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Randomised, siteless study to compare systematic atrial fibrillation screening using enrichment by a risk prediction model with standard care in a Swedish population aged ≥ 65 years: CONSIDERING-AF study design

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ABSTRACT

Introduction Atrial fibrillation (AF) is the most common arrhythmia and confers an increased risk of mortality, stroke, heart failure and cognitive decline. There is growing interest in AF screening; however, the most suitable population and device for AF detection remains to be elucidated. Here, we present the design of the CONSIDERING-AF (deteCtiON and Stroke preventIon by moDEl scRreenING for Atrial Fibrillation) study.

Methods and analysis CONSIDERING-AF is a randomised, controlled, siteless, non-blinded diagnostic superiority trial with four parallel groups and a primary endpoint of identifying AF during a 6-month study period set in Region Halland, Sweden. In each group, 740 individuals aged≥65 years will be included. The primary objective is to compare the intervention of AF screening enrichment using a risk prediction model (RPM), followed by 14 days of a continuous ECG patch, with no intervention (standard care). Primary outcome is defined as the incident AF recorded in the Region Halland Information Database after 6 months as compared with standard care. Secondary endpoints include the difference in incident AF between groups enriched or not by the RPM, with and without an invitation to 14 days of continuous ECG recording, and the proportions of oral anticoagulation treatment in the four groups.

Ethics and dissemination This study has ethical approval from the Swedish Ethical Review Authority. Results will be published in peer-reviewed international journals.

Trial registration number NCT05838781.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A prospective atrial fibrillation (AF) screening study, using a risk prediction model.
⇒ Siteless design, with mailed invitation and digital informed consent. Participants will self-apply and return the device after completion of recording.
⇒ Four-arm design making comparison between different subgroups possible. Control arms not invited to use the device, but still with detailed phenotyping available, including incident AF (if detected by standard care).
⇒ Primary endpoint is AF incidence in the different arms, although the study was not designed to assess clinical outcomes such as stroke and dementia.
⇒ A single ECG modality (14-day patch) is applied for the intervention arms.

INTRODUCTION

Background

Atrial fibrillation (AF) is the most prevalent arrhythmia and poses an increasing burden to patients, their next of kin, and the healthcare system. It is associated with a markedly increased risk for ischaemic stroke, and an increased risk for heart failure, cognitive decline, hospitalisations and death.

As reported from several nationwide reports,[1–4] the prevalence of diagnosed AF in the adult population is at least 3%.[4] However, the true prevalence is higher because many patients with AF have no or mild symptoms.[5] Epidemiological projections estimate at least a doubling of the number of patients with AF by the year 2060.[6]

Several risk factors for AF incidence have been identified. Advanced age and male sex are associated with AF,[4] as well as hypertension, heart failure, heart valve disease, diabetes, renal failure, obesity, sleep apnoea and alcohol consumption.[7] Furthermore, several specific cardiovascular biomarkers,

like excessive supraventricular ectopic activity,[8] enlarged left atrium[9] and elevated levels of the plasma biomarker NT-proBNP[10] are associated with AF as well. There has been an increasing interest in AF screening since it is an important healthcare problem with an early recognisable state, a suitable test for its detection is available and there is treatment that is generally accepted to be effective.[11]

The STROKESTOP pilot study was the first trial to use ambulatory ECG for AF screening and identified 7% at high risk in a 75-year-old population using intermittent handheld ECG.[12] The STROKESTOP study reported a modest net benefit in hard clinical endpoints by a reduction of a composite endpoint of stroke, systemic embolism, death and severe bleeding.[13]

The Danish LOOP study used implantable ECG loop recorders in a population aged 70–90 years enriched with one or more stroke risk factors. With the use of continuous ECG monitoring, AF was diagnosed in 32% of the participants randomised to implantable recorders over the course of 65 months. The reported reduction of stroke incidence in the intervention group was, however, not statistically different from the non-intervention group.[14]

The most suitable population and method for AF detection remains to be defined. In most AF screening studies, some form of enrichment of the screening population has been attempted, most commonly by age.

