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Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE)– rationale and design: a prospective observational study using chest and thumb- ECG.

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SCHOLARONE™
Manuscripts

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3 **Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE)–**
4 **rationale and design: a prospective observational study using chest and**
5 **thumb- ECG.**
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ABSTRACT

Introduction: Atrial fibrillation (AF) causes ischemic stroke and based on risk factor evaluation warrants anticoagulation therapy. In stroke survivors, AF is typically detected with short-term ECG monitoring in the stroke unit. Prolonged continuous ECG monitoring is impractical and requires substantial resources while insertable cardiac monitors are invasive and costly. Chest and thumb-ECG could provide an alternative for AF detection post-stroke.

The primary objective of our study is to assess the incidence of newly diagnosed AF during 28 days of chest and thumb-ECG monitoring in patients with cryptogenic stroke. Secondary objectives are to assess health-related quality of life (HRQoL) using SF-36 and the feasibility of the Coala Heart Monitor™ in patients with stroke.

Methods: Stroke survivors in Region Gävleborg, Sweden, will be eligible for the study from October 2017. Patients with a history of ischemic stroke without documented AF before or during ECG evaluation in the stroke unit will be evaluated by the chest and thumb-ECG system Coala Heart Monitor.™ The monitoring system is connected to a smartphone application which allows for remote monitoring and prompt advice on clinical management. Over a period of 28 days, patients will be monitored twice daily and may activate the ECG recording at symptoms. Upon completion, the system is returned by mail. This system offers a possibility to evaluate the presence of AF post-stroke, but the feasibility of this system in patients who recently suffered from a stroke is unknown. In addition HRQoL using SF-36 in comparison to Swedish population norms will be assessed. The feasibility of the Coala Heart Monitor™ will be assessed by a self-developed questionnaire.

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3 **Ethics and dissemination:** The study was approved by The Regional Ethical
4 Committee in Uppsala (2017/321) and registered at Clinical Trial Registration
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For peer review only

Strengths and limitations of this study

- Chest and thumb-ECG evaluation applied after 24-hour ECG Holter at the stroke unit after confirmation of ischemic stroke.
- Usage of a smartphone application for storage of chest and thumb-ECG which may improve compliance and facilitate fast evaluation by the health-care provider in order to prescribe an anticoagulant when indicated.
- Prospective design including consecutive patients which eliminate both selection and tertiary center bias.
- Management of short (30 seconds) AF episodes, detected by non 12-lead ECG, lack evidence from randomized controlled trials with regard to benefit of anticoagulation.
- The small sample size (n=100) may imply type-II errors in subgroup analyses.

Keywords: atrial fibrillation, cryptogenic stroke, ECG screening, health-related quality of life, SF-36, stroke, thumb-ECG

INTRODUCTION

Atrial fibrillation (AF) causes stroke and systemic embolization, but these devastating events can be prevented by anticoagulant therapy.¹ A non-vitamin K antagonist oral anticoagulant (NOAC) is the preferred choice and effectively reduce the risk of stroke and mortality.² A meta-analysis of the pivotal NOAC trials showed a 19% reduction of stroke/systemic embolism and 10% lower mortality compared to warfarin.² If AF is not diagnosed, antiplatelet medication is current practice following a stroke.³ According to the European Society of Cardiology (ESC), antiplatelet monotherapy should not be considered in the presence of AF, regardless of the stroke risk.⁴⁻⁶ Stroke is a leading cause of disability and death and is the incidence is increasing due to ageing populations and the growing prevalence risk factors such as diabetes and hypertension.⁷⁻⁹ At least 20-30% of patients with ischemic stroke have a documented episode of AF before, during, or after the event, but in a quarter of these patients, the stroke is cryptogenic, meaning that no etiologic factor can be determined.¹⁰⁻¹² However, the proportion of cryptogenic stroke from studies varies due to heterogeneity of cohorts and evaluation tools.

Possibilities for AF detection include monitoring in the hospital ward, repeated electrocardiograms (ECG), Holter monitoring, external event or loop recorders, and long-term outpatient monitoring. Insertable cardiac monitors in cryptogenic stroke yields an AF diagnosis in 8.9% at 6 months and 12.4% at 12 months, but this strategy has not been endorsed in current practice as it requires considerable resources and imply high costs.^{6,13} Episodes of AF may be silent, that is not recognized or reported by the patient, but are nevertheless associated with the same risk of embolization.¹⁴⁻¹⁶ In patients with either dual-chamber pacemakers or implantable defibrillators and with no documented history of AF, 10.1% had episodes

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3 of high-rate atrial tachycardia and this was also associated with an increased risk of
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5 stroke.¹⁷

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8 Sequential stratified ECG monitoring detected AF in 24% of stroke patients in one
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10 study.¹⁰ The diagnostic yield was 11.5% in a pooled analysis, but this yield varies
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12 with such study factors as timing, length of registration, and the monitoring tool.¹⁸ In
13
14 unselected stroke patients, 24-hour monitoring found AF in only 2.4%.¹⁹ This may
15
16 vary substantially with the recording technique; in a recent study, AF (defined as ≥ 30
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18 seconds in duration) was detected in 16.1% of patients monitored by an 30-day
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20 event-triggered recorder compared to 3.2% of patients monitored by 24-hour ECG.²⁰

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23 10 A large multicenter study of stroke patients on Holter monitoring reported new
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25 diagnoses of AF in 2.6% of patients at 24 hours and 4.3% at 72 hours.¹² In another
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27 study, AF was detected in 8.3% of stroke patients monitored by continuous ECG for
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29 a median of 89 hours in the stroke unit; ECG monitoring was superior to 24-hour
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31 Holter monitoring in detecting AF.²¹

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34 15 Thus, while ECG monitoring for an extended period is important for stroke survivors
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36 post-discharge Holter monitoring is impractical, ECG data storage is limited, and data
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38 interpretation requires considerable resources. Therefore, the thumb-ECG offers
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40 advantages in that it monitors conveniently (typically twice daily) and can be
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42 activated to capture symptomatic episodes. For example, AF was detected in 11.4%
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44 of post-stroke patients monitored by thumb-ECG over 21 days versus 2.8% in those
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46 20 continuously monitored for 48 hours.²²

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50 The thumb-ECG monitor system ZenicorTM (Zenicor Medical Systems AB, Stockholm,
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52 Sweden) has been shown to diagnose previously unknown AF in 3.0% of the general
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54 population in Sweden aged 75 years.²³ The ZenicorTM system has been developed
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3 and integrated into the chest and thumb-ECG Coala Heart Monitor™ (Coala Life AB,
4 Stockholm, Sweden). The monitoring system utilizes a smartphone application which
5 allows for remote monitoring by a clinician. This system may help to evaluate the
6 presence of AF post-stroke. However, feasibility of this system in patients who
7 recently suffered a stroke has not been studied. In addition health-related quality of
8 life (HRQoL) using SF-36 in comparison to Swedish population norms will be
9 assessed.^{24,25} The feasibility of the Coala Heart Monitor™ will be assessed by a self-
10 developed questionnaire (see Supplement).

20 OBJECTIVES

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23 10 The primary objective is to assess the incidence of newly diagnosed AF during 28
24 days of chest and thumb-ECG in cryptogenic stroke patients.

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28 The secondary objectives are to assesses HRQoL using SF-36 and the feasibility of
29 the Coala Heart Monitor™ in patients with stroke.

33 METHODS

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36 15 *Setting and selection*

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39 Patients with a clinically confirmed diagnosis of ischemic stroke will be recruited from
40 the catchment area of Region Gävleborg, Sweden. Eligible patients will be identified
41 from daily checks of the medical records in the stroke unit. The recruitment is
42 planned to start in October 2017.

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48 20 *Inclusion and exclusion*

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51 Patients, aged ≥ 18 years, with a validated diagnosis of ischemic cryptogenic stroke
52 are eligible for the study. For screening with chest and thumb-ECG, exclusion criteria
53 are as follows: previously known atrial arrhythmia with an indication for
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3 anticoagulation, implantable defibrillator, pacemaker or insertable cardiac monitor,
4 pregnancy, permanent indication for anticoagulation (including low-molecular weight
5 heparin) due to atrial arrhythmia, mechanical heart valve, deep vein thrombosis, or
6 pulmonary embolism. Patients with a life expectancy ≤ 6 months (e.g. severe heart
7 failure New York Heart Association [NYHA] functional class IV or malignancy) are
8 likewise excluded.

