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**TRIAL DESIGN**

# The NORwegian atrial fibrillation self-SCREENing (NORSCREEN) trial: rationale and design of a randomized controlled trial

**Miroslav Boskovic [1,2], Jarle Jortveit [3], Marius Blørstad Haraldsen[4], Trygve Berge [4,5,6], Johan Engdahl [7], Maja-Lisa Løchen [8,9], Peter Schuster [10,11], Edvard Liljedahl Sandberg [3], Jostein Grimsmo [12,13], Dan Atar [4,14], Ole-Gunnar Anfinsen [15], Are Hugo Pripp [16], Bjørnar Leangen Grenne [17,18], and Sigrun Halvorsen [4,14]***

[1]Faculty of Medicine, University of Oslo, Oslo, Norway; [2]Department of Cardiology, Sorlandet Hospital, Kristiansand, Norway; [3]Department of Cardiology, Sorlandet Hospital, Arendal, Norway; [4]Department of Cardiology, Oslo University Hospital Ullevaal, P.O. Box 4956 Nydalen, N-0424 Oslo, Norway; [5]Department of Medical Research, Vestre Viken Hospital, Baerum Hospital, Rud, Norway; [6]Department of Internal Medicine, Vestre Viken Hospital, Baerum Hospital, Rud, Norway; [7]Department of Clinical Sciences, Karolinska Institutet, Danderyds Hospital, Stockholm, Sweden; [8]Department of Cardiology, University Hospital of North Norway, Tromsø, Norway; [9]Department of Clinical Medicine, UiT, The Arctic University of Norway, Tromsø, Norway; [10]Department, Haukeland University Hospital, Bergen, Norway; [11]Faculty of Medicine, Department of Clinical Science, University of Bergen, Bergen, Norway; [12]Department of Cardiac Rehabilitation, Lovisenberg Rehabilitation, Cathinka Guldbergs Hospital, Oslo, Norway; [13]LHL (The National Patient Organization for Heart, Vascular and Lung Diseases, Allergy, Stroke, Aphasia and their Relatives), Jessheim, Norway; [14]Institute of Clinical Medicine, University of Oslo, P.O. Box 1171 Blindern, N-0318 Oslo, Norway; [15]Department of Cardiology, Oslo University Hospital Rikshospitalet, Oslo, Norway; [16]Oslo Centre of Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway; [17]Clinic of Cardiology, St. Olavs Hospital, Trondheim, Norway; and [18]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway

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**Aims** Atrial fibrillation (AF) is a common arrhythmia, and many cases of AF may be undiagnosed. Whether screening for AF and subsequent treatment if AF is detected can improve long-term outcome remains an unsettled question. The primary aim of the NORwegian atrial fibrillation self-SCREENing (NORSCREEN) trial is to assess whether self-screening for AF with continuous electrocardiogram (ECG) for 3–7 days in individuals aged 65 years or older with at least one additional risk factor for stroke, and initiation of guideline-recommended therapy in patients with detected AF, will reduce the occurrence of stroke.

**Methods and results** This study is a nationwide open, siteless, randomized, controlled trial. Individuals ≥65 years of age are randomly identified from the National Population Register of Norway and are invited to take a digital inclusion/exclusion test. Individuals passing the inclusion/exclusion test are randomized to either the intervention group or the control group. A total of 35 000 participants will be enrolled. In the intervention group, self-screening is performed continuously over 3–7 days at home with a patch ECG device (ECG247) at inclusion and after 12–18 months. If AF is detected, guideline-recommended therapy will be initiated. Patients will be followed up for 5 years through national health registries. The primary outcome is time to a first stroke (ischaemic or haemorrhagic stroke). The first participant in the NORSCREEN trial was enrolled on 1 September 2023.