The availability of digital health data has enabled the identification of individuals with high risk of AF, with detailed phenotyping. A risk prediction model (RPM) for AF incidence has been previously developed.[15] The model was initially developed by using a German real-world insurance claims dataset of patients with and without known AF.[15] The prediction model has subsequently been validated.[16]

Novel ambulatory ECG-recording modalities have made long-term continuous monitoring possible, in a device which can be applied without assistance from healthcare professionals.[17] The combination of the RPM and ECG patch recording has the potential of improving both the AF identification and participation in AF screening. Uptake in AF screening studies has been lower than in other established screening programmes. In the STROKESTOP studies,[18–20] uptake was approximately 50%, while in digital, siteless studies, uptake was even lower.[21 22]

The purpose of this randomised controlled trial is to test the hypothesis that AF screening in a population with high-risk features, defined by a risk prediction algorithm based on risk factors using a data-driven healthcare approach, is superior to standard care in detecting new AF in patients aged≥65 years.

Study objectives

Primary objective

To compare the rate of identification of newly diagnosed AF using 14-day continuous ECG patch recording in a population aged ≥65 years and an increased risk for AF, according to the RPM, compared with standard of care in Region Halland (RH; no systematic screening), that is, a comparison of rate of identification between RPM/intervention and general/control arms.

Secondary objectives

1. To compare the rate of identification of newly diagnosed AF using 14-day continuous ECG patch in a population aged ≥65 years with an increased risk for AF according to the RPM, compared with a population with increased risk according to the RPM without intervention, that is, comparison of yield between RPM/intervention and RPM/control arms.
2. To compare the rate of identification of newly diagnosed AF using 14-day continuous ECG patch in a general population aged ≥65 years compared with a population with increased risk, according to the RPM, without intervention, that is, comparison of yield between general/intervention and RPM/control arms.
3. To compare the rate of identification of newly diagnosed AF using 14-day continuous ECG patch in a general population aged≥65 years compared with a general population without intervention, that is, comparison of yield between general/intervention and general/control arms.
4. To study the proportion of patients starting oral anticoagulation treatment among those with newly diagnosed with AF, in both general and RPM cohorts.
5. To study the uptake of self-application of patch ECG in the general and RPM intervention arms respectively.

Trial design

CONSIDERING-AF (deteCtiON and Stroke preventIon by moDEl scRreenING for Atrial Fibrillation) is a randomised, controlled, siteless, non-blinded diagnostic superiority trial with four parallel groups and a primary endpoint of identifying incident AF during a 6-month study period.

METHODS AND ANALYSIS

Study population

The study will be conducted in RH, located in southwestern Sweden, with an approximate population of 330 000 residents. RH has built up an information data platform, the Region Halland Information platform (RHIP) since 2009.[23] The data include primary healthcare, emergency department, hospital admissions and hospital outpatient care and inpatient care.

RHIP also contains data on patient mortality, including the date of death. Data regarding dispensed drugs are retrieved from the National Prescribed Drug Register.

Data are made available for research, in pseudonymised form, after ethical approval from the EPM (Swedish Ethical Review Authority) and, RH's internal processes for Data Privacy Impact Assessment and data extraction. Privacy agreements will be established, if required. The RHIP is updated once a week and data are validated by the department for information-driven care in RH. Consent

from private primary care operators will be obtained as well.

Study design

The study consists of two steps: first, the retrospective phase, which is calibrating the RPM to the local population; and second the prospective phase, assessing the effectiveness of AF screening with the RPM combined with ECG patch recording.

Step 1

The RPM will be calibrated in the Swedish healthcare system by using a dataset which includes patients with known AF and patients with no record of AF, from RHIP.

The population in step 1 will, in order to align with the initial studies using the algorithm, be patients with a record of incident AF diagnosis between 1 January 2016 and 31 December 2019 (observation period). We will include patients≥45 years of age at index date, which is the first date of an AF diagnosis recorded in the observation period. Patients will be excluded if they have an AF diagnosis recorded in the previous 10 years. The control will be those patients aged≥45 years of age, at random pseudo-index dates during the study period between 1 January 2016 and 31 December 2019, that did not have any record of an AF diagnostic code in their healthcare records at RH. The index date for the controls will be a random pseudo-index date during the observation period.

Step 2

This step is a prospective randomised controlled trial of the effectiveness and feasibility of the RPM combined with diagnostic testing in detecting undiagnosed AF in a real-world setting. Eligible patients are residents in RH, aged≥65 years, and there are several reasons for choosing the age group≥65 years.

