Program for Identification of "Actionable" Atrial Fibrillation (PIAAF):

Home-Based Screening for Early Detection of Atrial Fibrillation in Primary Care Patients Aged 75 Years and Older: the SCREEN-AF Randomized Trial

Principal Investigator:
Dr. David Gladstone, University of Toronto

Co-Principal Investigators:
Dr. F. Russell Quinn, University of Calgary
Dr. Noah Ivers, University of Toronto
Dr. Jeff Healey, McMaster University

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Coordinating Centre:
Population Health Research Institute
Hamilton General Hospital
237 Barton Street East
Hamilton, Ontario, Canada L8L 2X2

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SAP Author(s):
David Gladstone, SCREEN-AF, Principal Investigator
Tamara Marsden, SCREEN-AF, Study Statistician
Purnima Rao-Melacini, Sr. Biostatistician (Final SAP Review)

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LIST OF ABBREVIATIONS

AF	Atrial Fibrillation or Atrial Flutter
ASA	Acetyl Salicylic Acid
APB	Atrial premature beats
BP	Blood Pressure
CIHR	Canadian Institute of Health Research
CRF	Case Report Form
C-SPIN	Canadian Stroke Prevention Intervention Network
ECG	Electrocardiography
e-CRF	Electronic Case Report Form
GCP	Good Clinical Practice
HR	Heart Rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PHRI	Population Health Research Institute
PIAAF	Program for the Identification of "Actionable" Atrial Fibrillation
QALY	Quality Adjusted Life Year
TIA	Transient ischemic attack

1. INTRODUCTION

1.1 Preamble

The statistical analysis plan (SAP) specifies the details of the statistical analysis of SCREEN-AF trial described in the Clinical Study Protocol (version 1.1, dated 2015-01-08). The SAP is a working document that will be amended as the trial progresses. Approval is provided for the content of the appendices at the time of approval. Appendices may be updated as required during the closure of the study without obtaining approval for the changes; however, the author will inform those approving this document of updates to the appendices. The final version of the SAP will be signed off prior to database lock and any review of data summarized by treatment group.

1.2 Background

Atrial fibrillation (AF) is one of most common and treatable risk factors for stroke. Anticoagulant therapy for AF is highly beneficial for stroke prevention, but AF may go undetected and untreated because it is frequently paroxysmal and asymptomatic. The public health consequences of undiagnosed and untreated AF are enormous, and screening strategies for early detection and treatment of AF are widely considered to be part of the solution. Most guidelines do not contain recommendations for routine AF screening in primary care, and randomized evidence is lacking regarding which patients, if any, merit screening, with which devices, for how long, and at what cost. To improve patient care and outcomes, randomized trials are needed to determine the effectiveness and cost-effectiveness of AF screening interventions. Home-based self-diagnosis and remote health monitoring solutions are becoming the way of the future, and this trial investigates new technology devices that appear promising for AF screening in primary care. If more individuals with AF can be detected, then more individuals can be appropriately anticoagulated, and more strokes (including stroke-related deaths, disability and dementia) should be prevented.

There is considerable interest in investigating AF screening strategies for three key reasons: (1) recent advances in new portable device technologies are likely to make AF screening easier and more effective; (2) the availability of newer and safer oral anticoagulants means that it is more important than ever to improve the early detection of candidates who will benefit from such treatment; and (3) the prevalence of AF is rising significantly due to an aging population. The proportion of total strokes that are caused by AF is on the rise and likely will continue to increase in the future. AF is well-suited for screening to improve early detection and treatment and it fulfills the World Health Organization criteria for conditions that merit screening programs.[i]

Recent studies lend strong support for testing AF screening in primary care. In pacemaker patients, the ASSERT trial found that subclinical AF was present in nearly 40% of patients and increased the risk of stroke almost threefold.[ii] In patients with a recent cryptogenic ischemic stroke or transient ischemic attack, the EMBRACE trial demonstrated that ambulatory ECG monitoring for a target of 30 days with an external

