18
19 255 examinations and performed biopsies compared to a diagnostic
20
21 256 pathway using PSA ≥ 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 ≥ 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 ≥ 3) and targeted
45
46 270 biopsies (S3M+TBx) to a diagnostic pathway using systematic biopsies in
47
48 271 men with PSA ≥ 3 ng/ml (PSA+SBx) with respect to number of diagnosed
49
50 272 clinically significant cancer (ISUP grade group ≥ 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
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 ≥ 3 ng/ml or PSA ≥ 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 criteria**

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) e.g. 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 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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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 19 340 **5.4.5 Technology**

20 21 341 **Cut-offs for performing the STHLM3 test**

22
23 342 The STHLM3 test will be performed for men with a PSA ≥ 1.5 ng/ml

24 25 343 **Cut-offs for entering randomization**

26
27 344 Participants with PSA ≥ 3.0 ng/ml or STHLM3-test $\geq 11\%$ risk of Gleason
28 Score ≥ 7 cancer will be randomized and offered to undergo either MR or
29 systematic biopsies (See Process description).
30 345
31 346

32 33 347 **MRI technology**

34 35 348 *Location and MRI equipment*

36
37 349 Capio St Görans Hospital: General Electric, Architect, 3T
38
39 350 Globen Unilabs Healthcare: Siemens Magnetom Aera 1.5T

40 41 351 *Patient preparations*

42
43 352 Refraining from sexual activity with ejaculation 3 days prior to examination
44
45 353 Fasting patient 6 h
46
47 354 Minimal preparation enema prior to examination
48
49 355 Antispasmodic agent (Glucagon) just before the examination

50 51 356 *MRI Protocol*

52
53 357 A short (14 minutes) MRI protocol will be used. A detailed description is
54
55 358 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.
5
6
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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.
15
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18

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
24
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
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34 375 *Fusion biopsy technology*

35 376 *Brand/models*

36
37 377 BK Medical (BK Ultrasound ; www.bkultrasound.com/bk-medical/fusion)
38
39 378 The BK Medical fusion system is the only fusion device compatible with BK
40 379 Medicals ultrasound devices, used by the urology departments participating in
41 380 the study. The system represents a second-generation ultrasound system
42 381 with integrated MRI Fusion. MRI data is imported through HIPAA-compliant
43 382 PACS connection with the local radiology department.
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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
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1
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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
46 408 **Pathology**

47
48 409 Pathology is centralized to Unilabs/Capio St Görans hospital. Dr Axel
49
50 410 Glaessgen is responsible for the integrity of analyses of pathological
51
52 411 specimen. 2-3 uro-pathologists at dr Glaessgens department assesses all
53
54 412 pathological specimen with intermittent cross-validation between them.
55
56 413 Pathology preparation and reporting follow ISUP 2014 guidelines.

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

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 ≥ 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*

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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.

450 **5.6. Participant timeline**

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

453 **5.7. Sample size**

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

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

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

468 **Primary contrast**

469 Simulating 1000 trials (by bootstrapping from the STHLM3 data) under the
470 assumptions outlined in the preceding section 303 men need to be biopsied in
471 the SBx arm based on PSA ≥ 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 ≥ 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 ≥ 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.

18 480 **5.8. Recruitment and Process Description**

20 481 The STHLM3-MR Phase 2 will use existing solutions developed and
21 482 optimized in the previous studies STHLM3 and STHLM3-MR Phase 1 where
22 483 all major components of the process have been tested. First, participants will
23 484 follow the *paired design study process* where inclusion, blood-test and
24 485 delivery of recommendation letter is performed. Men with increased risk of
25 486 high-grade prostate cancer then enter the *randomized study process*, where
26 487 extended work-up including biopsies are performed.

34 488 **5.9. Data Collection, management, analysis**

37 489 **5.9.1. Data collection**

39 490 Primary data sources are

- 41 491 i. clinical variables collected from laboratory referral
- 42 492 ii. biopsy referrals and reports
- 43 493 iii. pathology reports
- 44 494 iv. MRI reports
- 45 495 v. blood concentrations of kallikreins, MSMB, MIC1, SNPs

46 496 Collection of i. – iv. is performed by study nurses (C Cavalli-Björkman) on
47 497 a weekly basis from participating urology sites, participating radiologists. For
48 498 v., this is digitally transferred from Karolinska University Laboratory.

54 499 **5.9.2. Data management**

56 500 Data is collected, entered, coded and stored at Department of Medical
57 501 Epidemiology and Biostatistics, Karolinska Institutet. Data is entered by Study
58 502 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. 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.