15 *Variables*

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18 Atrial arrhythmia is defined as AF, atrial flutter, or ectopic atrial tachycardia with a
19 duration of at least 30 seconds. Patients characteristics are age, sex, date of current
20 ischemic stroke, previous stroke, known AF, medication (warfarin, NOAC, antiplatelet
21 therapy), heart failure, hypertension, diabetes mellitus, vascular disease (peripheral
22 vascular disease, aortic plaque, coronary artery disease), National Institutes of
23 Health Stroke Scale (NIHSS), 12-lead ECG, and when applicable imaging from
24 carotid-Doppler, computerized tomography, echocardiography, or transesophageal
25 echocardiography, as well as coagulation laboratory examination.

36 *Outcome measurements*

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39 Outcome measurements are arrhythmias recorded by chest and thumb-ECG
40 obtained during scheduled twice-daily recordings or by patient-activated recordings.

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42 Each episode will be classified as AF, atrial flutter, ectopic atrial tachycardia,
43 ventricular tachycardia, premature ventricular complex, or supraventricular ventricular
44 complex. The date and time of each episode will be recorded.

51 *Research questions and endpoints*

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54 The primary endpoint is 28 day cumulative incidence of atrial arrhythmia at 28 days.

Secondary endpoints

- a) The prevalence of previously known atrial arrhythmia before cryptogenic stroke and the number of these patients who had anticoagulant therapy.
- b) Compliance with chest and thumb-ECG at week four (number of recorded scheduled ECG tracings).
- c) Patient-reported experience with chest and thumb-ECG measured at week six (questionnaire as Supplement).
- d) HRQoL (SF-36) at week 6 and at 12 months and the association with AF and compliance with chest and thumb-ECG.
- e) Cumulative incidence of stroke (and all-cause mortality) after three years in patients with AF versus without AF.

Chest and thumb-ECG

Patients will be asked to use the chest and thumb-ECG monitor device twice daily, once between the hours of 6:00 and 10:00 a.m. and again between 6:00 and 10:00 p.m.

If the patients feel palpitations or other symptoms suggestive of arrhythmia (e.g. sudden onset of tiredness, presyncope, syncope) they are asked to record the episode with the smartphone application. Each patient is monitored for four consecutive weeks, after which the device is returned by mail to the investigators.

Power analysis

A power analysis²⁶ based on previous research findings and estimation of outcome to 2.4%, 95% confidence interval, width of confidence interval 5, standard deviation 12

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3 results in a sample size of 89. There is likely to be drop-out of patients who are
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5 unable or unwilling to meet the monitoring requirements; thus, an estimated 120
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7 patients should be included in order to have 100 patients complete the chest and
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9 thumb-ECG evaluation.
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11 12 5 *Statistics*

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14 Descriptive data will be reported as frequencies, percentages, means, and
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16 percentiles. Continuous variables are summarized as means, standard deviations,
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18 and percentiles, and *t*-tests for group comparisons, while chi-squared test is used for
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20 categorical variables. Kaplan-Meier estimates are used to describe time to event
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22 analysis, and cumulative incidence at 1, 2, 3, and 4 weeks will be reported. Statistical
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24 significance is defined as a two-sided *p*-value of <0.05. The data will be stored in
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26 Excel 2010 (Microsoft Corporation, Redmond, WA) and imported into SPSS version
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28 22 (IBM, Armonk, NY) for analyses.
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32 33 *Ethics and dissemination*

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35 15 The Regional Ethical Committee in Uppsala approved the study the 20th of
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37 September 2017 (protocol number 2017/321). The study protocol, including variables
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39 and prespecified research questions, were registered at Clinical Trial Registration
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41 NCT03301662 and approved 3rd of October 2017. The documentaton of research
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43 data and management of the study follow the Guideline for Good Clinical Practice.²⁷
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46 20 Each patient is informed about the study by a physician and nurse and included after
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48 written consent. After the study is completed, the database will be closed and
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50 followed by statistical analyses, interpretation of results, and dissemination to
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52 scientific journals.
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55 56 **DISCUSSION**

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3 Since anticoagulation therapy has been proven effective in preventing ischemic
4 stroke in patients with AF, reliable AF detection following cryptogenic stroke is
5 crucial.⁶ Hence, prolonged ECG monitoring is reasonable, especially in patients at
6 high risk of embolization. Ischemic stroke risk stratification and the decision to
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11 5 prescribe anticoagulants is based on CHA2DS2-VASc scores; a prior history of
12 stroke counts for two points, which suffices as a rationale for anticoagulation.⁶ The
13 vast majority of stroke patients typically have multiple risk factors, and stroke risk
14 increases with more risk factors.²⁸ ESC guidelines already allow for prolonged
15 monitoring of these patients: "In stroke patients, additional ECG monitoring by long-
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22 10 term noninvasive or implanted loop recorders should be considered to document
23 silent atrial fibrillation" (Class IIa recommendation, level of evidence B).⁶ However,
24 since the CRYSTAL-AF trial¹³, current practice in Sweden remains unchanged with
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33 15 in that it provides an alternative and advantageous cost-benefit profile in mass
34 screening.³⁰ Stroke patients have a higher risk for recurrent stroke and higher
35 incidences of AF, so noninvasive thumb-ECG monitoring may be of even greater
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44 20 regard to healthcare economics.

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47 The use of the thumb-ECG has been studied in a Swedish setting for stroke patients,
48 but the study was retrospective, with data gathered at different times after the stroke,
49 and the monitoring method was selected based on the physician's preference, which
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55 25 implies bias. Our prospective study includes consecutive stroke patients without
56 referral center bias.³¹ This will provide a basis to estimate AF incidence over an
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3 extended period of 28 days. Continuous Holter monitoring may be associated with
4 poor compliance, technical difficulties, and time-consuming analyses of extensive
5 amounts of data by healthcare providers.^{31,32} The newly developed Coala Heart
6 Monitor™ with the proven detection algorithms from Zenicor™ using a smartphone
7 application seem to be a promising alternative, but feasibility remains to be studied.
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9 Therefore we added a questionnaire to address feasibility issues.
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16 Although a thumb-ECG may provide an attractive method of noninvasive AF
17 detection, there remain some controversies with regard to short-term anticoagulation
18 for AF. The potential benefits of anticoagulation therapy for short-term AF would be
19 challenging to study because it would require long-term follow-up, demands a large
20 sample size, and raises ethical concerns about withholding anticoagulation from a
21 stroke survivor. This proposed prospective observational trial of consecutive stroke
22 patients using thumb-ECG has the prerequisites to evaluate outcome at 28 days and
23 analyze the clinical feasibility of the Coala Heart Monitor.™
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44 **Author contributions**

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47 20 PM: idea, design, project management, and writing of the manuscript. HK: critical
48 revision GM: idea, design, project management, critical revision.
49
50

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3 Region Gävleborg funded this research project and Coala Life provided free product
4
5 Coala Heart Monitor™ during the study period.
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8 **Competing interests**

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10 The authors received free product from Coala Life.
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13 **5 Ethics approval**

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16 The study was approved by the Regional Ethical committee in Uppsala (Dnr
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18 2017/321).
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A protocol for a prospective observational study using chest and thumb- ECG: Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE) in Sweden.

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3 **A protocol for a prospective observational study using chest and thumb- ECG:**
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5 **Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE) in**
6
7 **Sweden.**
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ABSTRACT

Introduction: Atrial fibrillation (AF) causes ischemic stroke and based on risk factor evaluation warrants anticoagulation therapy. In stroke survivors, AF is typically detected with short-term ECG monitoring in the stroke unit. Prolonged continuous ECG monitoring is impractical and requires substantial resources while insertable cardiac monitors are invasive and costly. Chest and thumb-ECG could provide an alternative for AF detection post-stroke.

The primary objective of our study is to assess the incidence of newly diagnosed AF during 28 days of chest and thumb-ECG monitoring in patients with cryptogenic stroke. Secondary objectives are to assesses health-related quality of life (HRQoL) using SF-36 and the feasibility of the Coala Heart Monitor™ in patients with stroke.