First, diagnostic yield in AF screening is highly age dependent. Second, the performance of the model to predict already diagnosed cases is very different from finding new cases in a screening programme. Third, the recommendations from the European Society of Cardiology recommends AF screening from 65 years of age.[7] Further, with the use of the age range≥45 years, there is a risk that individuals with a low stroke risk, according to CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age≥75 years (doubled), Diabetes mellitus, Stroke/ Transient Ischaemic Attack (TIA) (doubled), Vascular disease, age 65–74 years and Sex category (female)), will be diagnosed since a number of the risk factors in the algorithm are not included in CHA_2DS_2-VASc. With the age cut-off of≥65 years, almost all participants diagnosed with AF will have an indication for anticoagulation treatment as age is an important stroke risk factor.

In step 2, participants will be randomised in a general cohort (n=24 000) and an RPM cohort (n=24 000), respectively.

A random subset of participants in the general cohort will then be randomised to either a general/control arm (n=740), where only clinical health records during the study period will be collected, or a general/intervention arm, (n=740) where the participants will be invited to participate in 14 days of continuous ECG monitoring.

Participants randomised to the RPM cohort will be subject to the application of the algorithm. A subset of participants with a prediction cut-off value greater than 5% will then be randomised to an RPM/control arm (n=740) or an RPM/intervention arm (n=740).

A schedule of trial time points for enrolment, intervention and data collection is outlined in table 1, in accordance with the Standardized Protocol Items: Recommendation for Interventional Trials guidelines.[24] A CONsolidated Standards of Reporting Trials diagram[25] is shown in figure 1.

Inclusion criteria

Alive residents in the RH aged 65 or older without a recorded diagnosis of AF.

Exclusion criteria

1. Previous known diagnosis of AF.
2. Death after pseudonymisation and extraction of the cohorts.
3. No longer resident in RH.
4. Patients with a pacemaker, implantable cardioverter defibrillator or insertable cardiac monitor.
5. Dementia.
6. Other indications for oral anticoagulation (OAC) (such as venous thromboembolism, mechanical heart valves, mitral stenosis, thromboprophylaxis post surgery).

Patient and public involvement

None.

Intervention arm

The study population is first randomised into two (general and RPM) cohorts. Each cohort is randomised into two (control and intervention) arms, resulting in two intervention (general/intervention and RPM/intervention) arms. The rationale behind the two-by-two factorial design is to examine the independent effects of RPM and 14 days of continuous ECG patch monitoring on the AF detection yield.

Individuals in the intervention arms will be invited to 14 days of continuous ECG patch monitoring with the Philips ePatch (Royal Philips, Amsterdam, the Netherlands, https://www.gobio.com/epatch). Requests for participation will be sent by postal mail and informed consent will be obtained via mobile phone digital identification. Two reminders will be sent for those who do not respond. To enable invitation, data for the intervention cohorts will be repersonalised. A case report form (CRF) number will be assigned to each individual. This will be done in an invitation database within RH and according to RH's regulations.

Table 1 A schedule of trial time points according to the Standardized Protocol Items: Recommendation for Interventional Trials guidelines (ref)

	Study period					
	Enrolment	Allocation	Post-allocation			Close-out
Timepoint*	$-t_1$	t_0	t_1	t_2	t_3	t_4
Enrolment						
Eligibility screen	X					
Assessment of AF risk		X				
Allocation		X				
Informed consent			X			
Interventions						
14-day continuous ECG monitoring (ePatch)				⟷		
Assessments						
Baseline characteristics and medical history			X			
Incident AF on ePatch (intervention)				⟷		
Incident AF in RHIP (control)						X

*-t1: activities prior to randomisation and treatment allocation; t0: randomisation and treatment allocation; t1: obtain informed consent; t2: send out mails containing an ePatch; t3: completing ePatch monitoring and assess AF diagnoses; collect AF diagnoses from RHIP.
AF, atrial fibrillation; RHIP, Region Halland Information Platform.

For those who accept participation, the ePatch device will be sent by postal mail together with instructions on how to apply the device, and a prepaid envelope for return. The participants will self-deploy the device by following the written instructions and, if needed, there will also be virtual support (phone, digital) available. Phone reminders are considered for those who have not attached the patch or have not returned it. Adherence to intervention can be obtained through ECG-monitoring time. Participants can end ECG monitoring prematurely in case of any dermal adverse events related to the ECG patch.