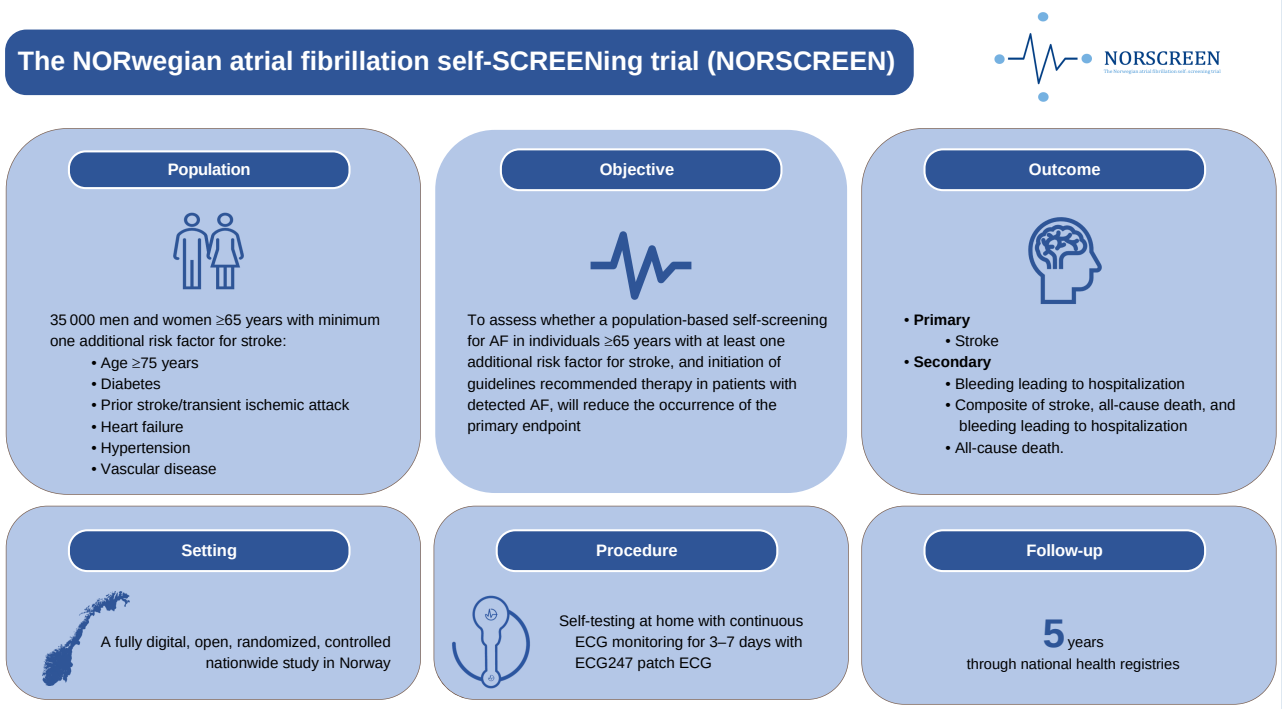
**Conclusion** The results from the NORSCREEN trial will provide new insights regarding the efficacy of digital siteless self-screening for AF with respect to stroke prevention in individuals at an increased risk of stroke.

**Trial registration** Clinical trials: NCT05914883.



* Corresponding author. Tel: +47 913 17 460. *E-mail address*: sigrun.halvorsen@medisin.uio.no

## Graphical Abstract




**Keywords** Atrial fibrillation • Screening • Randomized controlled trial

# Introduction

## Background

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, and its prevalence is increasing.[1,2] The number of elderly with AF in the European Union is predicted to increase by almost 6 800 000 new cases by the year 2060 due to ageing of the population and an increased prevalence of other risk factors for AF.[3] Many AF cases are undiagnosed due to the intermittent and often asymptomatic nature of the disease.[1] Atrial fibrillation confers a 2–10-fold increased risk of stroke depending on age and other patient characteristics, and 20–30% of all strokes are attributed to this arrhythmia.[1,4] In addition, AF is associated with an increased risk of premature mortality, heart failure, cognitive impairment, hospital admissions, depression, and reduced quality of life.[1] Early detection of AF and treatment with anticoagulation therapy may reduce the risk of stroke by as much as 60%.[1]

The European Society of Cardiology (ESC) recommends screening for AF in people ≥75 years of age and in individuals at an increased risk of stroke. However, randomized controlled trials (RCTs) confirming the benefits of screening for AF and informing the choice of optimal screening strategy are scarce and partly conflicting.[1] Different conclusions in recent trials such as the Systematic ECG Screening for Atrial Fibrillation Among 75-Year-Old Subjects in the Region of Stockholm and Halland (STROKESTOP) and Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals (LOOP) trials reinforce the need for a larger RCT.[5,6]

The Norwegian Atrial Fibrillation self-screening pilot study recently screened >2000 individuals at a mean age of 70.1 (4.2) years by using the ECG247 Smart Heart Sensor, showing the feasibility of a digital self-screening procedure for AF.[7] The study saw successful completion of the test in 87% of the participants, with >99% interpretable ECG self-screening tests and an estimated number needed to screen (NNS) of 45 to identify one individual with AF in the screened population.

The NORwegian atrial fibrillation self-SCREENing (NORSCREEN) trial aims to address the need for a large RCT investigating the health benefits of screening for AF and the subsequent initiation of guideline-recommended therapy in patients diagnosed with AF.