Methods: Stroke survivors in Region Gävleborg, Sweden, will be eligible for the study from October 2017. Patients with a history of ischemic stroke without documented AF before or during ECG evaluation in the stroke unit will be evaluated by the chest and thumb-ECG system Coala Heart Monitor.™ The monitoring system is connected to a smartphone application which allows for remote monitoring and prompt advice on clinical management. Over a period of 28 days, patients will be monitored twice daily and may activate the ECG recording at symptoms. Upon completion, the system is returned by mail. This system offers a possibility to evaluate the presence of AF post-stroke, but the feasibility of this system in patients who recently suffered from a stroke is unknown. In addition HRQoL using SF-36 in comparison to Swedish population norms will be assessed. The feasibility of the Coala Heart Monitor™ will be assessed by a self-developed questionnaire.

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3 **Ethics and dissemination:** The study was approved by The Regional Ethical
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5 Committee in Uppsala (2017/321) and registered at Clinical Trial Registration
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7 NCT03301662. The database will be closed after the last follow-up, followed by
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9 statistical analyses, interpretation of results, and dissemination to a scientific journal.
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Strengths and limitations of this study

- Chest and thumb-ECG evaluation applied after 24-hour ECG Holter at the stroke unit after confirmation of ischemic stroke.
- Usage of a smartphone application for storage of chest and thumb-ECG which may improve compliance and facilitate fast evaluation by the health-care provider in order to prescribe an anticoagulant when indicated.
- Prospective design including consecutive patients which eliminate both selection and tertiary center bias.
- Management of short (30 seconds) AF episodes, detected by non 12-lead ECG, lack evidence from randomized controlled trials with regard to benefit of anticoagulation.
- The small sample size (n=100) may imply type-II errors in subgroup analyses.

Keywords: atrial fibrillation, cryptogenic stroke, ECG screening, health-related quality of life, SF-36, stroke, thumb-ECG

INTRODUCTION

Atrial fibrillation (AF) causes stroke and systemic embolization, but these devastating events can be prevented by anticoagulant therapy.¹ A non-vitamin K antagonist oral anticoagulant (NOAC) is the preferred choice and effectively reduce the risk of stroke and mortality.² A meta-analysis of the pivotal NOAC trials showed a 19% reduction of stroke/systemic embolism and 10% lower mortality compared to warfarin.² If AF is not diagnosed, antiplatelet medication is current practice following a stroke.³ According to the European Society of Cardiology (ESC), antiplatelet monotherapy should not be considered in the presence of AF, regardless of the stroke risk.⁴⁻⁶ Stroke is a leading cause of disability and death and is the incidence is increasing due to ageing populations and the growing prevalence risk factors such as diabetes and hypertension.⁷⁻⁹ At least 20-30% of patients with ischemic stroke have a documented episode of AF before, during, or after the event, but in a quarter of these patients, the stroke is cryptogenic, meaning that no etiologic factor can be determined.¹⁰⁻¹² However, the proportion of cryptogenic stroke from studies varies due to heterogeneity of cohorts and evaluation tools.

Possibilities for AF detection include monitoring in the hospital ward, repeated electrocardiograms (ECG), Holter monitoring, external event or loop recorders, and long-term outpatient monitoring. Insertable cardiac monitors in cryptogenic stroke yields an AF diagnosis in 8.9% at 6 months and 12.4% at 12 months, but this strategy has not been endorsed in current practice as it requires considerable resources and imply high costs, even though cost-effectiveness has been suggested.^{6,13,14} Episodes of AF may be silent, that is not recognized or reported by the patient, but are nevertheless associated with the same risk of embolization.¹⁵⁻¹⁷ In patients with either dual-chamber pacemakers or implantable defibrillators and with

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3 no documented history of AF, 10.1% had episodes of high-rate atrial tachycardia and
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5 this was also associated with an increased risk of stroke.¹⁸
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8 Sequential stratified ECG monitoring detected AF in 24% of stroke patients in one
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10 study.¹⁰ The diagnostic yield was 11.5% in a pooled analysis, but this yield varies
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12 5 with such study factors as timing, length of registration, and the monitoring tool.¹⁹ In
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14 unselected stroke patients, 24-hour monitoring found AF in only 2.4%.²⁰ This may
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16 vary substantially with the recording technique; in a recent study, AF (defined as ≥ 30
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18 seconds in duration) was detected in 16.1% of patients monitored by an 30-day
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20 event-triggered recorder compared to 3.2% of patients monitored by 24-hour ECG.²¹
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23 10 A large multicenter study of stroke patients on Holter monitoring reported new
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25 diagnoses of AF in 2.6% of patients at 24 hours and 4.3% at 72 hours.¹² In another
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27 study, AF was detected in 8.3% of stroke patients monitored by continuous ECG for
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29 a median of 89 hours in the stroke unit; ECG monitoring was superior to 24-hour
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31 Holter monitoring in detecting AF.²²
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34 15 Thus, while ECG monitoring for an extended period is important for stroke survivors
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36 post-discharge Holter monitoring is impractical, ECG data storage is limited, and data
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38 interpretation requires considerable resources. Therefore, the thumb-ECG offers
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40 advantages in that it monitors conveniently (typically twice daily) and can be
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42 activated to capture symptomatic episodes. For example, AF was detected in 11.4%
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44 20 of post-stroke patients monitored by thumb-ECG over 21 days versus 2.8% in those
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46 continuously monitored for 48 hours.²³
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50 The thumb-ECG monitor system ZenicorTM (Zenicor Medical Systems AB, Stockholm,
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52 Sweden) has been shown to diagnose previously unknown AF in 3.0% of the general
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54 population in Sweden aged 75 years.²⁴ The ZenicorTM system has been developed
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3 and integrated into the chest and thumb-ECG Coala Heart Monitor™ (Coala Life AB,
4 Stockholm, Sweden). The monitoring system utilizes a smartphone application which
5 allows for remote monitoring by a clinician. This system may help to evaluate the
6 presence of AF post-stroke. However, feasibility of this system in patients who
7 recently suffered a stroke has not been studied. In addition health-related quality of
8 life (HRQoL) using SF-36 in comparison to Swedish population norms will be
9 assessed.^{25,26} The feasibility of the Coala Heart Monitor™ will be assessed by a self-
10 developed questionnaire (see Supplement).

20 OBJECTIVES

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23 10 The primary objective is to assess the incidence of newly diagnosed AF during 28
24 days of chest and thumb-ECG in cryptogenic stroke patients.

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28 The secondary objectives are to assesses HRQoL using SF-36 and the feasibility of
29 the Coala Heart Monitor™ in patients with stroke.

33 METHODS

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36 15 *Setting and selection*

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39 Patients with a clinically confirmed diagnosis of ischemic stroke will be recruited from
40 the catchment area of Region Gävleborg, Sweden. Eligible patients will be identified
41 from daily checks of the medical records in the stroke unit. The recruitment is
42 planned to start in October 2017.

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48 20 *Inclusion and exclusion*

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51 Patients, aged ≥ 18 years, with a validated diagnosis of ischemic cryptogenic stroke
52 are eligible for the study. Cryptogenic stroke is defined as cerebral ischemia of
53 unknown etiology i.e. not attributable to a source of cardiac embolism, large artery
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3 atherosclerosis, or small artery disease despite a standard vascular, cardiac, and
4 serologic evaluation.²⁷ For screening with chest and thumb-ECG, exclusion criteria
5 are as follows: previously known atrial arrhythmia with an indication for
6 anticoagulation, implantable defibrillator, pacemaker or insertable cardiac monitor,
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8 pregnancy, permanent indication for anticoagulation (including low-molecular weight
9 heparin) due to atrial arrhythmia, mechanical heart valve, deep vein thrombosis, or
10 pulmonary embolism. Patients with a life expectancy ≤ 6 months (e.g. severe heart
11 failure New York Heart Association [NYHA] functional class IV or malignancy) are
12 likewise excluded.
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23 *Variables*

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25 Atrial arrhythmia is defined as AF, atrial flutter, or ectopic atrial tachycardia with a
26 duration of at least 30 seconds. Patients characteristics are age, sex, date of current
27 ischemic stroke, previous stroke, known AF, medication (warfarin, NOAC, antiplatelet
28 therapy), heart failure, hypertension, diabetes mellitus, vascular disease (peripheral
29 vascular disease, aortic plaque, coronary artery disease), National Institutes of
30 Health Stroke Scale (NIHSS), 12-lead ECG, and when applicable imaging from
31 carotid-Doppler, computerized tomography, echocardiography, or transesophageal
32 echocardiography, as well as coagulation laboratory examination.
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44 *Outcome measurements*

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46 Outcome measurements are arrhythmias recorded by chest and thumb-ECG
47 obtained during scheduled twice-daily recordings or by patient-activated recordings.
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51 Each episode will be classified as AF, atrial flutter, ectopic atrial tachycardia,
52 ventricular tachycardia, premature ventricular complex, or supraventricular ventricular
53 complex. The date and time of each episode will be recorded.
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Research questions and endpoints

The primary endpoint is 28 day cumulative incidence of atrial arrhythmia at 28 days.