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**

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27
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29
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31
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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
48

49 50 51 578 **11. References**

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53 579 1 Ferlay J, Soerjomataram I, Dikshit R, *et al.* Cancer incidence and
54 580 mortality worldwide: Sources, methods and major patterns in
55 581 GLOBOCAN 2012. *Int J Cancer* 2014;:n/a–n/a. doi:10.1002/ijc.29210
56
57 582 2 Mistry K, Cable G. Meta-analysis of prostate-specific antigen and digital
58 583 rectal examination as screening tests for prostate carcinoma. *J Am Board*
59 584 *Fam Pract* 2003;**16**:95–101.

- 1
2
3 585 3 Nordström T, Aly M, Clements MS, *et al.* Prostate-specific antigen (PSA)
4 586 testing is prevalent and increasing in Stockholm County, Sweden,
5 587 Despite no recommendations for PSA screening: results from a
6 588 population-based study, 2003-2011. *Eur Urol* 2013;**63**:419–25.
7 589 doi:10.1016/j.eururo.2012.10.001
8
9
10 590 4 Schröder FH, Hugosson J, Roobol MJ, *et al.* Prostate-cancer mortality at
11 591 11 years of follow-up. *N Engl J Med* 2012;**366**:981–90.
12 592 doi:10.1056/NEJMoa1113135
13
14 593 5 Hugosson J, Carlsson S, Aus G, *et al.* Mortality results from the Göteborg
15 594 randomised population-based prostate-cancer screening trial. *Lancet*
16 595 *Oncol* 2010;**11**:725–32. doi:10.1016/S1470-2045(10)70146-7
17
18 596 6 Nationell kvalitetsrapport för diagnosår 2012. Regionala Cancercentrum i
19 597 Samverkan 2013. [http://npcr.se/wp-content/uploads/2013/04/20131121-](http://npcr.se/wp-content/uploads/2013/04/20131121-NPCR-Rapport-2012.pdf)
20 598 [NPCR-Rapport-2012.pdf](http://npcr.se/wp-content/uploads/2013/04/20131121-NPCR-Rapport-2012.pdf)
21
22 599 7 Grönberg H, Adolfsson J, Aly M, *et al.* Prostate cancer screening in men
23 600 aged 50-69 years (STHLM3): a prospective population-based diagnostic
24 601 study. *Lancet Oncol* 2015;**16**:1667–76.
25
26 602 8 Rider JR, Sandin F, Andrén O, *et al.* Long-term outcomes among
27 603 noncuratively treated men according to prostate cancer risk category in a
28 604 nationwide, population-based study. *Eur Urol* 2013;**63**:88–96.
29 605 doi:10.1016/j.eururo.2012.08.001
30
31 606 9 Loeb S, Bjurlin MA, Nicholson J, *et al.* Overdiagnosis and overtreatment
32 607 of prostate cancer. *Eur Urol* 2014;**65**:1046–55.
33 608 doi:10.1016/j.eururo.2013.12.062
34
35 609 10 Soares R, Di Benedetto A, Dovey Z, *et al.* Minimum 5-year follow-up of
36 610 1138 consecutive laparoscopic radical prostatectomies. *BJU Int*
37 611 2015;**115**:546–53. doi:10.1111/bju.12887
38
39 612 11 Aly M, Dyrdak R, Nordström T, *et al.* Rapid increase in multidrug-resistant
40 613 enteric bacilli blood stream infection after prostate biopsy-A 10-year
41 614 population-based cohort study. *Prostate* 2015;**75**:947–56.
42 615 doi:10.1002/pros.22979
43
44 616 12 Barrett T, Turkbey B, Choyke PL. PI-RADS version 2: what you need to
45 617 know. *Clin Radiol* 2015;**70**:1165–76. doi:10.1016/j.crad.2015.06.093
46
47 618 13 Barentsz JO, Weinreb JC, Verma S, *et al.* Synopsis of the PI-RADS v2
48 619 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging
49 620 and Recommendations for Use. *Eur Urol* 2015;**69**:41–9.
50 621 doi:10.1016/j.eururo.2015.08.038
51
52 622 14 Weinreb JC, Barentsz JO, Choyke PL, *et al.* PI-RADS Prostate Imaging -
53 623 Reporting and Data System: 2015, Version 2. *Eur Urol* 2015;**69**:16–40.
54 624 doi:10.1016/j.eururo.2015.08.052
55
56
57
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59
60