loop recorder was feasible (>80% patients completed at least 3 weeks of monitoring) and uncovered a substantial yield of subclinical AF (15%), with an incremental yield of monitoring over 30 days.[iii] In a Swedish population-based screening study of healthy community-dwelling seniors aged 75 or 76 years (STROKE-STOP), a 2-week intermittent AF screening intervention using a handheld ECG (twice daily 30-second ECG recordings) detected new AF in 3% of participants.[iv] In another Swedish study of patients with $CHADS_2$ score ≥1 attending family practice or hospital outpatient clinics (mean age 71 +/- 8 years; range 53-85), newly-detected AF was found in 35/928 (3.8%) with a 4-week screening intervention (10-second handheld ECG recordings twice daily and if palpitations).[v] Most of the AF detected in this study was asymptomatic (88%) and paroxysmal (83%). Only one-third of AF diagnoses were detected on day 1 of screening; the rest were detected on days 2-28. Most (82%) AF detected was found within the first 14 days of screening, and the mean time to first AF detection was 7 +/- 8 days (range 1-28). A limitation of the intermittent screening studies is the very short recording duration; with this approach, the duration of AF episodes and total AF burden remain uncertain, and the indication for anticoagulant therapy is unclear for those who may have only <30 seconds of AF detected.

Therefore, a continuous ECG monitoring strategy, rather than intermittent ECG, is advantageous as it is expected to detect a substantially greater prevalence of paroxysmal AF and also document total AF burden that is important for anticoagulant decision-making. To maximize AF detection, the present trial is investigating a more intensive non-invasive screening protocol than has been tested in previous studies.

1.3 Study Design

SCREEN-AF is an investigator-initiated, multicentre, open-label, two-group randomized controlled trial, investigating non-invasive, home-based AF screening. The trial targets patients aged 75 years and older without known AF who would be potential anticoagulant candidates if AF were detected. Eligible participants will be recruited from primary care practices and randomly allocated (1:1) to one of two groups:

i. The control group will receive standard care for 6 months (including a pulse check and heart auscultation by a physician at 6 months); or

ii. The intervention group will undergo ambulatory screening for AF with a 2-week continuous ECG patch monitor (ZIO XT Patch) worn at baseline and again at 3 months, in addition to standard care for 6 months (including a pulse check and heart auscultation by a physician at 6 months). The intervention group will also receive a home BP monitor with automatic AF detection capability to be used twice daily for 2 weeks during each of the ECG monitoring blocks.

For ease of understanding, we will refer to this group as the intervention group.

2. STUDY OBJECTIVES

2.1 Primary Objective

To determine if home screening (ZIO Patch monitor) is superior to standard care for the detection of new AF (atrial fibrillation or atrial flutter) at 6 months in primary care patients aged ≥75 years with hypertension.

2.2 Secondary Objectives

1. To determine whether the ambulatory ECG screening intervention significantly increases the proportion of participants who are prescribed oral anticoagulant therapy for AF at 6 months.
2. To determine if home screening (ZIO Patch monitor) is superior to standard care for the detection of new AF at 3 months
3. To assess patient satisfaction, tolerability and adherence with home AF screening devices in the intervention group.
4. To assess the incremental yield of screening according to monitoring duration in the intervention group.
5. To determine if there is an effect of the intervention, compared to standard care, on the 6 month risk of clinical events (ischemic stroke, transient ischemic attack, systemic embolism, major bleeding, hemorrhagic stroke and death). The combined endpoint of ischemic stroke or TIA or systemic embolism, and the combined endpoint of ischemic stroke or death will be considered.
6. To determine if there is a difference in the number of physician visits, ED visits, and hospitalizations, at six months, between the two arms.
7. To explore predictors of AF in the intervention arm only.
8. To evaluate the yield of intermittent AF screening using a home AF-BP monitor and calculate its sensitivity, specificity and false positive rate with a simultaneous continuous ECG monitor used as the gold standard.
9. To determine if the ZIO patch monitor will result in a higher rate of AF detection and if AF detection rates differ among the following subgroups: Age ≥ 80 years vs age < 80 years, , age>=85 years vs age< 85 years, $CHADS_2$ score 4-6 vs. 2-3 and prior history of ischemic stroke vs. no prior history of ischemic stroke.