Secondary endpoints

- a) Prevalence of previously known atrial arrhythmia before the inclusion in the study and the number of these patients who had anticoagulant therapy.
- b) Compliance with chest and thumb-ECG at week four (number of recorded scheduled ECG tracings).
- c) Patient-reported experience with chest and thumb-ECG measured at week six (questionnaire as Supplement).
- d) HRQoL (SF-36) at week 6 and at 12 months and the association with AF and compliance with chest and thumb-ECG.
- e) Cumulative incidence of stroke after three years in patients with AF versus without AF.
- f) All-cause mortality after three years in patients with AF versus no AF.

Chest and thumb-ECG

Patients will be asked to use the chest and thumb-ECG monitor device twice daily, once between the hours of 6:00 and 10:00 a.m. and again between 6:00 and 10:00 p.m.

- If the patients feel palpitations or other symptoms suggestive of arrhythmia (e.g. sudden onset of tiredness, presyncope, syncope) they are asked to record the episode with the smartphone application. Each patient is monitored for four consecutive weeks, after which the device is returned by mail to the investigators.

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3 Each recording is stored in a web-based application that is accessible to the
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5 investigators. The investigators daily check all recordings. In the case of an AF-
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7 episode, we contact the patient (or relative/health care provider) as soon as possible,
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9 typically the same day. The reason for this is that they require anticoagulation and
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11 they typically need prompt protection (time is recorded). In the case of an AF-
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13 episode, two investigators, of whom one is an experienced cardiologist within the
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15 field of arrhythmia, interpret the recording.

16 17 18 *Power analysis*

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21 A power analysis²⁸ based on previous research findings and estimation of outcome to
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23 10 2.4%, 95% confidence interval, width of confidence interval 5%, standard deviation
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25 12% results in a sample size of 89. There is likely to be drop-out of patients who are
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27 unable or unwilling to meet the monitoring requirements; thus, an estimated 120
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29 patients should be included in order to have 100 patients complete the chest and
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31 thumb-ECG evaluation.

32 33 34 35 15 *Statistics*

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38 Descriptive data will be reported as frequencies, percentages, means, and
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40 percentiles. Continuous variables are summarized as means, standard deviations,
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42 and percentiles, and *t*-tests for group comparisons, while chi-squared test is used for
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44 categorical variables. Kaplan-Meier estimates are used to describe time to event
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46 20 analysis, and cumulative incidence at 1, 2, 3, and 4 weeks will be reported. Statistical
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48 significance is defined as a two-sided *p*-value of <0.05. The data will be stored in
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50 Excel 2010 (Microsoft Corporation, Redmond, WA) and imported into SPSS version
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52 22 (IBM, Armonk, NY) for analyses.

53 54 55 *Ethics and dissemination*

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3 The Regional Ethical Committee in Uppsala approved the study the 20th of
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5 September 2017 (protocol number 2017/321). The study protocol, including variables
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7 and prespecified research questions, were registered at Clinical Trial Registration
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9 NCT03301662 and approved 3rd of October 2017. The documentaton of research
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11 data and management of the study follow the Guideline for Good Clinical Practice.²⁹
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13 Each patient is informed about the study by a physician and nurse and included after
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15 written consent. After the study is completed, the database will be closed and
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17 followed by statistical analyses, interpretation of results, and dissemination to
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19 scientific journals.
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22 23 10 **DISCUSSION**

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25 Since anticoagulation therapy has been proven effective in preventing ischemic
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27 stroke in patients with AF, reliable AF detection following cryptogenic stroke is
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29 crucial.⁶ Hence, prolonged ECG monitoring is reasonable, especially in patients at
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31 high risk of embolization. Ischemic stroke risk stratification and the decision to
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33 prescribe anticoagulants is based on CHA2DS2-VASc scores; a prior history of
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35 stroke counts for two points, which suffices as a rationale for anticoagulation.⁶ The
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37 vast majority of stroke patients typically have multiple risk factors, and stroke risk
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39 increases with more risk factors.³⁰ ESC guidelines already allow for prolonged
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41 monitoring of these patients: "In stroke patients, additional ECG monitoring by long-
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43 term noninvasive or implanted loop recorders should be considered to document
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45 20 silent atrial fibrillation" (Class IIa recommendation, level of evidence B).⁶ However,
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47 since the CRYSTAL-AF trial¹³, current practice in Sweden remains unchanged with
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49 invasive monitoring rarely used for AF detection in stroke patients and still not
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51 endorsed by national authorities.³¹ The noninvasive thumb-ECG has been advocated
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56 25 in that it provides an alternative and advantageous cost-benefit profile in mass

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3 screening.³² Stroke patients have a higher risk for recurrent stroke and higher
4 incidences of AF, so noninvasive thumb-ECG monitoring may be of even greater
5 benefit in this population. This has yet to be analyzed, and it is our hope that our
6 study will advance the knowledge of thumb-ECG in this population particularly with
7 regard to healthcare economics.
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14 The use of the thumb-ECG has been studied in a Swedish setting for stroke patients,
15 but the study was retrospective, with data gathered at different times after the stroke,
16 and the monitoring method was selected based on the physician's preference, which
17 implies bias. Our prospective study includes consecutive stroke patients without
18 referral center bias.³³ This will provide a basis to estimate AF incidence over an
19 extended period of 28 days. Continuous Holter monitoring may be associated with
20 poor compliance, technical difficulties, and time-consuming analyses of extensive
21 amounts of data by healthcare providers.^{33,34} The newly developed Coala Heart
22 MonitorTM with the proven detection algorithms from ZenicorTM using a smartphone
23 application seem to be a promising alternative, but feasibility remains to be studied.
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14 Although a thumb-ECG may provide an attractive method of noninvasive AF
15 detection, there remain some controversies with regard to anticoagulation for short-
16 term AF. The potential benefits of anticoagulation therapy for short-term AF would be
17 challenging to study because it would require long-term follow-up, demands a large
18 sample size, and raises ethical concerns about withholding anticoagulation from a
19 stroke survivor. This proposed prospective observational trial of consecutive stroke
20 patients using thumb-ECG has the prerequisites to evaluate outcome at 28 days and
21 analyze the clinical feasibility of the Coala Heart Monitor.TM

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5 Author contributions

PM: idea, design, project management, and writing of the manuscript. HK: critical revision GM: idea, design, project management, critical revision.

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Competing interests

The authors received free product from Coala Life.

Ethics approval

The study was approved by the Regional Ethical committee in Uppsala (Dnr 2017/321).

