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Cost-effectiveness of adding a non-invasive acoustic rule-out test in the evaluation of patients with symptoms suggestive of coronary artery disease. Rationale and design of the prospective, randomized, controlled, parallel-group multicenter FILTER-SCAD trial.

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Trial design

Cost-effectiveness of adding a non-invasive acoustic rule-out test in the evaluation of patients with symptoms suggestive of coronary artery disease. Rationale and design of the prospective, randomized, controlled, parallel-group multicenter FILTER-SCAD trial.

Short title: The FILTER-SCAD Trial Design

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ABSTRACT

Introduction
Most patients with symptoms suggestive of chronic coronary syndrome (CCS) have no obstructive coronary artery disease (CAD) and better selection of patients to be referred for diagnostic tests is needed. The CAD-score is a non-invasive acoustic measure that, when added to pre-test probability of CAD, has shown good rule-out capabilities. We aimed to test whether implementation of CAD-score in clinical practice reduces the use of diagnostic tests without increasing major adverse cardiac events (MACE) rates in patients with suspected CCS.

Methods and analysis
FILTER-SCAD is a randomized, controlled, multicenter trial aiming to include 2000 subjects ≥30 years without known CAD referred for outpatient assessment for symptoms suggestive of CCS. Subjects are randomized 1:1 to either the control group; standard diagnostic examination (SDE) according to current guidelines, or the intervention group; SDE plus a CAD-score. The subjects are followed for 12 months for the primary endpoint of cumulative number of diagnostic tests and a safety endpoint (MACE). Angina symptoms, quality of life, and risk factor modification will be assessed with questionnaires at baseline, 3 months, and 12 months after randomization. The study is powered to detect superiority in terms of a reduction of ≥15% in the primary endpoint between the two groups with a power of 80%, and non-inferiority on the secondary endpoint with a power of 90%. The significance level is 0.05. The non-inferiority margin is set to 1.5%. Randomization began October 2019. Follow-up is planned to be completed December 2022.

Ethics and dissemination
The study has been approved by the Danish Medical Agency (2019024326.), Danish National Committee on Health Research Ethics (H-19012579), and Swedish Ethical Review Authority (Dnr 2019-04252). All patient participating in the study will sign an informed consent. All study results will be attempted published as soon as possible.

Registration details
ClinicalTrials.gov identifier: NCT04121949.
STRENGTH AND LIMITATIONS OF THIS STUDY

- Multicenter randomized controlled trial of a novel acoustic-based risk stratification CAD-score for coronary artery disease.
- First randomized controlled trial to investigate the safety of CAD-score and the impact of the CAD-score in clinical practice.
- Study design follows newest international guidelines on Chronic Coronary Syndrome.
- The study is unblinded as the treatment is based on the value of the CAD-score.

KEYWORDS (3-10 keywords)
Stable Angina Pectoris, Stable Coronary Artery Disease, Chronic Coronary Syndrome, Acoustic Diagnostic Device, CAD-score, Diamond-Forrester Score, Pre-test Probability.
Trial design

ABBREVIATIONS

ACC/AHA = American College of Cardiology/American Heart Association

BMI = Body mass index

CABG = Coronary artery bypass graft

CAD = Coronary artery disease

CCS = Chronic coronary syndrome

CCTA = Coronary computed tomographic angiography

CEC = Clinical event committee

CMRI = Cardiac magnetic resonance imaging

ECG = Electrocardiogram

eCRF = electronic Case Report Form

ESC = European Society of Cardiology

GP = General Practitioner

HF = Heart Failure

ICA = Invasive coronary angiography

ICD = Implantable Cardioverter Defibrillator

IQR = Interquartile range

ITT = Intention-to-treat

MACE = Major adverse cardiac events

MI = Myocardial infarction

MPI = myocardial perfusion imaging

NICE = National Institute for Health and Care Excellence
Trial design

NIT = Non-invasive test

NPV = Negative predictive value

PCI = Percutaneous coronary intervention.

PTP = Pre-test probability

QOL = Quality of life

RCT = Randomized clinical trial

REDCap = Research Electronic Data Capture

SAE = Serious adverse events

SAQ = Seattle Angina Questionnaire

SDE = Standard diagnostic examination

SPECT = Single-photon emission computed tomography

UAP = Unstable angina pectoris
Trial design

BACKGROUND

Chest discomfort is a common symptom leading to cardiological assessment for chronic coronary syndrome (CCS) (1). According to European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines, the diagnostic work-up should be based on the pre-test probability (PTP) of obstructive coronary artery disease (CAD) estimated from sex, age and symptoms (2,3), as originally suggested by the Diamond-Forrester model (4,5). However, in clinical practice PTP models have limited sensitivity and specificity. In recent large studies, less than 10% of patients referred with symptoms suggestive of CAD needed revascularization, and their prognosis was good (6,7). The addition of risk factors to improve PTP precision have minor impact on prediction abilities (6,8). The current test strategy exposes patients to unnecessary procedure-related risks, medication, and radiation and the costs of diagnostic work-up may be unnecessarily high. Consequently, better methods of identifying patients with low probability of obstructive CAD and no need for diagnostic testing are needed.

The CAD-score is a risk stratification score for CAD obtained by the non-invasive acoustic device, CADScor®System (Acarix A/S), which has shown good rule-out capabilities in patient with suspected CAD (9). The device is approved for medical use, and mentioned in a Medtech innovation briefing in the NICE-guidelines as a rule-out test early in the diagnostic CAD work up before CCTA (10). However, the CAD-score has never been tested as a rule-out test in a clinical setting. Hence, the FILTER-SCAD trial will examine whether adding CAD-score to the standard diagnostic work-up reduces the number of diagnostic tests and associated health care costs without compromising safety in the outpatient assessment of patients with symptoms suggestive of CCS.
Trial design

OBJECTIVES

The primary objective of the FILTER-SCAD trial is to compare an initial diagnostic strategy based on a PTP according to guidelines plus CAD-score to a standard PTP-guided strategy when selecting patients with suspected CSS for diagnostic testing. The key secondary objective is to assess whether this strategy is non-inferior in terms of major adverse cardiac events (MACE). We hypothesized that an initial rule-out strategy guided by a PTP plus a CAD-score will reduce overall number of diagnostic procedures without compromising the safety when compared with a PTP-guided strategy alone over a follow-up period of 1 year.
Trial design

METHODS

Trial design

*Figure 1* shows an overview of the study design. The FILTER-SCAD trial is an investigator-initiated, prospective, randomized, controlled, parallel-group, multicenter trial planned to include 2000 subjects ≥30 years of age without known CAD referred for outpatient evaluation of symptoms suggestive of CCS at five-six sites; four-five in Denmark and one in Sweden. The protocol is available as supplementary material.

Study population

Study subjects are men and women ≥30 years of age without known CAD referred for evaluation of symptoms suggestive of suspected CAD in planned 5-6 cardiology outpatient clinics in Denmark and Sweden. Inclusion and exclusion criteria are listed in *table 1*.

Randomization and blinding

Randomization is done in a randomization module in the electronic CRF (eCRF) and will be unblinded as the physician must act on the given CAD-score and PTP. Eligible subjects are allocated in a 1:1 manner to control or intervention group using permuted block randomization stratified by study site and PTP-value (very low vs. low-intermediate) by a computer-generated allocation table.

The study was designed based on the 2013 ESC guidelines on the management of stable coronary artery disease (11). However, the ESC guidelines were updated in 2019 downgrading the PTP for obstructive CAD considerably (2), and the FILTER-SCAD trial protocol was adjusted to be in accordance with these state-of-the-art recommendations. The first 78 subjects in the FILTER-SCAD trial were randomized according to the first protocol based on the 2013 ESC guidelines. The remaining subjects will be enrolled in consistency with the updated protocol.

Standard diagnostic examination

Subjects randomized to the control group will undergo a standard diagnostic examination (SDE) according to ESC 2019 guidelines including clinical examination, PTP assessment based on age, sex and type of angina, risk factor assessment and echocardiography (2). The echocardiography will be done during the clinical investigation for CAD, but not necessarily on the day of
Trial design

randomization. The SDE will be followed by non-invasive tests (NIT) if indicated (figure 2) according to current European guidelines on CCS (2); Patients with very low PTP ≤ 5% should not receive further diagnostic testing, in patients with PTP 6-15% NIT may be considered based on the overall clinical likelihood, and patients with PTP > 15% should be offered NIT as standard first choice of diagnostic test. Invasive coronary angiography (ICA) may be offered to selected patients with very high clinical likelihood, but no patients should receive ICA based on their PTP alone.