## Study objectives and hypothesis

The primary objective of the NORSCREEN trial is to assess whether a population-based self-screening for AF with continuous electrocardiogram (ECG) monitoring for 3–7 days in individuals ≥65 years with at least one additional risk factor for stroke, and initiation of guideline-recommended therapy in patients with detected AF, will reduce the occurrence of the primary endpoint stroke in the screened group compared with the control group during follow-up.

The study hypothesis is that intervention as described will reduce the incidence of stroke in the screened group compared with the control group receiving usual care.

# Methods and analysis

## Study design

The NORSCREEN trial is a nationwide, digital, open, prospective, randomized, controlled study in Norway.

## Study population

The NORSCREEN trial will include 35 000 men and women aged ≥65 years from the general population. The inclusion criteria are as follows: age 65 years or older and at least one additional risk factor for stroke according to the $CHA_2DS_2$-VASc risk score [heart failure, hypertension, age ≥75 years (double), diabetes mellitus, previous stroke/transient ischaemic attack (double), and vascular disease].[8] Female gender is omitted as a risk factor for inclusion in order to avoid gender skewness in the study population. The exclusion criteria are as follows: a self-reported history of AF, the current use of anticoagulation therapy, implanted cardiac implantable electronic devices, or no access to a smartphone. If all inclusion criteria are fulfilled and no exclusion criteria exist, informed consent for study participation will be obtained digitally from the patients.

## Recruitment and randomization

Individuals ≥65 years of age are randomly identified from the National Population Register of Norway. The register contains information on all residents in Norway, and all Norwegians are identified with a unique national identity number. The age and gender selection for invitations will be adjusted after every 5000 included participants if the mean age of the included participants is <70 years or the per cent of female participants deviates from 50 ± 5%. The randomly selected individuals will be invited through a digital letter at 'Helsenorge' (www.helsenorge.no), which is the official Web service of the Norwegian Directorate of Health for secure access to health services for residents of Norway. Information about the digital letter is sent as an SMS and/or a push notification to the individual's mobile phone. The invitation letter provides access to a digital inclusion/exclusion test (*Figure 1*). Individuals passing the inclusion/exclusion test automatically proceed to sign a digital consent form for study participation using the Norwegian BankID (*Figure2*). BankID (www.bankid.no) is a personal electronic identification method for secure online authentication and digital signing. All study participants are automatically randomized to either the intervention group or the control group. Participants provide information in a web-based form ('Nettskjema') regarding their baseline characteristics, symptoms, health-related quality of life, and use of medication in a digital questionnaire. Nettskjema (www.nettskjema.no) is a tool for designing and conducting online surveys by the University of Oslo (UiO). All data are stored in a secure cloud service (the Services for Sensitive Data - TSD) with a full set of services for the collection, storage, and analysis of sensitive research data requiring a high level of security. The TSD is developed and operated by the UiO and used by researchers at several national research institutions.

## Screening device

The AF screening device, ECG247 Smart Heart Sensor (Appsens AS, Lillesand, Norway, www.ecg247.com) *(Figure3)*, is developed for research and commercial use. The system consists of a disposable ECG electrode patch, a reusable sensor, a medical grade smartphone app, and a secure medical back-end cloud service with real-time ECG analysis. This allows for continuous heart rhythm monitoring and is CE (2460)-certified according to the EU Medical Device Regulations. The system has improved diagnostic accuracy and usability compared with conventional Holter technology for ECG monitoring.[9] The ECG247 Smart Heart Sensor will be sent only to participants in the intervention group.

## Intervention

The ECG247 Smart Heart Sensor is sent free of charge by mail to all participants in the intervention group at inclusion and after 12–18 months from the study centre at Sorlandet Hospital, Arendal, Norway. User guides (paper, digital, and video) and user support by phone service are available. A minimum of three days of ECG monitoring is recommended. All ECG recordings will be reviewed by a group of trained and experienced study nurses and physicians. Expert cardiologists will supervise and verify pathological ECG findings.

The following variables will be registered from the ECG tests: heart rhythm [sinus rhythm, AF ≥30 s, atrial flutter ≥30 s, supraventricular tachycardias ≥ 30 s, ventricular arrhythmias (≥4 subsequent ventricular beats), sinoatrial/atrioventricular block/pause >4 s, and other clinically relevant arrhythmias], proportions of ectopic beats, timing, duration and heart rate of arrhythmias, and duration of heart rhythm recording.