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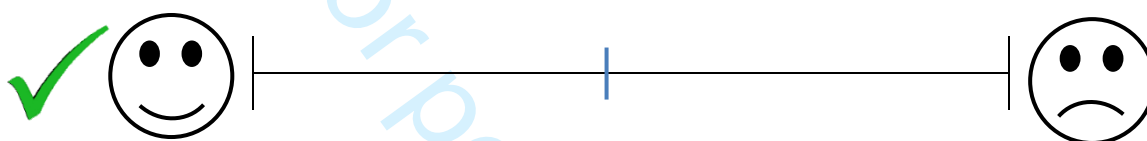
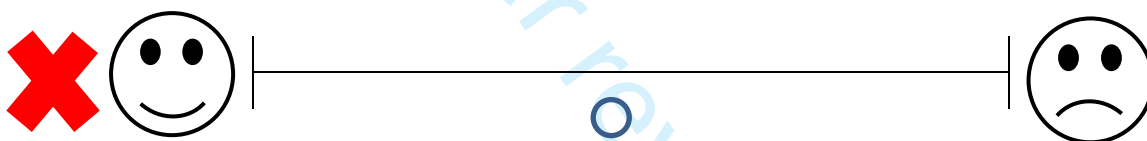
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10 34. Seet RCS, Friedman PA, Rabinstein AA. Prolonged rhythm monitoring for the
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12 5 detection of occult paroxysmal atrial fibrillation in ischemic stroke of unknown cause.
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14 *Circulation* 2011;124:477-86.
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Code

Name: _____

Personal ID: _____ - _____

Please describe your experience of using the chest- and thumb ECG. Follow the example below to make a clear vertical line.

Exemple: **Correct**Exemple: **Incorrect**

Frågor:

1. In summary, what do you think about the usage of the chest- and thumb ECG?



2. How was the technical feasibility of the chest- and thumb ECG?



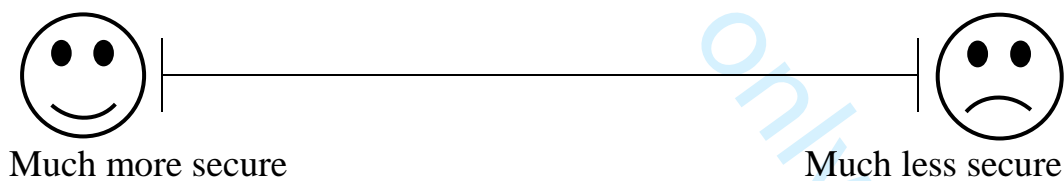
3. Did you remember to use the chest- and thumb ECG as scheduled?



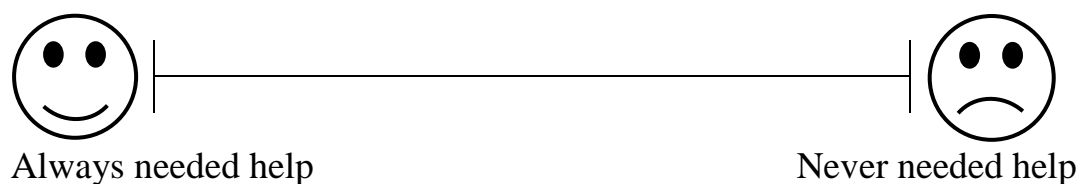
4. How was it physically to apply the chest- and thumb ECG?



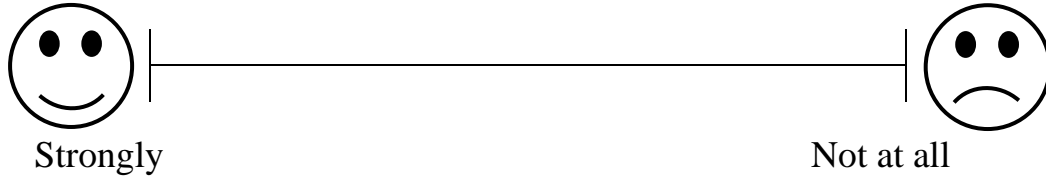
5. Did the ECG monitoring affect your feeling of security?



6. Did you need help from others to perform the ECG-monitoring?



7. Would you recommend other stroke patients to use the chest- and thumb ECG monitoring?



Would you like to add any comment about using the chest- and thumb ECG?
Please use the box below.

What symptoms remain after your stroke? Please underline the alternative that describes this best.

Speech ability impairment:	Severe	Moderate	Mildly	No
Impairment of ability to understand:	Severe	Moderate	Mild	No
Arm weakness:	Severe	Moderate	Mild	No
Leg weakness:	Severe	Moderate	Mild	No
Decreased sensibility:	Severe	Moderate	Mild	No
Memory deficit:	Severe	Moderate	Mild	No
Tiredness:	Severe	Moderate	Mild	No

Do you want add any further information, please use the box below.



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

Section/item	Item No	Description
Administrative information		
page 1, line 1 Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
page 3, line 1 Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
NA	2b	All items from the World Health Organization Trial Registration Data Set
page 3, line 1 Protocol version	3	Date and version identifier
page 13, line 1 Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	page 1, line 5a	Names, affiliations, and roles of protocol contributors
page 1, line 5b		Name and contact information for the trial sponsor
page 13, line 5		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
page 10, line 1 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)
Introduction		
page 9, line 1 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
NA	6b	Explanation for choice of comparators
page 7, line 10 Objectives	7	Specific objectives or hypotheses
page 1, line 1 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)

Methods: Participants, interventions, and outcomes

1			
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3			
4	page 7 line 15	Study setting	9
5			
6			
7			
8	page 7 line 20	Eligibility criteria	10
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12			
13	page 9 line 15	Interventions	11a
14			
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16	MA		11b
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21	MA	11c	
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24			
25		11d	
26	MA		
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28	page 9, line 1	Outcomes	12
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36	page 7, line 15	Participant timeline	13
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40	page 10, line 13	Sample size	14
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45	page 15 line 17	Recruitment	15
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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52	MA	Sequence generation	16a
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2	MA	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
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7	MA	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
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10	MA	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
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15			17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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Methods: Data collection, management, and analysis

20				
21	page 10, line 1	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
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30	MA		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
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34	page 10, line 21	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
35				
36	page 11, line 5			
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39	page 10, line 15	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
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44	page 10, line 15		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
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47			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)
48	MA			
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Methods: Monitoring

52				
53	page 10, line 5	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
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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

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Harms

22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

MA

Auditing

23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

page 11, line 2

Research ethics approval

24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

MA

Protocol amendments

25 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)

page 11, line 7

Consent or assent

26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

MA

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

page 11, line 5

Confidentiality

27 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

page 13, line 12

Declaration of interests

28 Financial and other competing interests for principal investigators for the overall trial and each study site

page 10, line 11

Access to data

29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

MA

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

page 11, line 7

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

MA

31b Authorship eligibility guidelines and any intended use of professional writers

MA

31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

MA	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
MA	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

*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.

BMJ Open

A protocol for a prospective observational study using chest and thumb- ECG: Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE) in Sweden.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-019933.R2
Article Type:	Protocol
Date Submitted by the Author:	19-Dec-2017
Complete List of Authors:	Magnusson, Peter; Karolinska Institutet, Cardiology Research Unit, Department of Medicine; Uppsala University, 2. Centre for Research and Development, Uppsala University/Region Gävleborg Koyi, Hirsh; Uppsala University, Centre for Research and Development, Uppsala University/Region Gävleborg Mattsson, Gustav; Uppsala University, Centre for Research and Development, Uppsala University/Region Gävleborg
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diagnostics
Keywords:	Adult cardiology < CARDIOLOGY, Pacing & electrophysiology < CARDIOLOGY, Cardiology < INTERNAL MEDICINE, Stroke medicine < INTERNAL MEDICINE

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Manuscripts

only

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3 **A protocol for a prospective observational study using chest and thumb- ECG:**
4
5 **Transient Electrocardiogram Assessment in Stroke Evaluation (TEASE) in**
6
7 **Sweden.**
8

9 Peter Magnusson^{1,2} Hirsh Koyi² Gustav Mattsson²

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ABSTRACT

Introduction: Atrial fibrillation (AF) causes ischemic stroke and based on risk factor evaluation warrants anticoagulation therapy. In stroke survivors, AF is typically detected with short-term ECG monitoring in the stroke unit. Prolonged continuous ECG monitoring requires substantial resources while insertable cardiac monitors are invasive and costly. Chest and thumb-ECG could provide an alternative for AF detection post-stroke.

The primary objective of our study is to assess the incidence of newly diagnosed AF during 28 days of chest and thumb-ECG monitoring in cryptogenic stroke. Secondary objectives are to assesses health-related quality of life (HRQoL) using SF-36 and the feasibility of the Coala Heart Monitor™ in stroke patients.