**Intervention (CAD-score)**

Patients randomized to the intervention group will receive a CAD-score measurement in addition to the SDE. The CAD-score is measured using the acoustic device CADScor® System (Acarix A/S).

The CAD-score is a risk stratification score scaled from 0 to 99 for obstructive CAD measured from advanced analysis of sounds originating from blood flow turbulence in the coronary arteries and myocardial motion combined with the patients age, sex, and blood pressure (9,12). The measurements are done by a non-invasive acoustic device, CADScor® System (Acarix A/S), which has shown good rule-out capabilities in patient with suspected CAD (9).

During a three minutes period with the patient lying in supine position, a transcutaneous recording of heart sounds is done by a microphone attached by a patch at the left fourth intercostal space (IC4) (13). Four times during the recording, the patient is asked to hold his/her breath for eight seconds. From eight acoustic features, a fully automatic algorithm estimates (software version 3.2) an acoustic score which combined with the risk factors sex, age, and hypertension by logistic regression results in the CAD-score (9,13). The CAD-score measurements are done by specially trained study staff. If the measurement fails, up to four measurement are attempted.

Success of the new strategy depends critically on the physician’s knowledge of strength and weakness of the CAD-score measure. At study start, each site will be trained in the CAD-score background literature and method. The training will be repeated after 3-6 months after enrollment of first patient. Moreover, every physician is provided written information about the study and the CAD-score. The training of the physicians is intended to made physicians comfortable with the CAD-score and its strengths and weaknesses.
Trial design

**Further diagnostic pathway**

All treating physicians are trained in the study protocol including the CAD-score. The physician is provided with a decision sheet with PTP, CAD-score and the recommended further diagnostic pathway (NIT or no further assessment) (figure 1). Based on the available information, the physician decides whether to follow the recommended diagnostic pathway or not. A crossover could be justified by the presence of cardiac risk factors with a higher perceived clinical likelihood.

**Diagnostic tests for both intervention and control group**

Patients with intermediary-high PTP in the control group or high CAD-score > 20 in the intervention group are referred for further standard diagnostic testing including NIT and ICA, and this is done as standard procedure of each site. All decisions regarding diagnostic testing, including choice of testing modality, and medical/surgical treatment of the patient is done at the discretion of the treating physician, and is not a part of the study protocol.

**Study periods**

A run-in period with an expected duration of three months at each site is intended to serve as a training period where the study staff and attending cardiologists will be made familiar with performing and interpreting the CAD-score measurement by obtaining CAD-score around 50-100 subjects at each participating site.

The planned duration of the study is 24 months; 12 months for the inclusion period, defined as first patient first visit to last patient first visit, for the main study starting after the run-in period, and approximately 12 months for the follow-up period. However, due to the COVID-19 pandemic and associated study delay, the enrollment period is extended with 15 months. Hence, follow-up is planned to be completed December 2022.

End of study will be when all the following have occurred: 1) at least 2000 patients have been randomized, and 2) 12±1 month (1 year) have elapsed since the last patient was randomized.

The study population will be followed for one year after randomization.

**Endpoints**

*Primary endpoint*
Trial design

The primary endpoint defined as the cumulative number of NIT and invasive procedures after one year. NITs include exercise electrocardiogram (ECG), Coronary computed tomographic angiography (CCTA), Rubidium-PET CT, myocardial perfusion imaging (MPI), Cardiac magnetic resonance imaging (CMRI), and stress echocardiography. Invasive procedures include ICA only.

If the analysis shows a significant difference in the primary endpoint, a cost-effectiveness analysis will be conducted alongside the trial. The potential cost-effectiveness analysis will be based on information from the trial, as well as data from health registers. The register linkage will provide information at individual level on health care utilization, including general practice, medication, etc.; as well as labour market consequences and other societal costs. The cost-effectiveness analysis will apply two different effectiveness measures: procedures avoided, cf. the primary endpoint, and quality adjusted life-years (QALY’s) based on the reporting of EQ-5D in the trial (14).

Secondary endpoints
The key secondary endpoint is the safety endpoint MACE; a combined endpoint of all-cause mortality, non-fatal myocardial infarction (MI), hospitalization for unstable angina pectoris (UAP), heart failure (HF), ischemic stroke and major complication of cardiovascular procedures or diagnostic testing at one year after end of randomization. An independent clinical event committee (CEC) will adjudicate MACE endpoints blinded to the allocated intervention. Definitions of all-cause mortality, MI, UAP, HF and ischemic stroke follow the ACC/AHA description of key data elements and definitions for cardiovascular endpoint events in clinical trials (15). Major complication of cardiovascular procedures or diagnostic testing is defined as major bleeding, renal failure, stroke, or anaphylaxis that occurred within 72 hours in accordance with the PROMISE Trial’s definition (7). Other individual secondary endpoints are 1) clinical endpoints: all-cause mortality, MI, hospitalization for UAP, HF and ischemic stroke, medication, time to CAD diagnosis, repeat referrals, and bleeding requiring hospitalization assessed one year after randomization, 2) procedure related endpoints: Numbers of first NITs, numbers of ICA, number of downstream tests (NITs and ICAs done after the first NIT), contrast dose, radiation dose, and adverse events related to the CAD-score measurement at one year after randomization, and 3) questionnaire endpoints: Change in chest pain assessed by the Seattle Angina
Trial design

Questionnaire (SAQ) (16), quality of life assessed by the EuroQol-5D (17), and lifestyle assessed by the HeartDiet Questionnaire (18). Questionnaires are collected at baseline, three months, and 12 months after randomization.

All endpoints are listed in supplementary table 1.

Data handling

Data is collected in the eCRF REDCap (Research Electronic Data Capture 10.3.3(19,20)) by trained study staff. Blood samples, ECG, and echocardiography data at baseline are standard test for ambulatory patients and will be collected from medical records and entered in the eCRF. Data on diagnosis, medications, diagnostic testing, repeat referrals, safety endpoints, and bleeding requiring hospitalization will be collected. All diagnostic test will be classified as positive, negative or inconclusive. This will be done at each individual site according to local criteria/guidelines.

Monitoring will be carried out by an external monitor and will include 100% monitoring of all potential serious adverse events (SAE) related to the CAD-score measurement, informed consent forms and power of attorneys, and 20% monitoring of inclusion and exclusion criteria.

Statistical methods

The study is powered to detect superiority in terms of a reduction of $\geq 15\%$ in the cumulative number of diagnostic tests (primary endpoint) between the intervention and control groups with a power of 80% and a significance level of 0.05 with a sample size of 521 subjects in each randomization group. The study is powered for non-inferiority on the secondary safety endpoint (MACE) with a power of 90% and a significance level of 0.05 with a sample size of 1914 subjects (957 in each randomization group). The non-inferiority margin is set to 1.5%.

The final sample size was chosen to be 2000 patients (1000 in each randomization group), allowing for a 4% loss to follow-up and drop-out. The power calculation remains unchanged after updating the study protocol to reflect the latest 2019 ESC guidelines on CCS.

The main analysis will be intention-to-treat (ITT) analysis. Analysis of the cumulative numbers of diagnostic test will be done with Poisson based test and visualized by Nelson-Aalen nonparametric estimator. The secondary safety endpoint MACE will be analyzed using a continuity-corrected modification of the Wilson’s score method.
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Pre-specified subgroup analysis will be performed investigating the following subgroups: PTP (≤5% vs. 5-15% vs. >15%), PTP (≤5% vs. >5%), PTP (≤5% vs. 5-15%), age (<65 years vs. ≥65 years), sex (male vs. female), hypertension (yes vs. no), dyslipidemia (yes vs. no), diabetes mellitus (yes vs. no), smoking (yes vs. no), family history of CAD (yes vs. no), and BMI (<30 kg/m2 vs. ≥30 kg/m2). An interim analysis for futility will be done after enrollment of at least 20% of the expected 2000 patients. We expect approximately 25% of the population to have low PTP or CAD-score ≤ 20 (table 2). The study is considered futile if more than 90% of the overall population undergo further NIT or ICA after the initial SDE.

All statistical tests will be made using statistical software R and will have a two-sided significance level of 0.05.

Trial registration

The trial is registered on ClinicalTrials.gov (identifier: NCT04121949).