After the monitoring period is completed, the device will be returned to the ECG patch provider. The ECGs will be interpreted in a core facility led by cardiologists. AF is defined as at least one episode of AF or atrial flutter with at least 30 s duration. Participants identified having AF will be offered an appointment with a physician for assessment regarding treatment including oral anticoagulation and will be managed accordingly. Patients with findings of significant arrhythmia apart from AF or atrial flutter (ie, second-degree or third-degree atrioventricular block, supraventricular tachyarrhythmias, ventricular tachyarrhythmias, markedly increased proportion of premature ventricular contractions or symptomatic sinus arrest) will be contacted for further clinical follow-up according to standard of care. For participants without significant arrhythmia, a letter will be sent with information on the result within 4 weeks from upload of ECG data.

The timeline is described in table 2. Within 4 weeks from data extraction, we intend to send out invitations to the intervention cohorts. Updated electronic health record data will be collected 4 weeks after data from the final ePatch has been analysed. Preliminary analysis of the ECGs will be performed within two office days.

Control arms

As previously described, the trial has a two-by-two factorial design, meaning the study group is first randomised into two (general and RPM) cohorts, with each cohort subsequently randomised into two (control and intervention) arms. Accordingly, there are two control arms in the trial (general/control and RPM/control). These arms will not be contacted and pseudonymised data from standard care will be collected during the study period as routine for the health plan organisation, without informed consent.

Data entry

Two sources will be used for data extraction: electronic health records and a secure web-based database operated by Biotel/Philips, where all ECG data (ePatch) is uploaded. Medical records, baseline characteristics, including comorbidities, will be collected as well as the occurrence of a diagnosis of AF during follow-up. The extraction will be directly to the standalone database, via the search and report function. The Biotel/Philips database ECG data, linked to the unique study number, will be uploaded by Biotel/Philips. The ECG data will, accordingly, be pseudonymised for the cardiologist/investigator interpreting the ECGs. The ECG data will manually be entered into the standalone database by the investigators. A time and event schedule for data collection is shown in table 2.

Primary outcome

In the alive population aged at least 65 years and free from AF in RH, what is the difference in incident AF

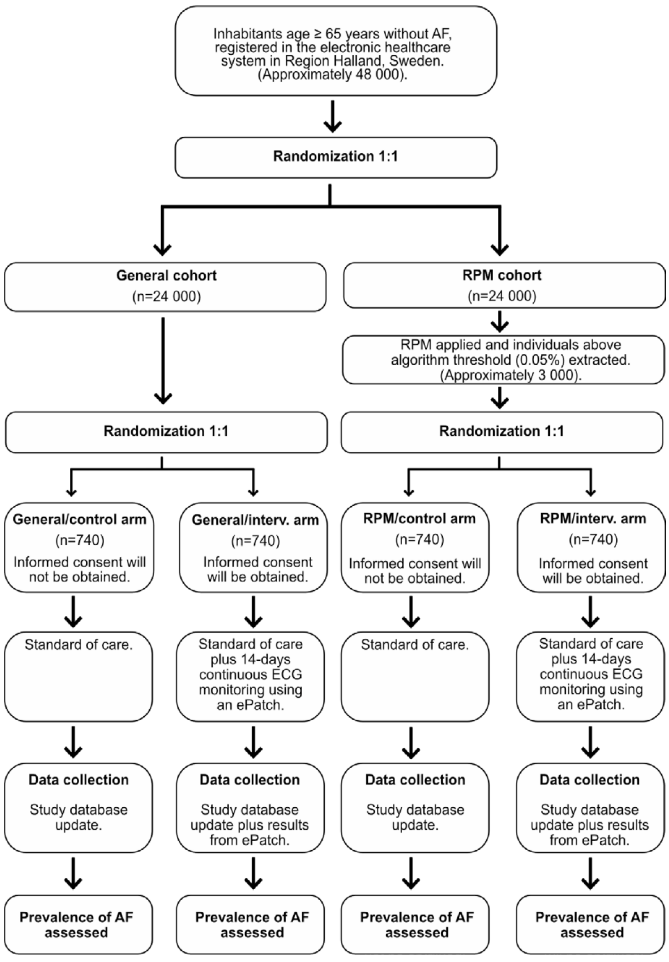

Figure 1 CONSIDERING-AF (deteCtiON and Stroke preventIon by moDEl scRreenING for Atrial Fibrillation) trial flow chart according to the CONsolidated Standards of Reporting Trials guidelines.[26] AF, atrial fibrillation; RPM, risk prediction model.

diagnosed in RHIP between those with increased risk of incident AF, according to the RPM and invited to 14 days of ambulatory continuous ECG patch recording, and those not invited to any intervention (standard care) during a 6-month screening period?