Methods: Stroke survivors in Region Gävleborg, Sweden, will be eligible for the study from October 2017. Patients with a history of ischemic stroke without documented AF before or during ECG evaluation in the stroke unit will be evaluated by the chest and thumb-ECG system Coala Heart Monitor.™ The monitoring system is connected to a smartphone application which allows for remote monitoring and prompt advice on clinical management. Over a period of 28 days, patients will be monitored twice daily and may activate the ECG recording at symptoms. Upon completion, the system is returned by mail. This system offers a possibility to evaluate the presence of AF post-stroke, but the feasibility of this system in patients who recently suffered from a stroke is unknown. In addition HRQoL using SF-36 in comparison to Swedish population norms will be assessed. The feasibility of the Coala Heart Monitor™ will be assessed by a self-developed questionnaire.

Ethics and dissemination: The study was approved by The Regional Ethical Committee in Uppsala (2017/321) and registered at Clinical Trial Registration NCT03301662. The database will be closed after the last follow-up, followed by statistical analyses, interpretation of results, and dissemination to a scientific journal.

5

For peer review only

Strengths and limitations of this study

- Chest and thumb-ECG evaluation applied after 24-hour ECG Holter at the stroke unit after confirmation of ischemic stroke.
- Usage of a smartphone application for storage of chest and thumb-ECG which may improve compliance and facilitate fast evaluation by the health-care provider in order to prescribe an anticoagulant when indicated.
- Prospective design including consecutive patients which eliminate both selection and tertiary center bias.
- Management of short (30 seconds) AF episodes, detected by non 12-lead ECG, lack evidence from randomized controlled trials with regard to benefit of anticoagulation.
- The small sample size (n=100) may imply type-II errors in subgroup analyses.

Keywords: atrial fibrillation, cryptogenic stroke, ECG screening, health-related quality of life, SF-36, stroke, thumb-ECG

INTRODUCTION

Atrial fibrillation (AF) causes stroke and systemic embolization, but these devastating events can be prevented by anticoagulant therapy.¹ A non-vitamin K antagonist oral anticoagulant (NOAC) is the preferred choice and effectively reduce the risk of stroke and mortality.² A meta-analysis of the pivotal NOAC trials showed a 19% reduction of stroke/systemic embolism and 10% lower mortality compared to warfarin.² If AF is not diagnosed, antiplatelet medication is current practice following a stroke.³ According to the European Society of Cardiology (ESC), antiplatelet monotherapy should not be considered in the presence of AF, regardless of the stroke risk.⁴⁻⁶ Stroke is a leading cause of disability and death and is the incidence is increasing due to ageing populations and the growing prevalence risk factors such as diabetes and hypertension.⁷⁻⁹ At least 20-30% of patients with ischemic stroke have a documented episode of AF before, during, or after the event, but in a quarter of these patients, the stroke is cryptogenic, meaning that no etiologic factor can be determined.¹⁰⁻¹² However, the proportion of cryptogenic stroke from studies varies due to heterogeneity of cohorts and evaluation tools.

Possibilities for AF detection include monitoring in the hospital ward, repeated electrocardiograms (ECG), Holter monitoring, external event or loop recorders, and long-term outpatient monitoring. Insertable cardiac monitors in cryptogenic stroke yields an AF diagnosis in 8.9% at 6 months and 12.4% at 12 months, but this strategy has not been endorsed in current practice as it requires considerable resources and imply high costs, even though cost-effectiveness has been suggested.^{6,13,14} Episodes of AF may be silent, thus not recognized or reported by the patient, but are nevertheless associated with the same risk of embolization.¹⁵⁻¹⁷ In patients with either dual-chamber pacemakers or implantable defibrillators and with

1
2
3 no documented history of AF, 10.1% had episodes of high-rate atrial tachycardia and
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5 this was also associated with an increased risk of stroke.¹⁸
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7
8 Sequential stratified ECG monitoring detected AF in 24% of stroke patients in one
9
10 study.¹⁰ The diagnostic yield was 11.5% in a pooled analysis, but this yield varies
11
12 5 with such study factors as timing, length of registration, and the monitoring tool.¹⁹ In
13
14 unselected stroke patients, 24-hour monitoring found AF in only 2.4%.²⁰ This may
15
16 vary substantially with the recording technique; in a recent study, AF (defined as ≥ 30
17
18 seconds in duration) was detected in 16.1% of patients monitored by an 30-day
19
20 event-triggered recorder compared to 3.2% of patients monitored by 24-hour ECG.²¹
21
22

23 10 A large multicenter study of stroke patients on Holter monitoring reported new
24
25 diagnoses of AF in 2.6% of patients at 24 hours and 4.3% at 72 hours.¹² In another
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27 study, AF was detected in 8.3% of stroke patients monitored by continuous ECG for
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29 a median of 89 hours in the stroke unit; ECG monitoring was superior to 24-hour
30
31 Holter monitoring in detecting AF.²²
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34 15 Thus, while ECG monitoring for an extended period is important for stroke survivors
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36 post-discharge Holter monitoring is impractical, ECG data storage is limited, and data
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38 interpretation requires considerable resources. Therefore, the thumb-ECG offers
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40 advantages in that it monitors conveniently (typically twice daily) and can be
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42 activated to capture symptomatic episodes. For example, AF was detected in 11.4%
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44 20 of post-stroke patients monitored by thumb-ECG over 21 days versus 2.8% in those
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46 continuously monitored for 48 hours.²³
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50 The thumb-ECG monitor system ZenicorTM (Zenicor Medical Systems AB, Stockholm,
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52 Sweden) has been shown to diagnose previously unknown AF in 3.0% of the general
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54 population in Sweden aged 75 years.²⁴ The ZenicorTM system has been developed
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3 and integrated into the chest and thumb-ECG Coala Heart Monitor™ (Coala Life AB,
4 Stockholm, Sweden). The monitoring system utilizes a smartphone application which
5 allows for remote monitoring by a clinician. This system may help to evaluate the
6 presence of AF post-stroke. However, feasibility of this system in patients who
7 recently suffered a stroke has not been studied. In addition health-related quality of
8 life (HRQoL) using SF-36 in comparison to Swedish population norms will be
9 assessed.^{25,26} The feasibility of the Coala Heart Monitor™ will be assessed by a self-
10 developed questionnaire (see Supplement).

20 OBJECTIVES

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23 10 The primary objective is to assess the incidence of newly diagnosed AF during 28
24 days of chest and thumb-ECG in cryptogenic stroke patients.

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28 The secondary objectives are to assesses HRQoL using SF-36 and the feasibility of
29 the Coala Heart Monitor™ in patients with stroke. In addition, stroke patients not
30 eligible for the chest and thumb-ECG monitoring, will be analyzed with regard to
31 prevalence of previous atrial arrhythmia (including whether they were
32 anticoagulated), cumulative incidence of stroke after three years, and all-cause
33 mortality after three years in patients with AF versus no AF.
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35 15

42 METHODS

45 *Setting and selection*

46
47 20 Patients with a clinically confirmed diagnosis of ischemic stroke will be recruited from
48 the catchment area of Region Gävleborg, Sweden. Eligible patients will be identified
49 from daily checks of the medical records in the stroke unit. The recruitment is
50 planned to start in October 2017.
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Inclusion and exclusion

Patients, aged ≥ 18 years, with a validated diagnosis of ischemic cryptogenic stroke are eligible for the study. Cryptogenic stroke is defined as cerebral ischemia of unknown etiology i.e. not attributable to a source of cardiac embolism, large artery atherosclerosis, or small artery disease despite a standard vascular, cardiac, and serologic evaluation.²⁷ For screening with chest and thumb-ECG, exclusion criteria are as follows: previously known atrial arrhythmia with an indication for anticoagulation, implantable defibrillator, pacemaker or insertable cardiac monitor, pregnancy, permanent indication for anticoagulation (including low-molecular weight heparin) due to atrial arrhythmia, mechanical heart valve, deep vein thrombosis, or pulmonary embolism. Patients with a life expectancy ≤ 6 months (e.g. severe heart failure New York Heart Association [NYHA] functional class IV or malignancy) are likewise excluded.