Patient and public involvement

Patients and the public were not involved in the phase of the study, as the study addresses the physician’s decision-making in the diagnostic strategy for ischemic heart disease. However, the results will be relevant for both patients and the general public, and the result will be attempted published through patient organizations and public media. The study results will be distributed directly to the study participants.
ETHICS AND DISSEMINATION

The FILTER-SCAD trial is conducted in compliance to the principles of the Declaration of Helsinki of the World Medical Association, and laws of Denmark and Sweden. The study has been approved by the Danish Medical Agency (2019024326.), Danish National Committee on Health Research Ethics (H-19012579), and Swedish Ethical Review Authority (Dnr 2019-04252). All patient participating in the study will sign an informed consent. All study results will be attempted published as soon as possible.
RESULTS

Three study sites are currently enrolling. Our preliminary baseline data with of the first 300 enrolled subjects shows successful randomization with even distribution of baseline characteristic between the two groups including sex, age, and PTP. First subject was randomized on October 22, 2019, and by December 20, 2020 489 patients (24% of planned total) have been enrolled. Follow-up is planned to be completed December 2022. Table 2 shows the baseline characteristics on the first 300 (59% women) with a median age of 63 years IQR (53.00-72.00) years and. Among the enrolled patients 16.3% were classified as low PTP (≤5%), and 42.6% of the intervention group had a CAD-score ≤ 20. Hence our preliminary data confirm the potential of reducing the number of patients referred to NIT with up to one third by adding a CAD-score to the SDE in patients with suspected CCS.
DISCUSSION

The FILTER-SCAD trial will investigate whether adding a CAD-score to the SDE is a feasible way to reduce use of excess diagnostic testing without compromising safety in the assessment of patients with symptoms suggestive of CCS.

CAD-score probabilities

The diagnostic performance of the CAD-score has been thoroughly examined (9,12,13).

In a retrospective pooled study of 2245 patients undergoing CCTA the diagnostic sensitivity and specificity for obstructive CAD of the CAD-score were 88.7% and 41.5%, respectively, with ≥ 50% stenosis on ICA as gold standard (12). In this population with a 9.4% prevalence of obstructive CAD verified on ICA, the negative predictive value (NPV) was 96% at a CAD-score cut-off ≤ 20, which stresses the potential of the CAD-score as a rule-out test for obstructive CAD (12). In addition, the CAD-score’s capability of reclassifying patients was simulated in the study; by adding a CAD-score to the patients with intermediate PTP of obstructive CAD, one third of the patients were downgraded to the low likelihood of CAD group, and might accordingly have been ruled-out at that step without any further excess NIT, potentially reducing the accompanying risks and costs (12). This reclassification only slightly insignificantly increased the CAD-prevalence in the low-risk group from 3.1% to 4.0% (12). The previous CAD-score studies are based on the former ECS 2013 PTP. However, the non-invasive sound-based CAD-score tool, remains effective as a rule-out test also following implementation of the adjusted PTP in the recent 2019 ESC guidelines on CCS; four out of 10 patients evaluated by the latest PTP were reclassified to low likelihood of obstructive CAD after adding a CAD-score (21). The FILTER-SCAD trial will, to our knowledge, be the first study to test the CAD-score’s ability in a clinical setting as a rule-out tool in patients with suspected CCS, testing both the efficacy and the safety in a randomized prospective study. Thereby, the current study may enhance and simplify the diagnostic pathway for patients referred with suspected CCS, possibly allowing a reduction in excess use for NIT and ICA.

Safety

We are aware of the risk of incorrectly ruling out patient with CAD with a (false negative) low CAD-score. As for all other diagnostic tests, there will always be a risk of false negative test; Sensitivity of exercise stress echocardiography, exercise stress SPECT, and CCTA are 80-85%,
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73-92%, and 95-99%, respectively, and false negative test will occur (11). However, these tests are more comprehensive and expensive than a simple CAD-score measurement. Also, current ESC guidelines recommend no further investigation with NIT in patients with PTP ≤ 5%. Thus, guidelines accept ruling out a proportion of patient with unacknowledged obstructive CAD to avoid large numbers of false positive tests and unnecessary exposure of patients to diagnostic test and accompanying risk. Moreover, the prognosis of patients referred with symptoms suggestive of CSS appears good (7,22,23), especially among the patients classified with low PTP (6), but also in both suspected CCS and confirmed CAD (24). The good prognosis is independent of treatment with percutaneous coronary intervention (PCI) or optimal medical therapy including antianginal medication (25).

In the FILTER-SCAD study, risks are mitigated in several ways; The participants are contacted by the study nurse after three months and one year, where angina symptoms are assessed. In case of worsening of symptoms, the nurse can contact the treating physician who can decide to schedule a follow-up visit. Also, the patients are instructed to contact the study nurse or their general practitioner if their symptoms continues or worsens. Finally, the treating physician may choose to disregard the recommended action according to protocol and cross the patient over to NIT despite a CAD-score ≤ 20 if e.g. cardiovascular risk factors deemed to increase the patient’s likelihood for CAD, the treating physician require further investigation, or choose to schedule a follow-up visit.

Notably, the CAD-score system is CE-marked and approved for clinical use in patients ≥ 40 years of age, and is stated as a rule-out test early in the diagnostic CAD work up in the NICE-guidelines Medtech innovation briefing (10). Thus, the FILTER-SCAD trial aims to test the implementation of an already approved clinical rule-out device in a clinical setting and its impact as an add-on device in the current diagnostic work up, and not to test the diagnostic accuracy of the device.

Endpoints
The low diagnostic yield of the current work up for patients with suspected CCS has questioned the value of the currently recommended diagnostic test strategy (26–28). Many patients may be exposed to unnecessary procedure-related risks, medication, and radiation without achieving any benefits, and the costs of diagnostic work-up may be unnecessarily high. This study aims to investigate if a CAD-score added as a rule-out test in patients with suspected CCS will reduce
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unnecessary testing and thus increase the cost-effectiveness of the diagnostic workup. Hence, comparison of the cumulative number of NIT and ICA in two groups with and without CAD-score as rule-out test is relevant. Moreover, not compromising safety for patients by adding a CAD-score as a rule-out test is essential. Therefore, a key secondary composite safety endpoint MACE of numbers of all-cause death, myocardial infarction, unstable angina pectoris, heart failure, ischemic stroke, and major complication of cardiovascular procedures or diagnostic within 72 is relevant and will enlighten the accuracy of excluding obstructive disease in patient groups with and without CAD-score measurement.

Another important secondary endpoint is angina symptom control, quality of life and patients’ satisfaction with the diagnostic work up. These are assessed with validated questionnaires (16,17). Other secondary endpoints in the study include medication, time to diagnosis, contrast and radiation dose, and adverse events related to the CAD-score measurement.

CONCLUSION

The FILTER-SCAD trial study will investigate the cost-effectivity and safety in a clinical setting of adding an advanced acoustic tool; the CAD-score as a rule-out test in the diagnostic work up of patients with symptoms suggestive of CCS.

AUTHORS’ CONTRIBUTIONS

EP, SG and KWH designed and initiated the study. LBH, KWH, EP, and SG obtained funding. LBH performed data analysis and wrote the report. All authors approved the final version of the report after revision.
Trial design

COMPETING INTEREST
LHB: None.

KWH: None.

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AUTHORS’ NOTE
The CADScor®System and analysis relating hereto will be offered freely by Acarix A/S.
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Trial design

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Trial design

## TABLES

### Table 1 – Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|-------------------|-------------------|
| - Signed informed consent form. | Related to pre-test likelihood of obstructive CAD: |
| - Male or female, aged 30 years or above. | - Prior non-invasive testing for stable CAD or ICA within 6 months of randomization. |
| - Patients able and willing to comply with the clinical investigational plan. | Related to feasibility of performing a CAD-score measurement: |
| - Symptoms suggestive of stable coronary artery disease. | - Implanted donor heart, mechanical heart, mechanical heart pump. |
| - No history of coronary artery disease (prior MI, PCI or CABG). | - Pacemaker or Cardioverter Defibrillator (ICD). |

**Exclusion criteria**

Related to pre-test likelihood of obstructive CAD:

- Prior non-invasive testing for stable CAD or ICA within 6 months of randomization.

Related to feasibility of performing a CAD-score measurement:

- Implanted donor heart, mechanical heart, mechanical heart pump.
- Pacemaker or Cardioverter Defibrillator (ICD).
- Implanted electronic equipment in the area above and around the heart.
- Significant operation scars, abnormal body shape, fragile or compromised skin in the fourth left intercostal space recording area.
- Receiving same day treatment with nitroglycerine on the day of randomization.

Related to women of childbearing potential:

- Pregnancy.