Table 2 Time and event schedule for data collection

Time	Data gathered/endpoint	Instrument
t0	Prediction of AF risk (RPM arm)	BMS AF prediction algorithm
t1	Baseline characteristics and medical history	EHR
t2–t3	Incident AF at least 30 s on ePatch	ECG database
t4	Incident AF in RHIP	EHR

t0: allocation; t1: mail Nr 1: participation request; t3: return of ePatch; t4: close-out.
AF, atrial fibrillation; EHR, electronic health record; RHIP, Region Halland Information Platform; RPM, risk prediction model.

Secondary outcomes

- What is the difference in incident AF between those with increased risk of incident AF, according to the RPM and invited to 14 days of ambulatory continuous ECG patch recording, and those with increased risk of incident AF according to the RPM not invited to any intervention during a 6-month screening period?
- What is the difference in incident AF between those without RPM enrichment, and invited to 14 days of ambulatory continuous ECG patch recording, and those with increased risk of incident AF according to the RPM not invited to any intervention during a 6-month screening period?
- What is the difference in incident AF between those without RPM enrichment, invited to 14 days of ambulatory continuous ECG patch recording, and those without enrichment not invited to any intervention during a 6-month screening period?

Explorative outcomes

- What is the difference in proportion of patients with AF and treatment with OAC, recorded in the RHIP in the control and interventions arms in the general and RPM cohorts, respectively, during a 6-month, 12-month and 18-month period?
- What is the uptake of self-application of patch ECG, in the general and RPM intervention arms, respectively, defined as the fraction of mailed out ECG patches resulting in the upload of at least 7 days of readable ECG signal during 6-month screening period?
- What is the proportion of patients diagnosed with AF within the first 24 and 48 hours of their ECG patch recording? Cost-effectiveness using a Markov model divided into two parts. The first part will analyse the screening procedure, the second part will describe anticoagulation treatment, and the risk of stroke, bleeding and mortality.

Data validation

To ensure the accuracy and quality of data entered into the database, we will perform validation checks at different stages during the data collection process. A validation sample will be used to set the data mining routine from the electronic healthcare system. The sample will be checked manually to ensure that all required data are present and to compare source and target data fields, thereby identifying changes that will be required of the source data to match the schema in the target database. In addition, incomplete counts, incorrect formats, duplicate data and null field values will be identified. To ensure the proper entering of ECG data into the target database, validation checks will be built into the input function. Validation checks that will be used are data type checks (ensures correct data type that is, only accepting numeric data), format checks (ensures correct data format that is, dates in fixed format), code checks (ensures the value is selected from a valid list or following certain formatting rules) and range checks (ensures the value falls within the

Table 3 Risk factors, ORs, the original International Classification of Diseases Tenth revision (ICD10) and Anatomical Therapeutic Chemical (ATC) codes, and the adjusted ones for the Swedish healthcare system for incident AF, adopted from ref 15

Risk factor	OR	Original ICD10 (and ATC codes)	Adjusted ICD10 (and ATC codes)
Age			
Age 45–49 years	0.08		
Age 50–54 years	0.13		
Age 55–59 years	0.19		
Age 60–64 years	0.30		
Age 65–69 years	0.46		
Age 70–74 years	0.71		
Age 80–84 years	1.45		
Age 85–89 years	1.91		
Age≥90 years	2.24		
Male sex	1.52		
Hypertension, treated	1.76	I10, I11; I12; I13; 115 (C02; C03)	I10, I11; I12; I13; 115 (C02; C03; C08CA; C09A-D)
Heart failure, treated	1.54	I50 (C09A; C07; C03DA)	I50 (C09A; C07; C03DA; C09A-D; A10BK)
Valvular heart disease	1.42	I05.- I08.; I34.-I39.	I05.- I08.;
Chronic kidney disease	1.21	N18	N18
Stroke, not specified as haemorrhage or infarction	2.43	I64	I63
Hemiplegia	3.04	G81	G81
Other pulmonary heart diseases	1.60	I27	I27
Paroxysmal tachycardia	2.20	I47	I47
Other cardiac arrhythmias	2.11	I49	I49
Ulcer of lower limb (not elsewhere classified)	1.65	L97	L97, I70.2
Personal history of medical treatment	1.62	Z92	Z92

specified range). Suitable data validation checks will be used for each field.