Variables

Atrial arrhythmia is defined as AF, atrial flutter, or ectopic atrial tachycardia with a duration of at least 30 seconds. Patients characteristics are age, sex, date of current ischemic stroke, previous stroke, known AF, medication (warfarin, NOAC, antiplatelet therapy), heart failure, hypertension, diabetes mellitus, vascular disease (peripheral vascular disease, aortic plaque, coronary artery disease), National Institutes of Health Stroke Scale (NIHSS), 12-lead ECG, and when applicable imaging from carotid-Doppler, computerized tomography, echocardiography, or transesophageal echocardiography, as well as coagulation laboratory examination.

Outcome measurements

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3 Outcome measurements are arrhythmias recorded by chest and thumb-ECG
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5 obtained during scheduled twice-daily recordings or by patient-activated recordings.
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8 Each episode will be classified as AF, atrial flutter, ectopic atrial tachycardia,
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10 ventricular tachycardia, premature ventricular complex, or supraventricular ventricular
11
12 5 complex. The date and time of each episode will be recorded.
13

14 *Research questions and endpoints*

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17 The primary endpoint is 28 day cumulative incidence of atrial arrhythmia at 28 days.
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19

20 *Secondary endpoints*

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23 a) Prevalence of previously known atrial arrhythmia before the inclusion in the study
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25 10 and the number of these patients who had anticoagulant therapy.
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28 b) Compliance with chest and thumb-ECG at week four (number of recorded
29
30 scheduled ECG tracings).
31

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33 c) Patient-reported experience with chest and thumb-ECG measured at week six
34
35 (questionnaire as Supplement).
36

37
38 15 d) HRQoL (SF-36) at week 6 and at 12 months and the association with AF and
39
40 compliance with chest and thumb-ECG.
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43 e) Cumulative incidence of stroke after three years in patients with AF versus without
44
45 AF.
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48 f) All-cause mortality after three years in patients with AF versus no AF.
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50 20 *Chest and thumb-ECG*

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53 Patients will be asked to use the chest and thumb-ECG monitor device twice daily,
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55 once between the hours of 6:00 and 10:00 a.m. and again between 6:00 and 10:00
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3 p.m. The monitoring will start within a few days when the diagnosis of stroke has
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5 been confirmed and standard evaluation is complete, typically 1-5 days.
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8 If the patients feel palpitations or other symptoms suggestive of arrhythmia (e.g.

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10 sudden onset of tiredness, presyncope, syncope) they are asked to record the

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12 5 episode with the smartphone application. Each patient is monitored for four

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14 consecutive weeks, after which the device is returned by mail to the investigators.
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16
17 Each recording is stored in a web-based application that is accessible to the

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19 investigators. The investigators daily check all recordings. In the case of an AF-

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21 episode, we contact the patient (or relative/health care provider) as soon as possible,
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24 10 typically the same day. The reason for this is that they require anticoagulation and

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26 they typically need prompt protection (time is recorded). In the case of an AF-

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28 episode, two investigators, of whom one is an experienced cardiologist within the

29
30 field of arrhythmia, interpret the recording.
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32 33 *Power analysis*

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35 15 A power analysis²⁸ based on previous research findings and estimation of outcome to

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37 2.4%, 95% confidence interval, width of confidence interval 5%, standard deviation

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39 12% results in a sample size of 89. There is likely to be drop-out of patients who are

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41 unable or unwilling to meet the monitoring requirements; thus, an estimated 120

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43 patients should be included in order to have 100 patients complete the chest and

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45 20 thumb-ECG evaluation.
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47 48 49 *Statistics*

50
51 Descriptive data will be reported as frequencies, percentages, means, and

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53 percentiles. Continuous variables are summarized as means, standard deviations,

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55 and percentiles, and *t*-tests for group comparisons, while chi-squared test is used for
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3 categorical variables. Kaplan-Meier estimates are used to describe time to event
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5 analysis, and cumulative incidence at 1, 2, 3, and 4 weeks will be reported. Statistical
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7 significance is defined as a two-sided p -value of <0.05 . The data will be stored in
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9 Excel 2010 (Microsoft Corporation, Redmond, WA) and imported into SPSS version
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11 5 22 (IBM, Armonk, NY) for analyses.

14 *Ethics and dissemination*

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17 The Regional Ethical Committee in Uppsala approved the study the 20th of
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19 September 2017 (protocol number 2017/321). The study protocol, including variables
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21 and prespecified research questions, were registered at Clinical Trial Registration
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23 10 NCT03301662 and approved 3rd of October 2017. The documentaton of research
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25 data and management of the study follow the Guideline for Good Clinical Practice.²⁹
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27 Each patient is informed about the study by a physician and nurse and included after
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29 written consent. After the study is completed, the database will be closed and
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31 followed by statistical analyses, interpretation of results, and dissemination to
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34 15 scientific journals.

37 **DISCUSSION**

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40 Since anticoagulation therapy has been proven effective in preventing ischemic
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42 stroke in patients with AF, reliable AF detection following cryptogenic stroke is
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44 crucial.⁶ Hence, prolonged ECG monitoring is reasonable, especially in patients at
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46 20 high risk of embolization. Ischemic stroke risk stratification and the decision to
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48 prescribe anticoagulants is based on CHA2DS2-VASc scores; a prior history of
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50 stroke counts for two points, which suffices as a rationale for anticoagulation.⁶ The
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52 vast majority of stroke patients typically have multiple risk factors, and stroke risk
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54 increases with more risk factors.³⁰ ESC guidelines already allow for prolonged
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3 monitoring of these patients: “In stroke patients, additional ECG monitoring by long-
4 term noninvasive or implanted loop recorders should be considered to document
5 silent atrial fibrillation” (Class IIa recommendation, level of evidence B).⁶ However,
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7 since the CRYSTAL-AF trial¹³, current practice in Sweden remains unchanged with
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12 5 invasive monitoring rarely used for AF detection in stroke patients and still not
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14 endorsed by national authorities.³¹ The noninvasive thumb-ECG has been advocated
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16 in that it provides an alternative and advantageous cost-benefit profile in mass
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18 screening.³² Stroke patients have a higher risk for recurrent stroke and higher
19
20 incidences of AF, so noninvasive thumb-ECG monitoring may be of even greater
21
22 10 benefit in this population. This has yet to be analyzed, and it is our hope that our
23
24 study will advance the knowledge of thumb-ECG in this population particularly with
25
26 regard to healthcare economics.
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28
29 The use of the thumb-ECG has been studied in a Swedish setting for stroke patients,
30
31 but the study was retrospective, with data gathered at different times after the stroke,
32
33 15 and the monitoring method was selected based on the physician’s preference, which
34
35 implies bias. Our prospective study includes consecutive stroke patients without
36
37 referral center bias.³³ This will provide a basis to estimate AF incidence over an
38
39 extended period of 28 days. Continuous Holter monitoring may be associated with
40
41 poor compliance, technical difficulties, and time-consuming analyses of extensive
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43
44 20 amounts of data by healthcare providers.^{33,34} The newly developed Coala Heart
45
46 MonitorTM with the proven detection algorithms from ZenicorTM using a smartphone
47
48 application seem to be a promising alternative, but feasibility remains to be studied.
49
50 Therefore we added a questionnaire to address feasibility issues.
51

52
53 Although a thumb-ECG may provide an attractive method of noninvasive AF
54
55 25 detection, there remain some controversies with regard to anticoagulation for short-
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3 term AF. The potential benefits of anticoagulation therapy for short-term AF would be
4
5 challenging to study because it would require long-term follow-up, demands a large
6
7 sample size, and raises ethical concerns about withholding anticoagulation from a
8
9 stroke survivor. This proposed prospective observational trial of consecutive stroke
10
11 5 patients using thumb-ECG has the prerequisites to evaluate outcome at 28 days and
12
13 analyze the clinical feasibility of the Coala Heart Monitor.TM
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15

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18
19 The authors acknowledge editing by Jo Ann LeQuang of LeQ Medical who reviewed
20
21 the manuscript for American English. Ulf Tossman, David Fällman, and Philip Siberg
22
23 10 from Coala Life for support regarding the Coala Life Monitor.TM
24
25

26 **Author contributions**

27
28
29 PM: idea, design, project management, and writing of the manuscript. HK: critical
30
31 revision GM: idea, design, project management, critical revision.
32
33