*The exclusion criteria “Diamond-Forrester score > 85%” was removed after updating the study according to the 2019 ESC guidelines on CCS.*

**Legend:**

- **CAD** = Coronary artery disease
- **CABG** = Coronary artery bypass graft
- **ICA** = Invasive coronary angiography
- **MI** = Myocardial infarction
- **PCI** = Percutaneous coronary intervention
### Table 2 – Baseline characteristics

| Description                                      | Count (%)  |
|--------------------------------------------------|------------|
| Number of patients                               | 300        |
| Allocated group, intervention                    | 148 (49.3) |
| Age (median [IQR])                               | 63.00 [53.00, 72.00] |
| Sex, female                                      | 177 (59.0) |
| **Symptom characteristics**                      |            |
| Typical angina                                   | 54 (18.0)  |
| Atypical angina                                  | 81 (27.0)  |
| Non-anginal chest pain                           | 149 (49.7) |
| Dyspnea on exertion                              | 16 (5.3)   |
| Hypertension                                     | 120 (40.0) |
| Hypercholesterolemia*                            | 218 (72.7) |
| Family history of IHD**                          | 65 (21.7)  |
| **Smoking status**                               |            |
| Never smoker                                     | 91 (30.3)  |
| Current smoker                                   | 61 (20.3)  |
| Former smoker                                    | 148 (49.3) |
| Diabetes mellitus                                | 26 (8.7)   |
| Low PTP***                                       | 49 (16.3)  |
| Intermediate PTP****                             | 251 (83.7) |
| CAD-score, median [IQR]                          | 23.00 [12.00; 37.00] |
| CAD-score ≤ 20                                   | 63 (42.6+) |

**Table 2. Preliminary data – baseline characteristics:** Numbers are counts (%) unless otherwise stated. IHD = Ischemic heart disease; IQR = interquartile range; PTP = pre-test probability. *Medical treatment or totaled cholesterol > 5 mmol/L. **Coronary artery disease among 1st degree relatives (male < 55 years, female < 65 years). ***Low PTP defined as <15% according to Diamond Forrester calculation in the 2013 ESC guidelines and PTP ≤ 5% according to the 2019 ESC guidelines. ****Intermediate PTP defined as 15-85% according to Diamond Forrester calculation in the 2013 ESC guidelines and PTP > 5% according to the 2019 ESC guidelines. †% of intervention group.
Trial design

FIGURE LEGENDS

Figure 1. Study design. CAD = Coronary artery disease; MACE = Major adverse cardiac event; NIT = Non-invasive test; SDE = Standard diagnostic examination.

Figure 2. Flow chart. ICA = Invasive coronary angiography; NIT = Non-invasive test; PTP = Pre-test probability.
**Figure 1**

**Subject eligibility:**
Age ≥ 30 years, referred for outpatient assessment of symptoms suggestive of CAD, no known heart disease
N ~ 2000

**Screening and consent**

**Visit 1:**
Questionnaires (SAQ, QOL, and lifestyle)
Randomization 1:1

**Standard diagnostic examination (SDE)**

**Intervention group:**
SDE + CAD-score

**Follow-up:**
Contact at 3 and 12 months

**Primary endpoint**
Numbers of NIT at 1 year

**Secondary endpoint**
MACE at 1 year
Figure 2

Randomization 1:1

Control group

PTP ≤ 5%

PTP > 5% - ≤ 15%

PTP > 15%

Clinical examination and risk factor evaluation

Ruled out

No further diagnostic testing. Risk factor optimization

NIT

Not ruled out by first NIT: Decision for 2nd NIT test or ICA.

Intervention group

PTP ≤ 5%

PTP > 5% - ≤ 15%

PTP > 15%

CAD-score assessment

CAD-score ≤ 20

CAD-score > 20

Ruled out

Not ruled out by first NIT: Decision for 2nd NIT test or ICA.

NIT

No further diagnostic testing. Risk factor optimization
### Supplementary table 1

| Supplementary table 1 – Endpoints |
|-----------------------------------|
| **Primary endpoint**              |
| NITs and invasive procedures      |
| **Key secondary endpoint**        |
| MACE (All-cause death, non-fatal MI, UAP, HF or ischemic stroke) |
| **Other secondary endpoints**     |
| All-cause death                   |
| MI                                |
| UAP                               |
| HF                                |
| Ischemic stroke                   |
| Symptoms/type of chest pain       |
| Quality of life                   |
| Change in basic lifestyle         |
| NIT                               |
| ICA                               |
| Time to CAD diagnosis             |
| Medication                        |
| Contrast dose                     |
| Radiation dose                    |
| Bleeding requiring hospitalization|
| Adverse events related to the CADScor®System |
| Repeat referrals                  |

**Supplementary table 1. Endpoints:** CAD = Coronary artery disease; HF = Heart failure; ICA = Invasive coronary angiography; MACE = Major adverse cardiac event; MI = Myocardial infarction; NIT = Non-invasive test; UAP = Unstable angina pectoris.
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description                                                                                                                                                                                                 | Page Number on which item is reported |
|--------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| **Administrative information**                                                                                                                     |                                      |
| Title        | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym                                                                                      | Page 1                                |
| Trial registration | 2a   | Trial identifier and registry name. If not yet registered, name of intended registry                                                                                                                   | P. 2 & 13                             |
|              | 2b     | All items from the World Health Organization Trial Registration Data Set                                                                                                                                    | -                                     |
| Protocol version | 3     | Date and version identifier                                                                                                                                                                                | Supplementary material; protocol v. 5.0: title page |
| Funding      | 4       | Sources and types of financial, material, and other support                                                                                                                                               | P. 21                                 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors                                                                                                                                                  | P. 1 & 21                             |
|              | 5b     | Name and contact information for the trial sponsor                                                                                                                                                       | P. 1                                  |
|              | 5c     | 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 | P. 21                                 |
|              | 5d     | 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) | P. 8, 11 & 12                         |
| Introduction                                                                 | |
|---|---|
| **Background and rationale** | 6a | 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 | P. 6-7, 16-18 |
| 6b | Explanation for choice of comparators | P. 8-10 |
| **Objectives** | 7 | Specific objectives or hypotheses | P. 6-7 |
| **Trial design** | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | P. 8-13 |
| **Methods: Participants, interventions, and outcomes** | |
| **Study setting** | 9 | 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 | P. 8 |
| **Eligibility criteria** | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | P. 8 & 24 (table 1) |
| **Interventions** | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | P. 8-10 |
| 11b | 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) | Supplementary material; protocol |
| 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | Supplementary material; protocol |
| 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | NA |
| **Outcomes** | 12 | 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 | P. 10-11, 17-18 & 28 (supplementary table 2) |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | P. 10 & 26 (Figure 1) |
|----------------------|---|--------------------------------------------------------------------------------------------------------------------------------|------------------|
| Sample size          | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | P. 12-13 |
| Recruitment          | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | P. 8-10 |

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

| Allocation:        |   |   |
|--------------------|---|---|
| **Sequence generation** | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | P. 8 |
| **Allocation concealment mechanism** | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | P. 8 |
| **Implementation** | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | P. 8-10 + Supplementary material; protocol |
| **Blinding (masking)** | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | P. 8 |
|                     | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial | NA |
| Methods: Data collection, management, and analysis |
|--------------------------------------------------|
| **Data collection methods**                      |
| 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | P. 12 |
| 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | Supplementary Supplementary material; protocol section 7.6 |
| **Data management**                              |
| 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | P. 12 |
| **Statistical methods**                          |
| 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | P. 12-13 |
| 20b Methods for any additional analyses (eg, subgroup and adjusted analyses) | P. 13 |
| 20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | P. 12 + Supplementary Supplementary material; protocol section 13.3.3. |
| **Methods: Monitoring**                         |
| **Data monitoring**                              |
| 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | P. 12 |
| 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | P. 13 |
| 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | P. 12 |
| 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |

**Ethics and dissemination**

| Research ethics approval | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | P. 2 & 14 |
| Protocol amendments | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Supplementary material; protocol |
| Consent or assent | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Supplementary material; protocol section 10.5. |
| 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | P. 12 + supplementary material; protocol section 12 |
| Declaration of interests | Financial and other competing interests for principal investigators for the overall trial and each study site | P. 22-23 |
| Access to data | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Supplementary material; protocol section 12 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | Supplementary material; protocol section 14.3. |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | P. 12-16 + supplementary material; protocol |
| 31b | Authorship eligibility guidelines and any intended use of professional writers | Supplementary material; protocol section 15. |
| 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | - |

**Appendices**

| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | P. 10 |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*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” license.*
Cost-effectiveness of adding a non-invasive acoustic rule-out test in the evaluation of patients with symptoms suggestive of coronary artery disease. Rationale and design of the prospective, randomized, controlled, parallel-group multicenter FILTER-SCAD trial.

| Journal:       | BMJ Open                        |
|---------------|---------------------------------|
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| **Secondary Subject Heading**: | Cardiovascular medicine |
| **Keywords**: | Coronary heart disease < CARDIOLOGY, CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY |
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Trial design

Cost-effectiveness of adding a non-invasive acoustic rule-out test in the evaluation of patients with symptoms suggestive of coronary artery disease. Rationale and design of the prospective, randomized, controlled, parallel-group multicenter FILTER-SCAD trial.