All participants with ECG-detected arrhythmias will receive information about the test results by a personal phone call and by a physical letter. Participants with AF or other arrhythmias will be advised to contact their general practitioner (GP) for further diagnostic assessment and management. A separate digital letter will be sent to the GP, and guideline-recommended treatment including oral anticoagulation therapy will be strongly advised to all participants with AF.

No study-related interventions will be performed for participants in the control group.

## Follow-up

The target follow-up duration is an average of 5 years per participant. Follow-up of the participants will be through linkage of their personal identification number to the following nationwide health registries of Norway: the Norwegian Stroke Registry (NSR), the Norwegian Population Registry, the Norwegian Patient Registry (NPR), the Norwegian Cause of Death Registry, and the Norwegian Prescribed Drug Registry. The next section provides more information on these registries.

Additional digital questionnaires for self-reporting of new AF diagnosis, heart failure hospitalizations, or bleeding leading to hospitalization will be sent to all participants every 6 months throughout the study period by e-mail. Reminders will be sent after 7 days to non-responders. Self-reported information including baseline characteristics will be verified and supplemented with data from the nationwide health registries of Norway.

## Outcomes

The primary outcome of the study is time to a first stroke (ischaemic or haemorrhagic stroke). The secondary outcomes include all-cause death, bleeding leading to hospitalization (at least one overnight stay), and a composite of stroke, all-cause death, and bleeding leading to hospitalization. Additional outcomes include the occurrence of stroke subtypes (ischaemic or haemorrhagic stroke), a new diagnosis of vascular dementia, a new diagnosis of heart failure, myocardial infarction, and cause-specific mortality. The detection rate of AF and the uptake of anticoagulation will also be reported. A cost-efficacy analysis will be performed at a later stage.

Subgroup analyses will be performed on the occurrence of AF-related complications in patients with different AF patterns (duration, frequency, and heart rate) and in patients with different AF-related symptoms.

Information on the primary outcome of stroke will be collected from the NSR, which has a high degree of completeness in the Norwegian population.[10] The reliability of stroke events in the NSR is secured by the pre-existing internal monitoring of the registry.

Information on death will be obtained from the Norwegian Population Registry, which includes the vital status of all Norwegian residents. Information on causes of death will be retrieved through linkage with the Norwegian Cause of Death Registry. Information on other cardiovascular events will be retrieved through linkage with the NPR, which includes International Classification of Disease (ICD) codes and is a mandatory register for all hospital admissions in Norway. The ICD codes identifying these events in the NPR are listed in *Table 1*. Information about the use of oral anticoagulation therapy and other relevant drug therapies during follow-up will be retrieved from the Norwegian Prescribed Drug Registry.

## Definitions

Atrial fibrillation is defined according to the ESC guidelines, as a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation with a minimum duration of at least 30 s.[1]

The primary outcome stroke includes ischaemic stroke, haemorrhagic stroke, and stroke of unknown type, as defined in the NSR.

## Sample size calculation

The calculation of sample size was based on the results of the previous studies, STROKESTOP and LOOP, as well as data from the NSR.[5,6,11] Based on the occurrence of stroke in the relevant age group in Norway, we assumed an event rate of 1.24% per year in the control group. In the STROKESTOP study, an 8% reduction in risk of ischaemic stroke was observed in the