   In the intervention arm only, to determine the number of primary outcome events among those who wore the 1st Zio patch for >=24 hours, those with frequent APB (≥30 per hour) vs. infrequent APB (less than 30 per hour), patients with 1st ZIO Patch <=10 days vs patients with 1st ZIO Patch >10 days, patients with 1st and 2nd ZIO Patch for <=10 days vs all the other groups.
10. To compare blood pressure control between the two groups at 3 months and 6 months post-randomization.
11. a. To compare the average time to first detection of AF in between the two groups.
    b. To summarize the duration and number of AF episodes, and duration of the longest AF episode (categories: < 30 seconds, 30 seconds to < 5 minutes, 5 minutes to < 30 minutes, 30 minuets to < 12 hours, 12 hours to 24 hours, > 24

hours; and also 30 seconds to < 6 minutes, 6 minutes to < 6 hours, 6 hours to < 12 hours)in the intervention arm.

c. To determine AF burden in the intervention arm.
d. To document potentially clinically important non-AF arrhythmias detected by the ZIO Patch in the intervention arm.

3. HYPOTHESES

3.1 Primary Hypothesis

Among primary care patients aged ≥75 years without known AF (who would be potential candidates for oral anticoagulant therapy if AF were detected), we hypothesize that home-based AF screening with an ambulatory ECG patch monitor will be superior to standard care for new AF detection at 6 months.

3.2 Secondary Hypotheses

1. The ECG patch monitor will result in significantly more patients treated with oral anticoagulant therapy for AF at 6 months compared with standard care.
2. The ECG patch monitor will be superior to standard care for new AF detection at 3 months.
3. There will be an incremental yield of AF detection by the ECG patch monitor with increasing duration of screening, as assessed descriptively, in the intervention group only.
4. The screening strategies will be feasible to implement in this patient population with acceptable rates of patient adherence, satisfaction, and tolerability.
5. The screening intervention will reduce the risk of clinical events (ischemic stroke, transient ischemic attack, systemic embolism, or death) at 6 months.
6. The home screening intervention will result in an increased number of physician visits but not ED visits or hospitalizations within 6 months, compared to standard care.
7. In the intervention arm only, we will consider two models: one with baseline variables including age, systolic blood pressure, history of stroke or transient ischemic attack, history of myocardial infarction or coronary artery disease, history of diabetes, and ABP count will be predictors of the primary outcome of AF >5 minutes at 6 months. Another model will assess 3 predictor variables: age, CHADS2 score, and APB count.
8. Continuous screening with an ECG patch monitor for 2 weeks will be superior to intermittent screening with an AF-BP monitor for detection of paroxysmal AF, and the AF-BP monitor will have a false-positive screen rate >10%.

3.3 Subgroup Hypotheses

The ZIO patch monitor will result in a higher rate of AF detection and detection rates will differ among the following pre-specified subgroups: Age ≥ 80 years vs age < 80

years, $CHADS_2$ score 4-6 vs. 2-3, prior history of ischemic stroke vs. no prior history of ischemic stroke.

4. POPULATIONS TO BE ANALYZED

Full Analysis set

All randomized participants will be included in the group to which they were randomized, regardless of device utilized, adherence to the protocol or duration of trial participation (intention-to-screen).

Per Protocol set

A planned per-protocol analysis will evaluate the primary outcome in only patients with good compliance with the intervention, defined as those who wore the ZIO Patch twice, and each ZIO Patch was worn for at least 12 days (or 288 hours) of the 14 days assigned. Patients who die at the end of the first ZIO Patch with at least 12 days compliance will also be included in this set.

We would also consider the number of days of wear time of ZIO Patch as a predictor of AF detection and report the proportion of patients with the primary outcome according to different categories of total wear time, i.e.:
1 week
2 weeks
3 weeks
4 weeks

5. BASELINE CHARACTERISTICS

Standard methods will be used to provide tabular and graphical summaries as appropriate for continuous and categorical variables. Summaries of normally distributed continuous variables will include the number of subjects (N), mean and standard deviation. Summaries of non-normally distributed variables will include number of subjects, median, and interquartile range. Frequency distributions (N and %) will be given for categorical data.

Sample summary tables of baseline characteristics, medical history, and medication use are shown in Appendix A.

6. COMPLIANCE

The total duration of ECG monitoring will be automatically recorded (time stamped) by the ZIO Patch monitor. Patients are instructed to wear the ZIO patch for 14 days at baseline and for another 14 days 3 months later. Note: participants who die or drop out prior to the monitoring period (at 3 months) will be excluded from the calculation at 3 months.