Short title: The FILTER-SCAD Trial Design

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Word count: 3786 (excepting title page, abstract, references, and tables).
ABSTRACT

Introduction
Most patients with symptoms suggestive of chronic coronary syndrome (CCS) have no obstructive coronary artery disease (CAD) and better selection of patients to be referred for diagnostic tests is needed. The CAD-score is a non-invasive acoustic measure that, when added to pre-test probability of CAD, has shown good rule-out capabilities. We aimed to test whether implementation of CAD-score in clinical practice reduces the use of diagnostic tests without increasing major adverse cardiac events (MACE) rates in patients with suspected CCS.

Methods and analysis
FILTER-SCAD is a randomized, controlled, multicenter trial aiming to include 2000 subjects ≥30 years without known CAD referred for outpatient assessment for symptoms suggestive of CCS. Subjects are randomized 1:1 to either the control group; standard diagnostic examination (SDE) according to current guidelines, or the intervention group; SDE plus a CAD-score. The subjects are followed for 12 months for the primary endpoint of cumulative number of diagnostic tests and a safety endpoint (MACE). Angina symptoms, quality of life, and risk factor modification will be assessed with questionnaires at baseline, 3 months, and 12 months after randomization. The study is powered to detect superiority in terms of a reduction of ≥15% in the primary endpoint between the two groups with a power of 80%, and non-inferiority on the secondary endpoint with a power of 90%. The significance level is 0.05. The non-inferiority margin is set to 1.5%. Randomization began October 2019. Follow-up is planned to be completed December 2022.

Ethics and dissemination
The study has been approved by the Danish Medical Agency (2019024326.), Danish National Committee on Health Research Ethics (H-19012579), and Swedish Ethical Review Authority (Dnr 2019-04252). All patient participating in the study will sign an informed consent. All study results will be attempted published as soon as possible.

Registration details
ClinicalTrials.gov identifier: NCT04121949.
STRENGTH AND LIMITATIONS OF THIS STUDY

- Multicenter randomized controlled trial of a novel acoustic-based risk stratification CAD-score for coronary artery disease.
- First randomized controlled trial to investigate the safety of CAD-score and the impact of the CAD-score in clinical practice.
- Study design follows newest international guidelines on Chronic Coronary Syndrome.
- The study is unblinded as the treatment is based on the value of the CAD-score.

KEYWORDS (3-10 keywords)
Stable Angina Pectoris, Stable Coronary Artery Disease, Chronic Coronary Syndrome, Acoustic Diagnostic Device, CAD-score, Diamond-Forrester Score, Pre-test Probability.
Trial design

ABBREVIATIONS

ACC/AHA = American College of Cardiology/American Heart Association

BMI = Body mass index

CABG = Coronary artery bypass graft

CAD = Coronary artery disease

CCS = Chronic coronary syndrome

CCTA = Coronary computed tomographic angiography

CEC = Clinical event committee

CMRI = Cardiac magnetic resonance imaging

ECG = Electrocardiogram

eCRF = electronic Case Report Form

ESC = European Society of Cardiology

GP = General Practitioner

HF = Heart Failure

ICA = Invasive coronary angiography

ICD = Implantable Cardioverter Defibrillator

IQR = Interquartile range

ITT = Intention-to-treat

MACE = Major adverse cardiac events

MI = Myocardial infarction

MPI = myocardial perfusion imaging

NICE = National Institute for Health and Care Excellence
Trial design

NIT = Non-invasive test

NPV = Negative predictive value

PCI = Percutaneous coronary intervention.

PTP = Pre-test probability

QOL = Quality of life

RCT = Randomized clinical trial

REDCap = Research Electronic Data Capture

SAE = Serious adverse events

SAQ = Seattle Angina Questionnaire

SDE = Standard diagnostic examination

SPECT = Single-photon emission computed tomography

UAP = Unstable angina pectoris
Trial design

BACKGROUND
Chest discomfort is a common symptom leading to cardiological assessment for chronic coronary syndrome (CCS) (1). According to European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines, the diagnostic work-up should be based on the pre-test probability (PTP) of obstructive coronary artery disease (CAD) estimated from sex, age and symptoms (2,3), as originally suggested by the Diamond-Forrester model (4,5). However, in clinical practice PTP models have limited sensitivity and specificity. In recent large studies, less than 10% of patients referred with symptoms suggestive of CAD needed revascularization, and their prognosis was good (6,7). The addition of risk factors to improve PTP precision have minor impact on prediction abilities (6,8). The current test strategy exposes patients to unnecessary procedure-related risks, medication, and radiation and the costs of diagnostic work-up may be unnecessarily high. Consequently, better methods of identifying patients with low probability of obstructive CAD and no need for diagnostic testing are needed.

The CAD-score is a risk stratification score for CAD obtained by the non-invasive acoustic device, CADScor®System (Acarix A/S), which has shown good rule-out capabilities in patient with suspected CAD (9). The device is approved for medical use, and mentioned in a Medtech innovation briefing in the NICE-guidelines as a rule-out test early in the diagnostic CAD work up before CCTA (10). However, the CAD-score has never been tested as a rule-out test in a clinical setting. Hence, the FILTER-SCAD trial will examine whether adding CAD-score to the standard diagnostic work-up reduces the number of diagnostic tests and associated health care costs without compromising safety in the outpatient assessment of patients with symptoms suggestive of CCS.
OBJECTIVES
The primary objective of the FILTER-SCAD trial is to compare an initial diagnostic strategy based on a PTP according to guidelines plus CAD-score to a standard PTP-guided strategy when selecting patients with suspected CSS for diagnostic testing. The key secondary objective is to assess whether this strategy is non-inferior in terms of major adverse cardiac events (MACE). We hypothesized that an initial rule-out strategy guided by a PTP plus a CAD-score will reduce overall number of diagnostic procedures without compromising the safety when compared with a PTP-guided strategy alone over a follow-up period of 1 year.
Trial design

METHODS

Trial design

Figure 1 shows an overview of the study design. The FILTER-SCAD trial is an investigator-initiated, prospective, randomized, controlled, parallel-group, multicenter trial planned to include 2000 subjects ≥30 years of age without known CAD referred for outpatient evaluation of symptoms suggestive of CCS at five-six sites; four-five in Denmark and one in Sweden. The protocol is available as supplementary material.

Study population

Study subjects are men and women ≥30 years of age without known CAD referred for evaluation of symptoms suggestive of suspected CAD in planned 5-6 cardiology outpatient clinics in Denmark and Sweden. Inclusion and exclusion criteria are listed in table 1.

Randomization and blinding

Randomization is done in a randomization module in the electronic CRF (eCRF) and will be unblinded as the physician must act on the given CAD-score and PTP. Eligible subjects are allocated in a 1:1 manner to control or intervention group using permuted block randomization stratified by study site and PTP-value (very low vs. low-intermediate) by a computer-generated allocation table.

The study was designed based on the 2013 ESC guidelines on the management of stable coronary artery disease (11). However, the ESC guidelines were updated in 2019 downgrading the PTP for obstructive CAD considerably (2), and the FILTER-SCAD trial protocol was adjusted to be in accordance with these state-of-the-art recommendations. First subject was randomized on October 22, 2019. The first 78 subjected in the FILTER-SCAD trial were randomized according to the first protocol based on the 2013 ESC guidelines. The remaining subjects will be enrolled in consistency with the updated protocol.

Standard diagnostic examination

Subjects randomized to the control group will undergo a standard diagnostic examination (SDE) according to ESC 2019 guidelines including clinical examination, PTP assessment based on age, sex and type of angina, risk factor assessment and echocardiography (2). The echocardiography will be done during the clinical investigation for CAD, but not necessarily on the day of
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randomization. The SDE will be followed by non-invasive tests (NIT) if indicated (figure 2) according to current European guidelines on CCS (2); Patients with very low PTP ≤ 5% should not receive further diagnostic testing, in patients with PTP 6-15% NIT may be considered based on the overall clinical likelihood, and patients with PTP > 15% should be offered NIT as standard first choice of diagnostic test. Invasive coronary angiography (ICA) may be offered to selected patients with very high clinical likelihood, but no patients should receive ICA based on their PTP alone.