34 **Funding**

35
36
37 15 Region Gävleborg funded this research project and Coala Life provided free product
38
39 Coala Heart MonitorTM during the study period.
40
41

42 **Competing interests**

43
44
45 The authors received free product from Coala Life.
46
47

48 **Ethics approval**

49
50 20 The study was approved by the Regional Ethical committee in Uppsala (Dnr
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52 2017/321).
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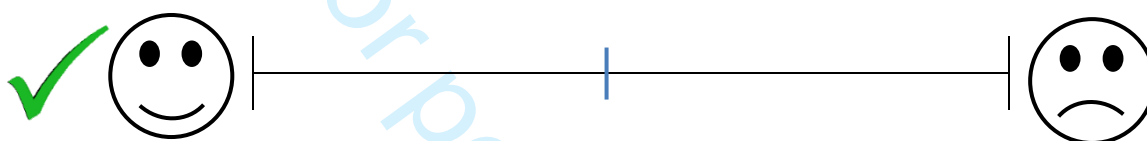
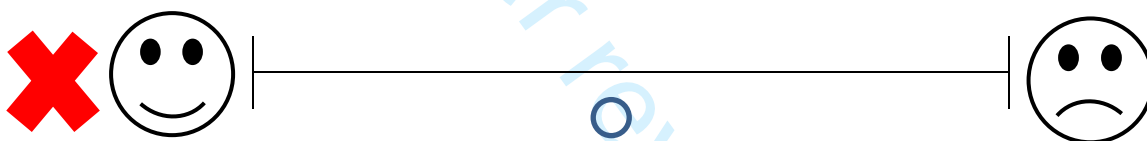
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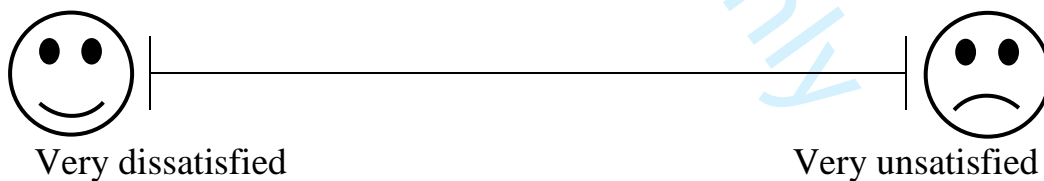
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Please describe your experience of using the chest- and thumb ECG. Follow the example below to make a clear vertical line.

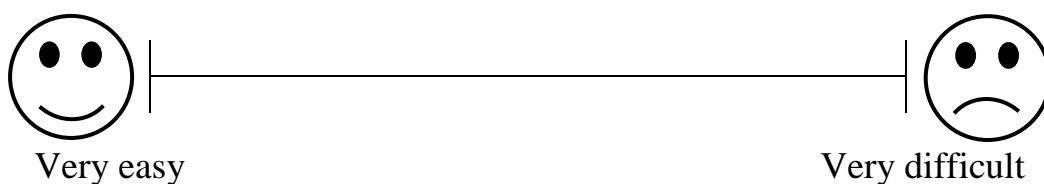
Exemple: **Correct**Exemple: **Incorrect**

Frågor:

1. In summary, what do you think about the usage of the chest- and thumb ECG?



2. How was the technical feasibility of the chest- and thumb ECG?



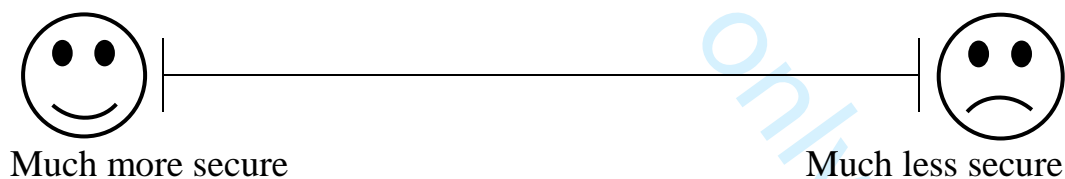
3. Did you remember to use the chest- and thumb ECG as scheduled?



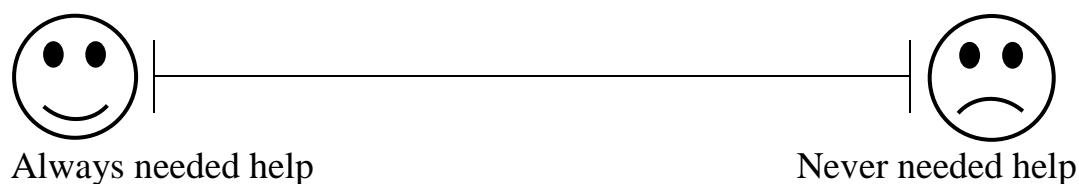
4. How was it physically to apply the chest- and thumb ECG?



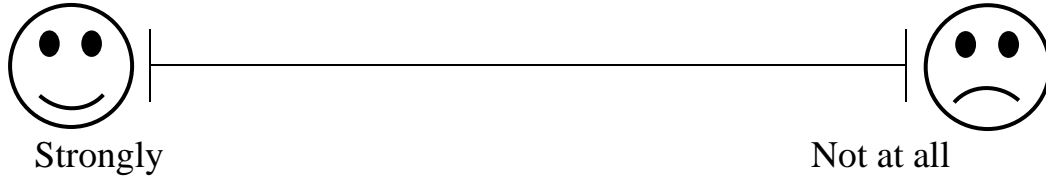
5. Did the ECG monitoring affect your feeling of security?



6. Did you need help from others to perform the ECG-monitoring?



7. Would you recommend other stroke patients to use the chest- and thumb ECG monitoring?



Would you like to add any comment about using the chest- and thumb ECG?
Please use the box below.

What symptoms remain after your stroke? Please underline the alternative that describes this best.

Speech ability impairment:	Severe	Moderate	Mildly	No
Impairment of ability to understand:	Severe	Moderate	Mild	No
Arm weakness:	Severe	Moderate	Mild	No
Leg weakness:	Severe	Moderate	Mild	No
Decreased sensibility:	Severe	Moderate	Mild	No
Memory deficit:	Severe	Moderate	Mild	No
Tiredness:	Severe	Moderate	Mild	No

Do you want add any further information, please use the box below.



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

Section/item	Item No	Description
Administrative information		
page 1, line 1 Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
page 3, line 1 Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
NA	2b	All items from the World Health Organization Trial Registration Data Set
page 3, line 1 Protocol version	3	Date and version identifier
page 13, line 1 Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	page 1, line 5a	Names, affiliations, and roles of protocol contributors
page 1, line 5b		Name and contact information for the trial sponsor
page 13, line 5		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
page 10, line 1 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)
Introduction		
page 9, line 1 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
NA	6b	Explanation for choice of comparators
page 7, line 10 Objectives	7	Specific objectives or hypotheses
page 1, line 1 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)

Methods: Participants, interventions, and outcomes

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4	page 7 line 15	Study setting	9
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8	page 7 line 20	Eligibility criteria	10
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13	page 9 line 15	Interventions	11a
14			
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16	MA		11b
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21	MA		11c
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25			11d
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28	page 9, line 1	Outcomes	12
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36	page 7, line 15	Participant timeline	13
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40	page 10, line 13	Sample size	14
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45	page 15 line 17	Recruitment	15
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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52	MA	Sequence generation	16a
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2	MA	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
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7	MA	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
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10	MA	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
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15			17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
16	MA			
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Methods: Data collection, management, and analysis

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21	page 10, line 1	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
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30	MA		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
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34	page 10, line 21	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
35				
36	page 11, line 5			
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39	page 10, line 15	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
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44	page 10, line 15		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
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47			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)
48	MA			
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Methods: Monitoring

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53	page 10, line 5	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
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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

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Harms

22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

MA

Auditing

23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

page 11, line 2

Research ethics approval

24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

MA

Protocol amendments

25 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)

page 11, line 7

Consent or assent

26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

MA

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

page 11, line 5

Confidentiality

27 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

page 13, line 12

Declaration of interests

28 Financial and other competing interests for principal investigators for the overall trial and each study site

page 10, line 11

Access to data

29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

MA

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

page 11, line 7

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

MA

31b Authorship eligibility guidelines and any intended use of professional writers

MA

31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

MA	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
MA	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

*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.