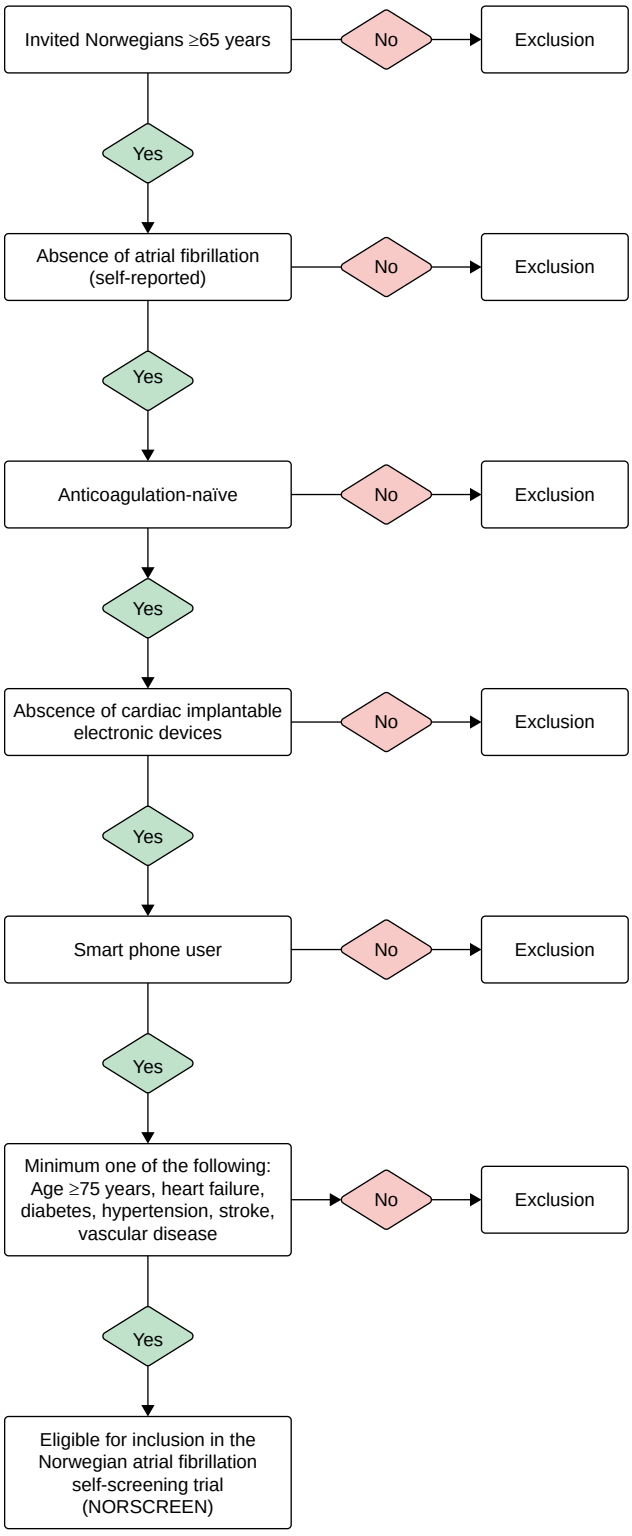



**Figure 1** The inclusion and exclusion test of the NORSCREEN trial.

intention-to-treat analysis, but in the adjusted as-treated analysis, the risk reduction was higher (17%, $P < 0.001$).[5] Due to a different study design (randomization after consent) in the NORSCREEN trial compared with STROKESTOP, and also an anticipated higher AF detection rate (5%) due to continuous screening for several days repeated after 12–18 months, a 15% relative risk reduction was anticipated in the NORSCREEN. A sample size of 28 000 (14 000 in each group) is needed to detect a 15% relative reduction in risk of stroke after 5 years with 90% statistical power using