Compliance will be summarized as:

- The min, max, and average duration (days) the ZIO Patch was worn at baseline, at 3 months, and total (among patients who had any ZIO Patch monitoring; i.e. exclude any patients who did not wear the ZIO patch). The average percentage of time the ZIO patch was worn at baseline and 3 months separately and together. It is calculated as the total days worn divided by 14 days (if separately, or 28 days if together) and multiplied by 100 (for the total number of participants assigned to wear the device according to the randomization).
- The min, max and average analyzable time (days) recorded by the ZIO patch at baseline, 3 months and together. The average percentage of analyzable time recorded by the ZIO patch at baseline and 3 months. This is calculated as the total analyzable time recorded by the ZIO patch divided by the total monitoring duration recorded by the ZIO patch. The analyzable time is defined as the total time the patient wore it minus the duration of artifact (duration of good quality ECG data that can be analyzed). For the analyzable time, we would take the value provided in the CRF/Zio Patch diaries. If this value is missing, we'd calculate it.

Adherence with the WatchBP monitoring will be documented according to participant completion of the home BP diary. Participants are instructed to take measurements twice daily during the 14 days they are wearing the ZIO patch monitor.
Compliance will be summarized as:

- The min, max and average number of measurements participants completed.
- The average percentage of measurements completed. This is calculated as the total number of measurements completed divided by 28 measurements (the total number of measurements prescribed by the protocol) per participant and multiplied by 100.

Reasons for non-compliance at baseline with both the ZIO patch and the WatchBP will be summarized.

7. STUDY FOLLOW-UP TIME

All efforts will be made to collect complete data for all patients in this study. Patients will be followed to the end of study (6 months) and will complete all required data collection, regardless of their compliance with the study protocol.

In general, missing values within follow up will be treated as 'missing'. No attempt will be made to impute missing post-randomization values and only observed values will be used for analysis.

Lost to follow-up:
All efforts will be made to collect information about the clinical outcomes for those participants lost to follow-up. In case of no contact, the participant will be censored on their last day of available contact during the study.

Missing date information
When an event date is not known, the site investigator will be asked to provide a best estimate as to when the event occurred. Even though the exact date of an event is unknown, the investigator often does know some information that would indicate the approximate date, such as the first week of a month, in the fall of a year, or the middle of a particular year or at least the date when the patient was last seen or contacted. This information can be meaningfully incorporated into the estimated date recorded, as this is likely to be closer to the true date than any produced by an uninformed computer program. This estimated date should be the middle date within the period that the event is known to have occurred. If the event is known to have occurred in the first week of a month, then the date in the middle of that week should be recorded as the estimate. If it occurred in the fall of a year, then the middle date in the fall is the appropriate estimate. If no information is known then the date in the middle of the plausible time period should be given, based on the last contact with the patient prior to the event and the date of contact when information about the event was known. This method for date estimation has been used in many studies and is recommended by Dubois and Hebert (Dubois & Hebert 2001).

Baseline, Time Windows and Calculated Visits
The randomization visit (Day 1) is the reference for all time-related analyses.

It is expected that the study period will include up to 2 follow-up visits based on the Screen-AF protocol. All patients will have a final follow-up form completed (CRF09).

Follow-up time will be defined as the time from randomization to the date of last contact for an individual from the final follow-up, or the death date, whichever occurs first + 1.

8. EFFICACY ANALYSIS

The primary analyses will be based on full analysis population set using the intention to screen principle, i.e. with participants analyzed in the group to which they were randomized.

8.1 Primary Outcome

Original definition: As stated in the study protocol, the primary outcome of the trial is ECG-confirmed detection of new AF (atrial fibrillation or atrial flutter) within 6 months post-randomization, with AF defined as at least one episode of continuous AF lasting >5 minutes (or AF documented on two separate12-lead ECGs performed >5 minutes apart).

Given the pragmatic nature of this trial, and to avoid missing any cases of clinical AF, the steering committee felt it was necessary to retain the above definition of AF but extend it to also include AF if it is documented by a single 12-lead ECG or if there is reliable source documentation of a convincing clinical diagnosis of AF.

Revised wording: The primary outcome of the trial is the detection of new AF (atrial fibrillation or atrial flutter) within 6 months post-randomization, with AF defined as at least one episode of continuous AF lasting >5 minutes or AF documented on at least one 12-lead ECG or a convincing clinical diagnosis of AF based on reliable source documentation.