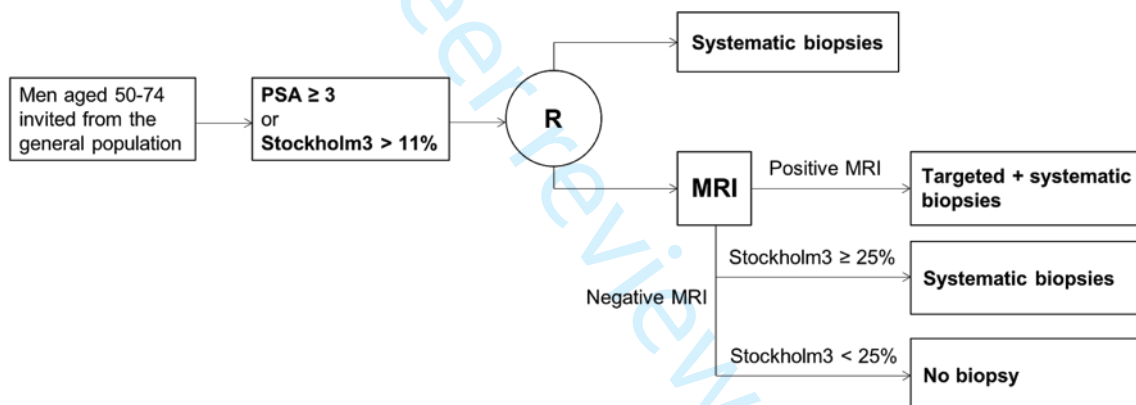
- 1
2
3 625 15 Muller BG, Shih JH, Sankineni S, *et al.* Prostate Cancer: Interobserver
4 626 Agreement and Accuracy with the Revised Prostate Imaging Reporting
5 627 and Data System at Multiparametric MR Imaging. *Radiology*
6 628 2015;**277**:741–50. doi:10.1148/radiol.2015142818
- 8
9 629 16 Ahmed HU, El-Shater Bosaily A, Brown LC, *et al.* Diagnostic accuracy of
10 630 multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a
11 631 paired validating confirmatory study. *Lancet* Published Online First: 19
12 632 January 2017. doi:10.1016/S0140-6736(16)32401-1
- 14 633 17 Moore CM, Robertson NL, Arsanious N, *et al.* Image-guided prostate
15 634 biopsy using magnetic resonance imaging-derived targets: a systematic
16 635 review. *Eur Urol* 2013;**63**:125–40. doi:10.1016/j.eururo.2012.06.004
- 18 636 18 Sonn GA, Margolis DJ, Marks LS. Target detection: magnetic resonance
19 637 imaging-ultrasound fusion-guided prostate biopsy. *Urol Oncol*
20 638 2014;**32**:903–11. doi:10.1016/j.urolonc.2013.08.006
- 23 639 19 Schoots IG, Roobol MJ, Nieboer D, *et al.* Magnetic Resonance Imaging-
24 640 targeted Biopsy May Enhance the Diagnostic Accuracy of Significant
25 641 Prostate Cancer Detection Compared to Standard Transrectal
26 642 Ultrasound-guided Biopsy: A Systematic Review and Meta-analysis. *Eur*
27 643 *Urol* 2014;**68**:438–50. doi:10.1016/j.eururo.2014.11.037
- 30 644 20 Kasivisvanathan V, Rannikko AS, Borghi M, *et al.* MRI-Targeted or
31 645 Standard Biopsy for Prostate-Cancer Diagnosis. *N Engl J Med*
32 646 2018;:NEJMoa1801993. doi:10.1056/NEJMoa1801993
- 34 647 21 Baco E, Ukimura O, Rud E, *et al.* Magnetic resonance imaging-transectal
35 648 ultrasound image-fusion biopsies accurately characterize the index
36 649 tumor: correlation with step-sectioned radical prostatectomy specimens in
37 650 135 patients. *Eur Urol* 2015;**67**:787–94. doi:10.1016/j.eururo.2014.08.077
- 40 651 22 Arnsrud Godtman R, Holmberg E, Lilja H, *et al.* Opportunistic Testing
41 652 Versus Organized Prostate-specific Antigen Screening: Outcome After 18
42 653 Years in the Göteborg Randomized Population-based Prostate Cancer
43 654 Screening Trial. *Eur Urol* 2014;**68**:354–60.
44 655 doi:10.1016/j.eururo.2014.12.006
- 46 656 23 Thompson IM, Pauler DK, Goodman PJ, *et al.* Prevalence of prostate
47 657 cancer among men with a prostate-specific antigen level. *N Engl J Med*
48 658 2004;**350**:2239–46. doi:10.1056/NEJMoa031918
- 51 659 24 Loeb S, Vellekoop A, Ahmed HU, *et al.* Systematic review of
52 660 complications of prostate biopsy. *Eur Urol* 2013;**64**:876–92.
53 661 doi:10.1016/j.eururo.2013.05.049
- 55 662 25 Nordström T, Bratt O, Örtengren J, *et al.* A population-based study on the
56 663 association between educational length, prostate-specific antigen testing
57 664 and use of prostate biopsies. *Scand J Urol* 2016;**50**:104–9.
58 665 doi:10.3109/21681805.2015.1113200