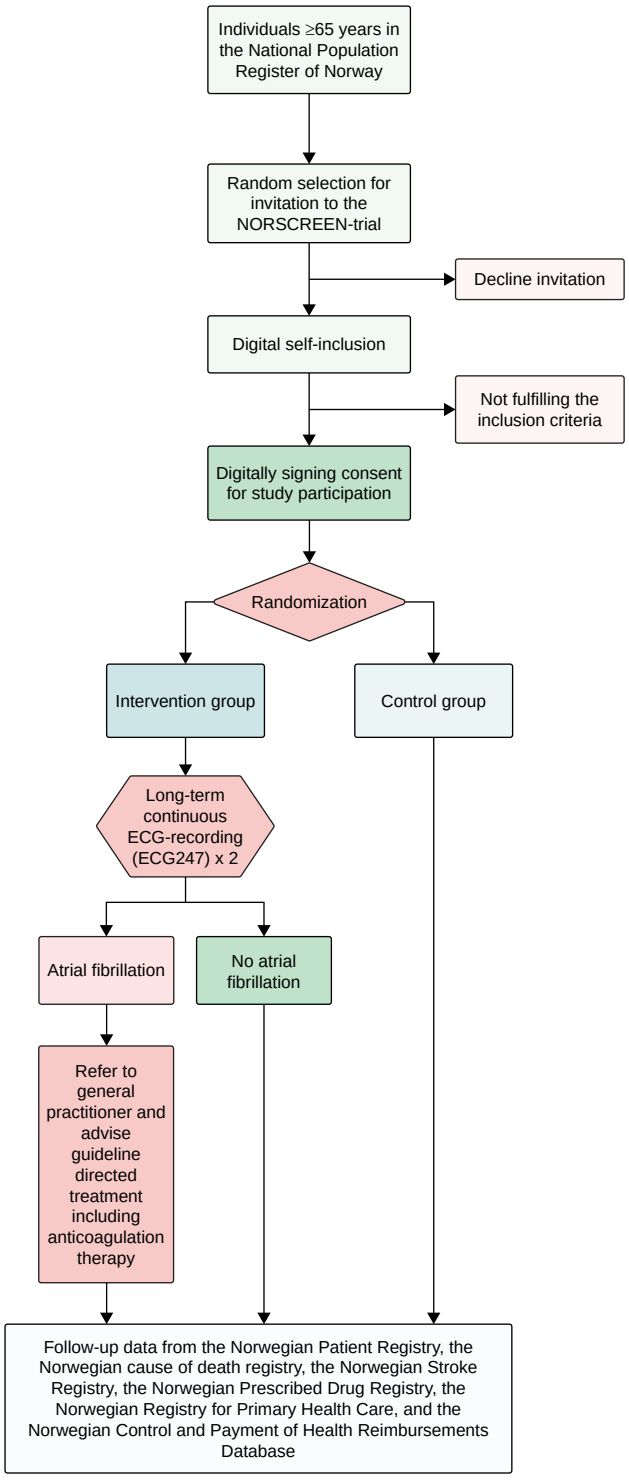



**Figure 2** The study flow chart.

a log-rank test with a two-sided significance level of 0.05. In total, 1574 outcome events will be required under these assumptions. We expect ~20% rate of non-performance of ECG testing in the intervention group and will include a total of 35 000 participants in the study. The stroke rate in the whole trial population will be assessed after 3 years, and the follow-up duration may be modified if the stroke rate differs from what is expected.

## Statistical analyses

Continuous variables will be presented as means ± standard deviations or medians (25th percentile, 75th percentile), and differences between groups will be analysed using independent sample *t*-tests or Mann–Whitney non-parametric tests, as appropriate. Categorical variables will be presented as

**Figure 3** The ECG screening device, ECG247 Smart Heart Sensor (www.ecg247.com).

**Table 1** Outcomes defined by ICD codes in the Norwegian Stroke Registry and the Norwegian Patient Registry

| Outcome | ICD-10 code |
|---|---|
| Stroke | I61, I63, I64 |
| AF and flutter | I48 |
| Non-traumatic subarachnoid haemorrhage | I60 |
| Vascular dementia | F01 |
| Myocardial infarction | I21–I22 |
| Heart failure | I50 |
| Gastrointestinal haemorrhages | K25–K29, K92.0–K92.2 |
| Other haemorrhages | K62.5, J66.1, I85.0, I98.3, N02, N93.9, N95.0, N50.1A, H11.3, H31.3, H35.6, H43.1, H45.0, H92.2, I31.2, J94.2, M25.0, R04, R58, D62.9 |

numbers and percentages, and differences between groups will be analysed by the $\chi^2$ test or Fisher's exact test. Incidences will be reported as the number of events per 100 years at risk. The primary analysis will be performed on the intention-to-treat population. The rate of the primary outcome (stroke) will be presented for the two randomization groups using the Kaplan–Meier method, and a comparison will be made between the groups using a log-rank test. The treatment effect as measured by the hazard ratio (HR) and 95% confidence interval (CI) will be derived by using the Cox proportional hazards model with the randomization group as the main covariate. The proportional hazards assumptions will be checked. The participants will be censored at the earliest of an event, death, withdrawal-of-consent, or end of follow-up.

## Patient and public involvement

The Steering Committee includes a user representative who was involved in the preparation of the study protocol. Feedback from the participants will be used to adjust the study procedure within the protocol frames.

## Ethics and regulatory approvals

This study will be conducted in accordance with the Declaration of Helsinki. The study protocol is consistent with Good Clinical Practice and applicable regulatory requirements. All patients must provide a digitally signed informed consent form prior to study participation. Patient data will be recorded in accordance with national personal data protection laws. The study protocol, including patient information and informed consent form, has been approved by the Norwegian Committee for Medical and Health Research Ethics (477781) and by the Data Protection Officer at Oslo University Hospital. The trial protocol is registered at clinicaltrials.org (NCT05914883).

## Study organization

The study is a collaboration involving all Norwegian health regions. The study is chaired, administered, and co-ordinated from the Oslo University Hospital Ullevaal, Norway. The Oslo University Hospital is responsible

for overseeing all aspects of the study. The practical aspects of the study are co-ordinated from a study centre at Sorlandet Hospital Arendal, Norway.

The National Steering Committee is composed of the study chair (S.H.), cardiologists from all regional health authorities in Norway, representatives from the study centre, an international collaborator with expertise in clinical AF studies, a statistician, and a user representative.

The Data and Safety Monitoring Board (DSMB) consists of two independent cardiologists. The DSMB members are not part of the study organization and have no competing interests. The DSMB will review all arrhythmias and the clinical trial data on an ongoing basis to ensure the safety of the study subjects and validity and integrity of the data.