Justification for the expanded definition: In drafting this statistical analysis plan, the steering committee realized that in clinical practice patients might receive only one ECG to document a diagnosis of AF. The steering committee was concerned by the stipulation of "two separate 12-lead ECGs performed >5 minutes apart", because participants who have true outcome event of AF would not be captured in the study results if a second ECG was not obtained, and that could potentially unfairly favour the intervention group in the study analysis. Therefore, a decision was made to count all adjudicated cases of AF if documented by at least one 12-lead ECG or if there is reliable clinical documentation indicating that a participant had a convincing diagnosis of AF based on source documents (e.g. physician consultations, hospital records, new prescription, etc.). This decision was made a priori as part the statistical analysis plan before locking the study database, before unblinding, and before any data analysis.

All site reported AF diagnoses (whether detected by the study devices or detected clinically) will be centrally adjudicated. The adjudicators are blinded to the group assignment for assessment of all site reported AF events and all other clinical outcome events (separate from the ZIO patches). All centrally adjudicated, confirmed AF events will be included in the analysis.

We will separately report AF detection by each of the study devices, by 2 separate 12 lead ECGs > 5min apart, by only 1 12 lead ECG with additional source documentation of a diagnosis of AF, only 1 12 lead ECG without additional source documentation, and source documentation of AF without 12 lead ECGs available.

We will also perform a sensitivity analysis to determine if site reported AF produces the same results as centrally adjudicated and confirmed AF.

We will calculate the relative risk in the intervention group vs. the control group using a modified Poisson regression model with robust error variances. Statistical significance will be tested using a Chi-square test. Results will be presented as the crude rates in each group and relative risk estimates with associated confidence interval.

A two-sided significance level of 0.05 will be used for all the analyses. No adjustment of multiple comparisons is needed, since there is only one primary outcome with one primary comparison.

8.2 Secondary Outcomes

The secondary outcomes are as follows:

1. Oral anticoagulant therapy at 3 and 6 months post-randomization. Participants will be counted as taking an oral anticoagulant at 3 and 6 months if they are taking at least one of: warfarin/Coumadin, dabigatran, apixaban, rivaroxiban or edoxaban, at 3 months and 6 months. Oral anticoagulant therapy will be assessed by comparing the relative risk of oral anticoagulant use between treatment groups using a Chi-square test. Results will be presented as the crude rates, crude relative risk estimates and associated confidence intervals, and p-values. Results will be presented for both oral anticoagulation prescribed for any reason, and oral anticoagulation prescribed for the indication of AF. A two-sided significance level of 0.05 will be used for all the analyses.

2. The secondary AF outcome is ECG-confirmed detection of new AF (atrial fibrillation or atrial flutter) within 6 months post-randomization, defined as at least one episode of continuous AF lasting >5 minutes (or AF documented on two separate12-lead ECGs performed >5 minutes apart).

3. Detection of the primary and secondary AF outcome at 3 months post-randomization. This will be analyzed and presented in the same manner as that described for the primary outcome above.

4. Patient adherence and satisfaction with the screening devices, and tolerability of the ECG patch monitor will be summarized in the intervention group. For all the times, N, mean and standard deviation will be presented. If the assumption of normality is not met, then N, median and IQR will be presented.
   a. The average time the ZIO patch is worn at baseline and 3 months, will be summarized.
   b. The average percentage of time the Zio patch is worn at baseline and 3 months will be summarized among patients who completed any monitoring. Percent will be calculated as the total days worn divided by 14 days and multiplied by 100 (the total number of participants are assigned to wear the device according to the study protocol).
   c. The average analyzable time recorded by the ZIO patch will be summarized at baseline and 3 months.
   d. The average percentage of analyzable time recorded by the ZIO patch at baseline and 3 months will be summarized. Percent of analyzable time recorded by the ZIO patch will be calculated as the total analyzable time divided by the total monitoring duration recorded by the ZIO patch and multiplied by 100.

   Adherence with the WatchBP monitoring will be documented according to participant completion of the home BP diary. Participants are instructed to take measurements twice daily during the 14 days they are wearing the ZIO patch monitor. Compliance will be summarized as:

e. The average number of measurements participants completed. The minimum and maximum number of measurements participants completed.
f. The average percentage of measurements completed calculated as the total measurements completed divided by 14 measurements and multiplied by 100 (the total number of measurements prescribed by the protocol) per participant.

Reasons for non-compliance with both the ZIO patch and the WatchBP will be summarized.