**Intervention (CAD-score)**

Patients randomized to the intervention group will receive a CAD-score measurement in addition to the SDE. The CAD-score is measured using the acoustic device CADScor®System (Acarix A/S).

The CAD-score is a risk stratification score scaled from 0 to 99 for obstructive CAD measured from advanced analysis of sounds originating from blood flow turbulence in the coronary arteries and myocardial motion combined with the patients age, sex, and blood pressure (9,12). The measurements are done by a non-invasive acoustic device, CADScor®System (Acarix A/S), which has shown good rule-out capabilities (cut-off: CAD-score ≤ 20) in patient with suspected CAD (9). In a population with a prevalence of obstructive CAD on 9.4% (n=2245) the sensitivity, specificity, negative predictive value and positive predictive value were 88.7%, 41.5%, 97.2% and 13.7%, respectively (12).

During a three minutes period with the patient lying in supine position, a transcutaneous recording of heart sounds is done by a microphone attached by a patch at the left fourth intercostal space (IC4) (13). Four times during the recording, the patient is asked to hold his/her breath for eight seconds. From eight acoustic features, a fully automatic algorithm estimates (software version 3.2) an acoustic score which combined with the risk factors sex, age, and hypertension by logistic regression results in the CAD-score (9,13). The CAD-score measurements are done by specially trained study staff. If the measurement fails, up to four measurement are attempted.

Success of the new strategy depends critically on the physician’s knowledge of strength and weakness of the CAD-score measure. At study start, each site will be trained in the CAD-score background literature and method. The training will be repeated after 3-6 months after
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enrollment of first patient. Moreover, every physician is provided written information about the study and the CAD-score. The training of the physicians is intended to made physicians comfortable with the CAD-score and its strengths and weaknesses.

Further diagnostic pathway

All treating physicians are trained in the study protocol including the CAD-score. The physician is provided with a decision sheet with PTP, CAD-score and the recommended further diagnostic pathway (NIT or no further assessment) (figure 1). Based on the available information, the physician decides whether to follow the recommended diagnostic pathway or not. A crossover could be justified by the presence of cardiac risk factors with a higher perceived clinical likelihood.

Diagnostic tests for both intervention and control group

Patients with intermediary-high PTP in the control group or high CAD-score > 20 in the intervention group are referred for further standard diagnostic testing including NIT and ICA, and this is done as standard procedure of each site. All decisions regarding diagnostic testing, including choice of testing modality, and medical/surgical treatment of the patient is done at the discretion of the treating physician, and is not a part of the study protocol.

Study periods

A run-in period with an expected duration of three months at each site is intended to serve as a training period where the study staff and attending cardiologists will be made familiar with performing and interpreting the CAD-score measurement by obtaining CAD-score around 50-100 subjects at each participating site.

The planned duration of the study is 24 months; 12 months for the inclusion period, defined as first patient first visit to last patient first visit, for the main study starting after the run-in period, and approximately 12 months for the follow-up period. However, due to the COVID-19 pandemic and associated study delay, the enrollment period is extended with 15 months. Hence, follow-up is planned to be completed December 2022.

End of study will be when all the following have occurred: 1) at least 2000 patients have been randomized, and 2) 12±1 month (1 year) have elapsed since the last patient was randomized. The study population will be followed for one year after randomization.
Trial design

Endpoints

Primary endpoint

The primary endpoint defined as the cumulative number of NIT and invasive procedures one year after randomization. NITs include exercise electrocardiogram (ECG), Coronary computed tomographic angiography (CCTA), Rubidium-PET CT, myocardial perfusion imaging (MPI), Cardiac magnetic resonance imaging (CMRI), and stress echocardiography. Invasive procedures include ICA only.

If the analysis shows a significant difference in the primary endpoint, a cost-effectiveness analysis will be conducted alongside the trial. The potential cost-effectiveness analysis will be based on information from the trial, as well as data from health registers. The register linkage will provide information at individual level on healthcare utilization, including general practice, medication, etc.; as well as labour market consequences and other societal costs. The cost-effectiveness analysis will apply two different effectiveness measures: procedures avoided, cf. the primary endpoint, and quality adjusted life-years (QALY’s) based on the reporting of EQ-5D in the trial (14).

Secondary endpoints

The key secondary endpoint is the safety endpoint MACE; a combined endpoint of all-cause mortality, non-fatal myocardial infarction (MI), hospitalization for unstable angina pectoris (UAP), heart failure (HF), ischemic stroke, and major complication from cardiovascular procedures or diagnostic testing at one year after end of randomization. An independent clinical event committee (CEC) will adjudicate MACE endpoints blinded to the allocated intervention. Definitions of all-cause mortality, MI, UAP, HF and ischemic stroke follow the ACC/AHA description of key data elements and definitions for cardiovascular endpoint events in clinical trials (15). Major complication from cardiovascular procedures or diagnostic testing is defined as major bleeding, renal failure, stroke, or anaphylaxis that occurred within 72 hours in accordance with the PROMISE Trial’s definition (7). Other individual secondary endpoints are 1) clinical endpoints: all-cause mortality, MI, hospitalization for UAP, HF and ischemic stroke, medication, time to CAD diagnosis, repeat referrals, and bleeding requiring hospitalization assessed one year after randomization, 2) procedure related endpoints: Numbers of first NITs, numbers of ICA, number of downstream tests (NITs and ICAs done after the first NIT), contrast dose, radiation
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dose, and adverse events related to the CAD-score measurement at one year after randomization, and 3) questionnaire endpoints: Change in chest pain assessed by the Seattle Angina Questionnaire (SAQ) (16), quality of life assessed by the EuroQol-5D (17), and lifestyle assessed by the HeartDiet Questionnaire (18). Questionnaires are collected at baseline, three months, and 12 months after randomization.

All endpoints are listed in supplementary table 1.

Data handling

Data is collected in the eCRF REDCap (Research Electronic Data Capture 10.3.3(19,20)) by trained study staff. Blood samples, ECG, and echocardiography data at baseline are standard test for ambulatory patients and will be collected from medical records and entered in the eCRF. Data on diagnosis, medications, diagnostic testing, repeat referrals, safety endpoints, and bleeding requiring hospitalization will be collected. All diagnostic test will be classified as positive, negative or inconclusive. This will be done at each individual site according to local criteria/guidelines.

Monitoring will be carried out by an external monitor and will include 100% monitoring of all potential serious adverse events (SAE) related to the CAD-score measurement, informed consent forms and power of attorneys, and 20% monitoring of inclusion and exclusion criteria.

Statistical methods

The study is powered to detect superiority in terms of an absolute reduction of ≥ 15% in the cumulative number of diagnostic tests (primary endpoint) between the intervention and control groups with a power of 80% and a significance level of 0.05 with a sample size of 521 subjects in each randomization group. The study is powered for non-inferiority on the secondary safety endpoint (MACE) with a power of 90% and a significance level of 0.05 with a sample size of 1914 subjects (957 in each randomization group). The non-inferiority margin is set to 1.5%.

The final sample size was chosen to be 2000 patients (1000 in each randomization group), allowing for a 4% loss to follow-up and drop-out. The power calculation remains unchanged after updating the study protocol to reflect the latest 2019 ESC guidelines on CCS.

The main analysis will be intention-to-treat (ITT) analysis. Analysis of the cumulative numbers of diagnostic test will be done with Poisson based test and visualized by Nelson-Aalen
nonparametric estimator. The secondary safety endpoint MACE will be analyzed using a continuity-corrected modification of the Wilson’s score method.

Pre-specified subgroup analysis will be performed investigating the following subgroups: PTP (≤5% vs. 5-15% vs. >15%), PTP (≤5% vs. >5%), PTP (≤5% vs. 5-15%), age (<65 years vs. ≥65 years), sex (male vs. female), hypertension (yes vs. no), dyslipidemia (yes vs. no), diabetes mellitus (yes vs. no), smoking (yes vs. no), family history of CAD (yes vs. no), and BMI (<30 kg/m2 vs. ≥30 kg/m2). An interim analysis for futility will be done after enrollment of at least 20% of the expected 2000 patients. We expect approximately 25% of the population to have low PTP or CAD-score ≤ 20. The study is considered futile if more than 90% of the overall population undergo further NIT or ICA after the initial SDE.