## Study status and estimated timeline

The first participant in the NORSCREEN trial was enrolled on 1 September 2023. A total of 132 588 potential study participants have been invited to the study as of 22 July 2024. Of them, 47 929 (36%) took the digital inclusion/exclusion test and 22 969 individuals fulfilled the inclusion criteria. Of the 22 969 individuals, 14 922 (65%) have signed the consent form for study participation. The mean age was 73 (5.2) years, and 46% were women. Of the 14 922 study participants, 7422 were randomized to the ECG screening test. Approximately 3800 of these participants have taken the AF screening test so far (as per 22 July 2024). Further study progression depends on the number of available ECG sensors, participant delay, postal delay, and available study staff. We estimate to include all participants within Q2, 2025.

# Discussion

The NORSCREEN trial will provide new information on the benefit and cost-effectiveness of AF screening in individuals ≥65 years of age with an increased risk of stroke.

Atrial fibrillation fulfils most criteria for a population screening exercise.[12] Atrial fibrillation–related complications represent an important health problem worldwide, it has a recognizable latent stage, acceptable and reliable tests are available, and preventive treatment is well-documented. However, the cost-effectiveness of AF screening remains an unsettled question. The ESC recommends opportunistic screening, but there is insufficient evidence to recommend screening of the general population.[1,13–16]

In the Swedish STROKESTOP study, a strategy with AF screening by thumb ECG twice daily for 2 weeks in 7165 individuals aged 75–76 years was found to reduce the composite primary endpoint (stroke, systemic embolism, bleeding leading to hospitalization, and all-cause death) by 4% and the risk of ischaemic stroke by 8% in the intervention group compared with the control group.[5] This broad AF screening strategy in an elderly population was also documented to be cost-effective.[17]

In the Danish randomized controlled LOOP study, AF screening with an implantable loop recorder in 1501 individuals aged 70–90 years resulted in a three-time increase in the number of patients with AF detected and anticoagulation initiated and a non-significant 20% reduction in the risk of stroke or systemic arterial embolism during follow-up (HR 0.80; 95% CI 0.61–1.05; $P = 0.11$).[6]

The randomized SCREEN-AF trial and the REHEARSE-AF trial demonstrated increased AF detection but no effect on clinical outcomes.[18,19] The GUARD-AF study was hampered by the coronavirus disease 2019 pandemic and enrolment was stopped without any conclusion being reached.[20] The non-randomized mSToPS study demonstrated improved clinical outcomes at 3 years relative to matched controls.[21] The smartwatch AF screening trials from Apple, Huawei, and Fitbit included participants from their own customer populations, required a final ECG confirmation step, and did not report a stroke outcome.[22–24]

The STROKESTOP II study included the use of N-terminal B-type natriuretic peptide (NT-proBNP) for risk stratification, but stroke outcome data were not reported.[25] The results from the large ongoing British Screening for Atrial Fibrillation with ECG to Reduce stroke (SAFER) trial are not yet ready.[26] Both studies utilize single-point ECG measurements (thumb ECG), while the NORSCREEN trial uses continuous ECG monitoring over several days.

Conventional AF screening trials may be time- and resource-intensive. A fully digital approach may shorten recruitment time, increase protocol adherence, and ensure representative sampling of study participants at a lower cost. However, the utility of a digital screening procedure for AF depends on the efficacy of the recruitment process, the method of ECG recording, the level of digital literacy in the invited-to-screen population, and the degree of adherence to treatment advice in patients who test positive for AF. Furthermore, a follow-up through linkage to nationwide health registries entails a risk of underestimating the number of endpoints. To avoid this, we will combine several registers and compare these with self-reported data. Of note, the level of compliance with the mandatory national health registries in Norway is very high.

Inclusion of a sufficient number of study participants in clinical studies may be challenging.[27] Digital study recruitment was effective in the Norwegian Atrial Fibrillation self-screening pilot study, but selection biases regarding age, gender, comorbidity, and digital literacy were introduced.[7] Similar findings were reported from a Swedish study of women with palpitations.[28] The NORSCREEN trial invites participants ≥65 years randomly from the National Population Register of Norway to minimize the risk of age and gender biases. However, several other barriers such as time commitment, procedural complexities, frailty, and concerns about health outcomes may hamper the inclusion and performance of the study. Frailty is common in elderly people, and frailty strongly impacts digital skills and outcome.[29–31] Digital inclusion is expected to cause less frailty burden but may introduce a certain, but inevitable, healthy user bias.

The control group will not receive any study-related interventions. However, it is difficult to avoid the Hawthorne effect (i.e. modifying behaviour in response to an awareness of being observed) in an RCT that requires signed consent.[32] In this study with fully digital inclusion and follow-up through linkage with registries (i.e. no clinical visits), the effect might be considered as small.