Patient satisfaction with both the ZIO patch and the WatchBP will be assessed using a 1-5 scale with 5 being the most satisfied and 1 being the least satisfied. Results will be summarized and presented as median average satisfaction level and associated interquartile range for each device. Patient satisfaction with the ZIO patch will also be assessed via a patient satisfaction survey which includes 35 Likert scale questions. Results for each question will be summarized with N, median value and interquartile range.

Tolerability of the ZIO patch device will be summarized as the total number and percent of adverse skin reactions among patients in the invention group.

5. The incremental yield of screening according to monitoring duration will be presented descriptively in the intervention group only. The number of AF episodes observed per day, and the cumulative number of AF episodes observed during the monitoring period will be summarized.

6. Adjudicated clinical events are ischemic stroke, hemorrhagic stroke, TIA, systemic embolism and death. Events will only be counted if they meet the study definition of the event. Final adjudicated events will be used in the analysis. A Cox proportional hazards regression analyses will be used for the time to the first occurrence of the events with treatment group as the only covariate. A log-rank test will be used to determine if the hazard functions differ between groups. Time to event will be determined from the date of randomization to the date of the event +1, or the last follow-up day for those without events. The proportional hazard assumption will be assessed by including a time-treatment interaction term in the Cox model (time log transformed) or graphically with the use of Schoenfield residuals. From this analysis, we will present hazard ratios, associated 95% confidence intervals and p-values. Tied event times using the exact method will be used. If the number of events is too low (<5), Fisher's exact tests will be used to present the N (%) and exact p-values.

   Major bleeding is reported as a binary outcome. Differences between the treatment group and the standard care group will be presented as crude rates, crude relative risk estimate and associated 95% confidence intervals and p values. If the number of events is low (<5), then Fisher's exact test will be employed and crude rates will be presented.

7. Physician visits, ED visits, and hospitalizations, at 3 months and 6 months, will be analyzed as count data. Differences between the treatment and the standard care group will be analyzed using a Poisson regression model and presented as incidence rate and associated 95% confidence intervals and p-values.

8. In the intervention group only, potential predictors of new AF at 6 months will be explored using log-binomial regression analysis. Potential predictor variables will first be entered into a univariate model. Variables that are significant (p<0.10) at the univariate level will then be entered into a multivariable poisson regression model. Stepwise variable selection will be used and variables that remain significant at p<0.05 level will be retained in the model. The following pre-specified variables will be considered as potential predictors: age, systolic blood pressure, history of stroke or transient ischemic attack, history of myocardial infarction or coronary artery disease, history of diabetes, and ABP count.

   We suspect that the number of AF events may be too low to model all of the above covariates as potential predictors of AF. We will hence also consider a second model that includes 3 predictor variables: age, CHADS2 score, and APB count.

9. Estimated sensitivity, specificity and false positive rate of a home AF-BP monitor (with ECG patch monitor as the gold standard).
   Summaries of sensitivity, specificity and false positive rates will be presented. Sensitivity will be calculated as the true positive cases divided by the total number of AF cases. Specificity will be calculated as the true positive cases divided by the total number of non-AF cases. False positive rate will be calculated as the number of false positives over the total number of non-AF cases.

10. Systolic and diastolic blood pressure at 6 months post-randomization will be compared between the intervention and the standard care group using t-tests, assuming normality of the distribution is not violated. Results will be presented as the mean and standard deviations, or median and IQR, in the case of non-normal distributions.

11. The following outcomes will be summarized for patients in the intervention group with the primary endpoint detected by the ZIO patch monitor. Outcomes will be summarized using descriptive statistics.

    a. The time to first detection of an AF episode (> 5 minutes), detected by the ZIO patch monitor. This will be calculated as the date and time of first AF occurrence from the date and time of diagnostic test initiation. The median time and associate interquartile range (IQR) will be presented.
    b. Detection of any AF episode will be summarized. The longest AF episode will be summarized according to the following categories; AF episodes < 30 seconds, 30 seconds to < 5 minutes, 5 minutes to < 30 minutes, 30 minuets to < 12 hours, 12 hours to 24 hours, > 24 hours.
    c. Total AF burden (%) will be summarized. We will use the reported value, and if it is missing, calculated values will be presented.

d. Total time in AF, number of AF episodes and number of symptomatic AF episodes will be summarized. Total time in AF will be summarized as hours and minutes.
e. Average duration per AF episode. This will be calculated as the total time spent in AF divided by the number of AF episodes.
f. Other potentially clinically important non-AF arrhythmias will be summarized according to the following categories; heart rate > 160 beats per minute (bpm) for ≥ 30 seconds, ventricular tachycardia (> 100 bpm for for ≥ 30 seconds), polymorphic VT of VF (any duration), heart rate < 40 bpm for ≥ 30 seconds, third decree AV block or Mobitz type 2 second degree AV block, pause ≥ 5 seconds, other.