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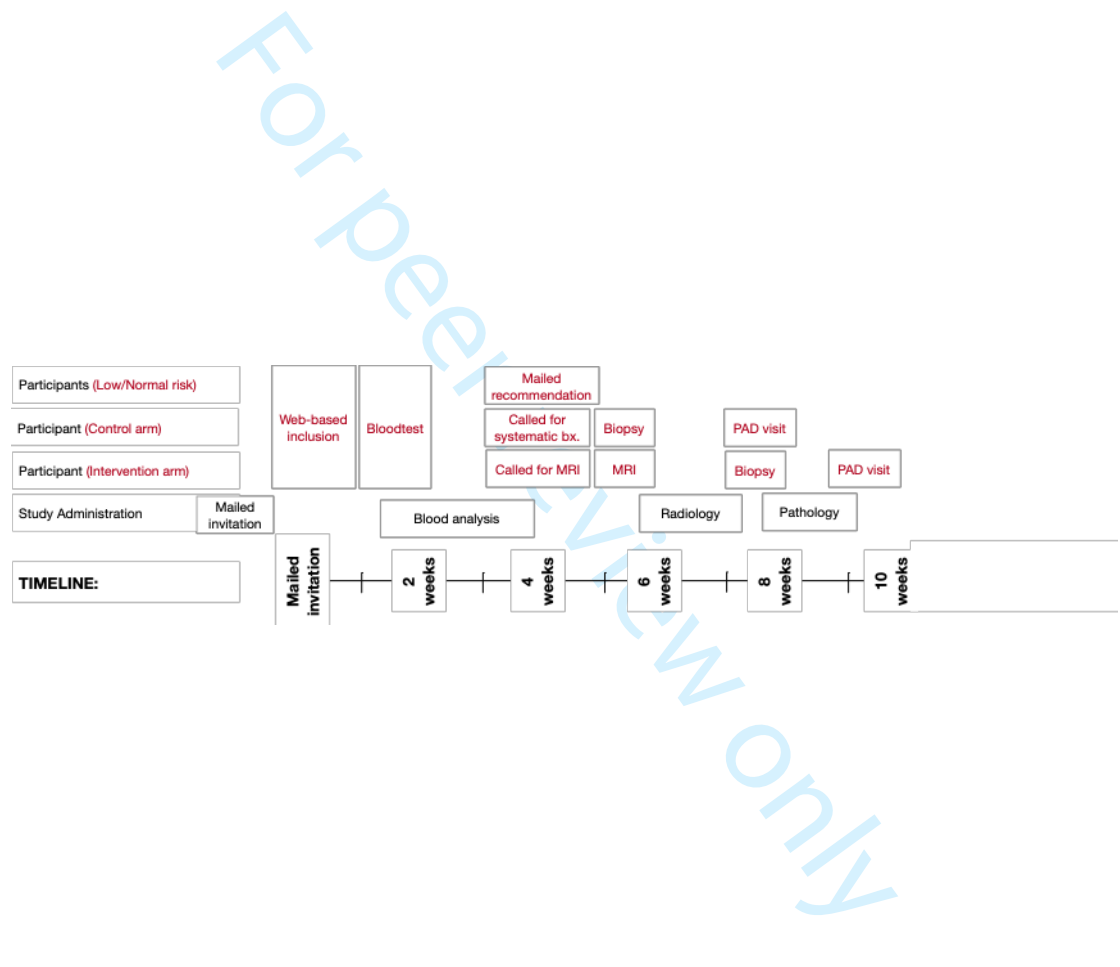
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For peer review only



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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
Title and abstract			
	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
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-7
	2b	Specific objectives or hypotheses	8-9
Methods			
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
Randomisation:			
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	-

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



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
Administrative information		
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)
Introduction		
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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10	Methods: Participants, interventions, and outcomes		
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			
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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)
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29		N/A	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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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
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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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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			
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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			
19	Blinding	N/A	Who will be blinded after assignment to interventions (eg, trial
20	(masking)		participants, care providers, outcome assessors, data analysts), and
21			how
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 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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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
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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	Appendices		
18			
19	Informed consent	Appendix	Model consent form and other related documentation given to
20	materials		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			

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