All statistical tests will be made using statistical software R and will have a two-sided significance level of 0.05.

**Trial registration**

The trial is registered on ClinicalTrials.gov (identifier: NCT04121949).

**Patient and public involvement**

Patients and the public were not involved in the phase of the study, as the study addresses the physician’s decision-making in the diagnostic strategy for ischemic heart disease. However, the results will be relevant for both patients and the general public, and the result will be attempted published through patient organizations and public media. The study results will be distributed directly to the study participants.
**ETHICS AND DISSEMINATION**

The FILTER-SCAD trial is conducted in compliance to the principles of the Declaration of Helsinki of the World Medical Association, and laws of Denmark and Sweden. The study has been approved by the Danish Medical Agency (2019024326.), Danish National Committee on Health Research Ethics (H-19012579), and Swedish Ethical Review Authority (Dnr 2019-04252). All patient participating in the study will sign an informed consent. All study results will be attempted published as soon as possible.
DISCUSSION

The FILTER-SCAD trial will investigate whether adding a CAD-score to the SDE is a feasible way to reduce use of excess diagnostic testing without compromising safety in the assessment of patients with symptoms suggestive of CCS.

CAD-score probabilities

The diagnostic performance of the CAD-score has been thoroughly examined (9,12,13). In a retrospective pooled study of 2245 patients undergoing CCTA the diagnostic sensitivity and specificity for obstructive CAD of the CAD-score were 88.7% and 41.5%, respectively, with ≥ 50% stenosis on ICA as gold standard (12). In this population with a 9.4% prevalence of obstructive CAD verified on ICA, the negative predictive value (NPV) was 97.2% at a CAD-score cut-off ≤ 20, which stresses the potential of the CAD-score as a rule-out test for obstructive CAD (12). In addition, the CAD-score’s capability of reclassifying patients was simulated in the study; by adding a CAD-score to the patients with intermediate PTP of obstructive CAD, one third of the patients were downgraded to the low likelihood of CAD group, and might accordingly have been ruled-out at that step without any further excess NIT, potentially reducing the accompanying risks and costs (12). This reclassification only slightly insignificantly increased the CAD-prevalence in the low-risk group from 3.1% to 4.0% (12). The previous CAD-score studies are based on the former ECS 2013 PTP. However, the non-invasive sound-based CAD-score tool, remains effective as a rule-out test also following implementation of the adjusted PTP in the recent 2019 ESC guidelines on CCS; four out of 10 patients evaluated by the latest PTP were reclassified to low likelihood of obstructive CAD after adding a CAD-score (21). The FILTER-SCAD trial will, to our knowledge, be the first study to test the CAD-score’s ability in a clinical setting as a rule-out tool in patients with suspected CCS, testing both the efficacy and the safety in a randomized prospective study. Thereby, the current study may enhance and simplify the diagnostic pathway for patients referred with suspected CCS, possibly allowing a reduction in excess use for NIT and ICA.

Safety

We are aware of the risk of incorrectly ruling out patient with CAD with a (false negative) low CAD-score. As for all other diagnostic tests, there will always be a risk of false negative test; Sensitivity of exercise stress echocardiography, exercise stress SPECT, and CCTA are 80-85%,
Trial design

73-92%, and 95-99%, respectively, and false negative test will occur (11). However, these tests are more comprehensive and expensive than a simple CAD-score measurement. Also, current ESC guidelines recommend no further investigation with NIT in patients with PTP ≤ 5%. Thus, guidelines accept ruling out a proportion of patient with unacknowledged obstructive CAD to avoid large numbers of false positive tests and unnecessary exposure of patients to diagnostic test and accompanying risk. Moreover, the prognosis of patients referred with symptoms suggestive of CSS appears good (7,22,23), especially among the patients classified with low PTP (6), but also in both suspected CCS and confirmed CAD (24). The good prognosis is independent of treatment with percutaneous coronary intervention (PCI) or optimal medical therapy including antianginal medication (25).

In the FILTER-SCAD study, risks are mitigated in several ways; The participants are contacted by the study nurse after three months and one year, where angina symptoms are assessed. In case of worsening of symptoms, the nurse can contact the treating physician who can decide to schedule a follow-up visit. Also, the patients are instructed to contact the study nurse or their general practitioner if their symptoms continues or worsens. Finally, the treating physician may choose to disregard the recommended action according to protocol and cross the patient over to NIT despite a CAD-score ≤ 20 if e.g. cardiovascular risk factors deemed to increase the patient’s likelihood for CAD, the treating physician require further investigation, or choose to schedule a follow-up visit.

Notably, the CAD-score system is CE-marked and approved for clinical use in patients ≥ 40 years of age, and is stated as a rule-out test early in the diagnostic CAD work up in the NICE-guidelines Medtech innovation briefing (10). Thus, the FILTER-SCAD trial aims to test the implementation of an already approved clinical rule-out device in a clinical setting and its impact as an add-on device in the current diagnostic work up, and not to test the diagnostic accuracy of the device.

Endpoints
The low diagnostic yield of the current work up for patients with suspected CCS has questioned the value of the currently recommended diagnostic test strategy (26–28). Many patients may be exposed to unnecessary procedure-related risks, medication, and radiation without achieving any benefits, and the costs of diagnostic work-up may be unnecessarily high. This study aims to investigate if a CAD-score added as a rule-out test in patients with suspected CCS will reduce
unnecessary testing and thus increase the cost-effectiveness of the diagnostic workup. Hence, comparison of the cumulative number of NIT and ICA in two groups with and without CAD-score as rule-out test is relevant. Moreover, not compromising safety for patients by adding a CAD-score as a rule-out test is essential. Therefore, a key secondary composite safety endpoint MACE of numbers of all-cause death, myocardial infarction, unstable angina pectoris, heart failure, ischemic stroke, and major complication from cardiovascular procedures or diagnostic within 72 is relevant and will enlighten the accuracy of excluding obstructive disease in patient groups with and without CAD-score measurement.

Another important secondary endpoint is angina symptom control, quality of life and patients’ satisfaction with the diagnostic work up. These are assessed with validated questionnaires (16,17). Other secondary endpoints in the study include medication, time to diagnosis, contrast and radiation dose, and adverse events related to the CAD-score measurement.

CONCLUSION

The FILTER-SCAD trial study will investigate the cost-effectivity and safety in a clinical setting of adding an advanced acoustic tool; the CAD-score as a rule-out test in the diagnostic work up of patients with symptoms suggestive of CCS.

AUTHORS’ CONTRIBUTIONS

EP, SG and KWH designed and initiated the study. LHB, KWH, EP, and SG obtained funding. LHB wrote the manuscript. LHB, KWH, TBS, JBS, HE, DE, SAHP, MH, JDH, MTJ, MK, SR, SS, SG and EP revised and approved the final version of the article.
Trial design

COMPETING INTEREST
LHB: None.
KWH: None.

TBS: Steering Committee member of the Amgen financed GALACTIC-HF trial; Advisory Board: Sanofi Pasteur; Advisory Board: Amgen; Speaker Honorarium: Novartis; Speaker Honorarium: Sanofi Pasteur; Research grant: GE Healthcare; Research grant: Sanofi Pasteur.

JBS: None.
HE: None.
DE: Advisory board for Acarix A/S.
SAHP: None.
MH: None.
JDH: None.
MK: None.
MTJ: None.
SR: None.
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AUTHORS’ NOTE
The CADScor® System and analysis relating hereto will be offered freely by Acarix A/S.
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TABLES

| Table 1 – Inclusion and exclusion criteria |
|-------------------------------------------|
| **Inclusion criteria**                    |
| - Signed informed consent form.          |
| - Male or female, aged 30 years or above.|
| - Patients able and willing to comply with the clinical investigational plan. |
| - Symptoms suggestive of stable coronary artery disease. |
| - No history of coronary artery disease (prior MI, PCI or CABG). |
| **Exclusion criteria**                    |
| Related to pre-test likelihood of obstructive CAD: |
| - Prior non-invasive testing for stable CAD or ICA within 6 months of randomization. |
| Related to feasibility of performing a CAD-score measurement: |
| - Implanted donor heart, mechanical heart, mechanical heart pump. |
| - Pacemaker or Cardioverter Defibrillator (ICD). |
| - Implanted electronic equipment in the area above and around the heart. |
| - Significant operation scars, abnormal body shape, fragile or compromised skin in the fourth left intercostal space recording area. |
| - Receiving same day treatment with nitroglycerine on the day of randomization. |
| Related to women of childbearing potential: |
| - Pregnancy. |

Table 1. Inclusion and exclusion criteria: *The exclusion criteria “Diamond-Forrester score > 85%” was removed after updating the study according to the 2019 ESC guidelines on CCS. CAD = Coronary artery disease; CABG = Coronary artery bypass graft; ICA = Invasive coronary angiography; MI = Myocardial infarction; PCI = Percutaneous coronary intervention.*
Trial design

FIGURE LEGENDS

Figure 1. Study design. CAD = Coronary artery disease; MACE = Major adverse cardiac event; NIT = Non-invasive test; SDE = Standard diagnostic examination.