Statistical analysis methods

In step 1, the RPM will be tested and calibrated in the RH population. For that, we will extract two cohorts, the AF cohort with an AF diagnosis, and the control cohort without any AF diagnosis in their history. Specifically, we are looking to calibrate the intercept (α) for the logistic regression, where we already have the odd ratios for the 13 risk factors from the German study previously mentioned[15] and listed in table 3.

Following a brute-force approach, we will test all values between range [−5, 5] and find the intercept that obtains the closest event rate compared with the original German study event rate.

In step 2, applying the algorithm on the selected population of the control cohort without any known AF diagnosis, the at-risk group will be extracted using the recommended cut-off value.

The clinical characteristics and demographics for both arms will be presented using descriptive data. Continuous variables will be presented using mean and SD. For continuous variables, Student's t-test will be used. For proportions, Fisher's exact test or χ^2 test will be used and summarised using frequency and percentages. Ordinal data will be analysed with the Mann-Whitney U or Kruskal-Wallis test. A sensitivity analysis will be performed on both arms. All statistical tests will be two-sided, unless otherwise specified, and $p<0.05$ will be used to identify significant differences. The primary objective will be analysed according to intention to screen, that is, all live individuals invited to the study will be in the numerator for the primary endpoint.

Power/sample size

The total living population aged≥65 years in RH with no previous diagnosis of AF in their EHR (queried June 2021) is around 48 000 adults. Among these, using the RPM, around half are detected as at-risk groups.

The prevalence of AF at RH in this age group (aged≥65 years) is 10.6%. Based on previous AF screening studies using continuous long-term ECG in this age group,[21 26] it is estimated that 6% of ePatch-screened participants will be diagnosed with AF, while in the usual clinical routine the rate is estimated at 1% per year. A participation of

50% is expected in the intervention group, resulting in an estimated AF detection of 3.5% among the invitees according to intention to screen. Having set alpha at 0.05, a sample size of 737 is needed to be recruited per each arm to reach the power of 90%.

Randomisation

Randomisation will be performed using a random computer number generator in a one-to-one block allocation ratio. The participants will be stratified based on age and sex, in both the intervention and control arms, to achieve a balance of participant characteristics.

Data monitoring and safety

The trial will not have a data monitoring committee. The reason is the short study time and there are no adverse events linked to the use of the RPM. However, adverse events may occur during the ECG screening process. These potential adverse events (skin redness and itching) are regarded as low risk both in terms of occurrence and consequences but will be reported to Biotel/Philips. The number of lost patches, that is, not attached or not returned, will be monitored. In the event of technical issues with the ePatch which cannot be resolved, a new ePatch will be sent out. If the ePatch is returned after study closure, the ECG data will not be included in the study analyses, but ECG data will be analysed, and the patient will be handled according to standard of care.

Ethics and dissemination

This protocol complies with the Declaration of Helsinki and International Conference on Harmonization-Good Clinical Practice.[27 28] The study was scrutinised and approved by the Swedish Ethics Review Authority, Dnr 2022-07235. All study-related information will be stored digitally by the sponsor and available only by double authentication. Informed consent will be obtained, digitally via Mobile Bank-ID (Finansiell ID-Teknik BID AB, News (bankid.com)) and QR-code, from patients randomised to one of the intervention arms. The consent will be stored in the invitation database by study staff responsible for the recruitment. After enrolment, each patient will be assigned a unique CRF number. The personal identity of patients will not be used for public purposes or publication. In publication, individuals will not be identifiable.

Informed Consent

Invitees should provide informed consent digitally before enrolment into the study. A participant consent form can be found in the online supplemental material 1 for the General Intervention group and online supplemental material 2 for the RPM Intervention group. Investigators must ensure that patients, or, in those situations where consent cannot be given by patients, their legally acceptable representatives are clearly and fully informed about the purpose of the study, potential risks, the patient's rights and responsibilities when participating in this study.

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Contributors JE and AM conceived the study. FE provided statistical expertise in clinical trial design and wrote the first draft of the manuscript. JH, PM, KM, TD, LS, SK, NY, PP, MW, AS and ES contributed to the trial design. Application to the Swedish Ethical Review Authority for was written by ES and JE. All authors critically revised the manuscript and approved the final version.

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Competing interests JE has received consultant or lecture honoraria from Pfizer, Bristol Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dome, Roche Diagnostics, Philips and Piotrode. JH and AM are employed at Pfizer AB. PM, LS, AS and SK are employed at Bristol Myers Squibb. PP and MW are employees of Philips.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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