Long-term continuous ECG monitoring improves the detection rate of intermittent AF.[33] Conventional Holter monitoring systems may be cumbersome to use, have short test periods, and may be sensitive to disturbances. Thumb ECG devices used in several AF screening trials have highly limited heart rhythm monitoring time and consequently lower sensitivity to intermittent arrhythmias.[5,25,34] The implantable loop recorder allows for continuous rhythm monitoring over years but requires surgical procedures to be performed. Electrocardiogram documentation of arrhythmias is necessary, and watches with heart rate monitoring based on arterial pressure wave (photoplethysmography) sensors cannot be used for final clinical diagnosis.[1,35] A patch ECG monitor system may address some of the challenges with other ECG recording systems and has shown to be well-suited for AF screening.[5,7,18,36] However, the diagnostic accuracy of the devices is crucial, and some arrhythmia episodes might be undetected by these systems.

Different definitions of AF may also impact the reported results of AF screening trials. The NOAH-AFNET 6 trial assessed the efficacy and safety of anticoagulation therapy in patients with device-detected atrial high-rate episodes.[37] Oral anticoagulation in these patients increased bleeding without reducing the composite endpoint. In contrast, patients with asymptomatic AF treated with apixaban in the ARTESIA trial had a reduced risk of stroke compared with patients with asymptomatic AF treated with aspirin.[38] A study-level meta-analysis of these two studies revealed complete consistency regarding the outcomes of stroke and major bleeding.[39]

Initiation of anticoagulation therapy in patients with AF and an increased risk of stroke is crucial to obtain the benefits of AF screening. The STROKESTOP and LOOP studies reported the initiation of anticoagulation therapy in 93% and 91% of the participants with AF, respectively.[5,6] However, these studies were conducted as traditional clinical studies with personal follow-up. The initiation of anticoagulation therapy was not reported in the Apple Heart Study or the Fitbit study.[22,23]

In the Norwegian Atrial Fibrillation self-screening pilot study, anticoagulation therapy was initiated in 83% of patients who tested positive for AF during screening, by local GPs.[40] Preliminary findings indicate a high rate of initiation of anticoagulation therapy in participants with AF in the NORSCREEN trial, probably due to close communication with the participants and their GPs.

# Conclusions

The NORSCREEN trial is the first large-scale RCT performing a digital siteless self-screening for AF with continuous ECG monitoring over several days. The NORSCREEN trial will provide new insights regarding the efficacy of AF screening and may change the future recommendations for AF screening in individuals at an increased risk of stroke.

# Authors' contribution

All authors contributed to the study design and conception. M.B., J.J., and S.H. drafted the manuscript, and M.B.H., T.B., J.E., M.-L.L., P.S., E.L.S., J.G., D.A., O.-G.A., A.H.P., and B.L.G. critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of this work, ensuring its integrity and accuracy.

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**Conflict of interest:** M.B. has received consultant fees from Pfizer. J.J. has received consultant or lecture fees from Amarin, Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Novartis, Pfizer, and Sanofi. He is a shareholder in Appsens AS and is partly employed in the company. T.B. has received consultant or lecture fees from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, and Pfizer. J.E. has received consultant or lecture fees from Roche Diagnostics, Pfizer, Bristol Myers Squibb, Organon, Piotrode, and Philips and research grants from the Swedish Research Council, the Swedish Heart and Lung Foundation, the Swedish Innovation Agency, and the Stockholm Region. M.-L.L. has received lecture fees from Bayer, Bristol Myers Squibb, Pfizer, and Sanofi. P.S. has received lecture fees from Johnson & Johnson. E.L.S. has received consultant or lecture fees from AstraZeneca and Pfizer. J.G. has received consultant or lecture fees from Bayer, Boehringer Ingelheim, Novartis, and Sanofi and fees for participating in an expert panel from Sanofi, unrelated to this work. D.A. has received consultant or lecture fees from Amarin, Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Merck & Co., Novartis, Pfizer, Pharmacosmos, Sanofi, and Vifor, as well as research funding to his institution from Bristol Myers Squibb, Pfizer, Medtronic, and Roche Diagnostics. B.L.G. has received consultant or lecture fees from Bristol Myers Squibb, Pfizer, Novartis, Astra Zeneca, Boehringer Ingelheim, and Bayer. S.H. has received consultant or lecture fees from Astra Zeneca, Bristol Myers Squibb, Novartis, Pfizer, and Sanofi. All other authors have no conflicts of interest.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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