Figure 2. Flow chart. ICA = Invasive coronary angiography; NIT = Non-invasive test; PTP = Pre-test probability.
Figure 1

**Subject eligibility:**
Age ≥ 30 years, referred for outpatient assessment of symptoms suggestive of CAD, no known heart disease
N ~ 2000

**Screening and consent**

Visit 1:
Questionnaires (SAQ, QOL, and lifestyle)
Randomization 1:1

Standard diagnostic examination (SDE)

Intervention group:
SDE + CAD-score

Follow-up:
Contact at 3 and 12 months

Primary endpoint
Numbers of NIT at 1 year

Secondary endpoint
MACE at 1 year
Figure 2

Randomization 1:1

Control group
- PTP ≤ 5%
- PTP > 5% - ≤ 15%
- PTP > 15%

Intervention group
- PTP ≤ 5%
- PTP > 5% - ≤ 15%
- PTP > 15%

Clinical examination and risk factor evaluation

Ruled out
- No further diagnostic testing.
- Risk factor optimization

NIT
- Not ruled out by first NIT:
  - Decision for 2nd NIT test or ICA.

Ruled out
- Not ruled out by first NIT: Decision for 2nd NIT test or ICA.

CAD-score assessment
- CAD-score ≤ 20
- CAD-score > 20
### Supplementary table 1

| **Primary endpoint** | NITs and invasive procedures |
|----------------------|-----------------------------|
| **Key secondary endpoint** | MACE (All-cause death, non-fatal MI, UAP, HF or ischemic stroke) |
| **Other secondary endpoints** | All-cause death |
| | MI |
| | UAP |
| | HF |
| | Ischemic stroke |
| | Symptoms/type of chest pain |
| | Quality of life |
| | Change in basic lifestyle |
| | NIT |
| | ICA |
| | Time to CAD diagnosis |
| | Medication |
| | Contrast dose |
| | Radiation dose |
| | Bleeding requiring hospitalization |
| | Adverse events related to the CADScor®System |
| | Repeat referrals |

**Supplementary table 1. Endpoints:** CAD = Coronary artery disease; HF = Heart failure; ICA = Invasive coronary angiography; MACE = Major adverse cardiac event; MI = Myocardial infarction; NIT = Non-invasive test; UAP = Unstable angina pectoris.
# SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

| Section/item          | Item No | Description                                                                                                                                                                                                 | Page Number on which item is reported |
|-----------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| **Administrative information** |                     |                                                                                                                                                                                                          |                                       |
| Title                 | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym                                                                                             | Page 1                                |
| Trial registration    | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry                                                                                                                       | P. 2 & 13                             |
|                       | 2b      | All items from the World Health Organization Trial Registration Data Set                                                                                                                                    | -                                     |
| Protocol version      | 3       | Date and version identifier                                                                                                                                                                                  | Supplementary material; protocol v. 5.0: title page |
| Funding               | 4       | Sources and types of financial, material, and other support                                                                                                                                                 | P. 21                                 |
| Roles and responsibilities | 5a     | Names, affiliations, and roles of protocol contributors                                                                                                                                                     | P. 1 & 21                             |
|                       | 5b      | Name and contact information for the trial sponsor                                                                                                                                                         | P. 1                                  |
|                       | 5c      | 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 | P. 21                                 |
|                       | 5d      | 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) | P. 8, 11 & 12                        |
| Introduction                                                                 |                                                                 |                                                                 |
|-----------------------------------------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------|
| Background and rationale                                                   | Description of research question and justification for         | P. 6-7, 16-18                                                     |
|                                                                             | undertaking the trial, including summary of relevant studies     |                                                                 |
|                                                                             | (published and unpublished) examining benefits and harms for    |                                                                 |
|                                                                             | each intervention                                               |                                                                 |
| 6b                                                                          | Explanation for choice of comparators                            | P. 8-10                                                         |
| Objectives                                                                  | Specific objectives or hypotheses                                | P. 6-7                                                          |
| Trial design                                                                | Description of trial design including type of trial (eg,        | P. 8-13                                                         |
|                                                                             | parallel group, crossover, factorial, single group, allocation  |                                                                 |
|                                                                             | ratio, and framework (eg, superiority, equivalence, noninferior|                                                                 |
|                                                                             | ity, exploratory)                                                |                                                                 |

Methods: Participants, interventions, and outcomes

| Study setting                                                               | Description of study settings (eg, community clinic, academic   | P. 8                                                              |
|                                                                             | hospital) and list of countries where data will be               |                                                                 |
|                                                                             | collected. Reference to where list of study sites can be        |                                                                 |
|                                                                             | obtained                                                       |                                                                 |
| Eligibility criteria                                                       | Inclusion and exclusion criteria for participants. If applicable,| P. 8 & 24                                                       |
|                                                                             | eligibility criteria for study centres and individuals who will | (table 1)                                                        |
|                                                                             | perform the interventions (eg, surgeons, psychotherapists)      |                                                                 |
| Interventions                                                               | Interventions for each group with sufficient detail to          | P. 8-10                                                         |
|                                                                             | allow replication, including how and when they will be           |                                                                 |
|                                                                             | administered                                                   |                                                                 |
| 11b                                                                        | Criteria for discontinuing or modifying allocated interventions  | Supplementary material; protocol                                 |
|                                                                             | for a given trial participant (eg, drug dose change in          |                                                                 |
|                                                                             | response to harms, participant request, or improving/worsening  |                                                                 |
|                                                                             | disease)                                                       |                                                                 |
| 11c                                                                        | Strategies to improve adherence to intervention protocols, and  | Supplementary material; protocol                                 |
|                                                                             | any procedures for monitoring adherence (eg, drug tablet return,|                                                                 |
|                                                                             | laboratory tests)                                              |                                                                 |
| 11d                                                                        | Relevant concomitant care and interventions that are permitted  | NA                                                               |
|                                                                             | or prohibited during the trial                                  |                                                                 |
| Outcomes                                                                   | Primary, secondary, and other outcomes, including the specific  | P. 10-11, 17-18 & 28 (supplementary table 2)                    |
|                                                                             | 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       |                                                                 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | P. 10 & 26 (Figure 1) |
|----------------------|----|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Sample size          | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | P. 12-13             |
| Recruitment          | 15 | Strategies for achieving adequate participant enrolment to reach target sample size                                                                 | P. 8-10              |

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

| Allocation: |
|-------------|

| Sequence generation 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | P. 8 |

| Allocation concealment mechanism 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | P. 8 |

| Implementation 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | P. 8-10 + Supplementary material; protocol |

| Blinding (masking) 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | P. 8 |

| 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial | NA |
| Methods: Data collection, management, and analysis |
|-----------------------------------------------|
| **Data collection methods** | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | P. 12 |
| 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | Supplementary material; protocol section 7.6 |
| **Data management** | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | P. 12 |
| **Statistical methods** | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | P. 12-13 |
| 20b | Methods for any additional analyses (e.g., subgroup and adjusted analyses) | P. 13 |
| 20c | Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation) | P. 12 + Supplementary material; protocol section 13.3.3. |

| Methods: Monitoring |
|---------------------|
| **Data monitoring** | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | P. 12 |
| Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | P. 13 |
| Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | P. 13 |
| Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | P. 12 |
| Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | NA |
| Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | P. 2 & 14 |
| Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | Supplementary material; protocol |
| Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | Supplementary material; protocol section 10.5. |
| Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | P. 12 + supplementary material; protocol section 12 |
| Financial and other competing interests for principal investigators for the overall trial and each study site | P. 22-23 |
| Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | Supplementary material; protocol section 12 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | Supplementary material; protocol section 14.3. |
|-------------------------------|----|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | P. 12-16 + supplementary material; protocol. |
|                              | 31b | Authorship eligibility guidelines and any intended use of professional writers | Supplementary material; protocol section 15. |
|                              | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | - |

**Appendices**

| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | P. 10 |
|----------------------------|----|-------------------------------------------------------------------------------------------------------------------------------|------|
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

*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" license.