8 SAFETY ANALYSIS

For the purpose of this study, safety reporting will consist of adverse device reactions related to the ZIO XT Patch only, specifically related to the device tolerability. It is not anticipated that there will be any Serious Adverse Device Events, however, if there are, they will be reported to the Principal Investigator, iRhythm Technologies Inc. and Health Canada.

Drug related Serious Adverse Drug Reactions will be collected in an unsolicited manner. If they occur, they will not be reported in the study database, but will be sent directly to the pharmaceutical company that markets the drug, as per standard practice in accordance with ICH-GCP guidelines (4.11 Investigator responsibilities Safety Reporting) and applicable regulatory requirements. Other non-drug related SAEs will not be collected in the database.

9 SUBGROUP ANALYSIS

All subgroups will be analysed using intention-to-screen population. If the value of the grouping variable cannot be determined for a subject, the subject will be excluded from the subgroup analysis. The subgroup analyses will be conducted using tests for interactions between the subgroup and treatment group in the modified Poisson regression model. We will infer a subgroup effect if the interaction term is statistically significant at $p < 0.05$. The following subgroups will be considered.

- Age group: age ≥ 80 vs. age < 80 years.
- Age group: age>=85 vs age < 85 years.
- CHADS2 score 4-6 vs. 2-3.
- Prior history of ischemic stroke vs. no history of ischemic stroke.

In the intervention group only, the following subgroups will be considered and event rates will be reported in each subgroup separately. There is no interaction term with the treatment.

- Among the patients who wore the 1st ZIO patch for >=24 hours, those with frequent APB (≥30 per hour) vs. infrequent APB (less than 30 per hour),
- Patients who wore the 1st ZIO Patch for upto 10 days vs. patients who wore the 1st ZIO Patch for >10 days
- Patients who wore the 1st ZIO Patch for upto 10 days and the 2nd ZIO Patch for upto 10 days vs the other groups (patient who wore 1st ZIO Patch >10 days and 2nd ZIO Patch >10 days, patients who wore 1st ZIO Patch >10 days and 2nd ZIO Patch <=10 days, patients who wore 1st ZIO Patch <=10 days and 2nd ZIO Patch >10 days, patients who wore both ZIO Patches <=10 days).

10 ADHERENCE TO THE PROTOCOL

All patients enrolled will be followed until 6 months post-randomization. Adherence to the requirements for the protocol will be monitored by the Study Coordinating Centre and those who did not meet the inclusion/exclusion criteria will be documented and summary tables will be provided.

APPENDIX A. SUMMARY TABLES

Intervention Group = ZIO Patch and BP monitoring

Inclusion and Exclusion Criteria

- Table with summaries by intervention group and Standard Care for all the inclusion and Exclusion Criteria.

Demographics and Clinical characteristics – Categorical

	Randomized (N=)					
	Overall (N=)		Intervention group (N=)		Standard care group (N=)	
	n	%	n	%	n	%
Female						
Ethnicity						
White/Caucasian						
Black/African descent						
Hispanic/Latino						
Asian						
Middle East						
Aboriginal/Native						
Other						
Living Situation						
Home						
Retirement Home						
Assisted Living						
Nursing Home						

Demographics and Clinical characteristics – Continuous Variables

	Overall		Intervention group		Standard care	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Age						
Pulse rate (bpm)						
Systolic BP (mmHg)						
Diastolic BP (mmHg)						
Height (cm)						
Weight (kg)						
BMI (kg/m^2)						
CHA_2DS_2 – VASc Score- Median (IQR)						
$CHADS_2$ Score- Median (IQR)						

Notes:

$CHADS_2$ Score consists of….

CHA_2DS_2 – VASc consists of….

Past Medical History

	Randomized (N=)					
	Overall (N=)		Intervention group (N=)		Standard care (N=)	
	n	%	n	%	n	%
Diabetes mellitus						
Congestive heart failure						
Ischemic stroke, TIA Systemic embolism						
Coronary artery disease						
Coronary angioplasty/ coronary stent						
Myocardial infarction						
Angina						
Hyperthyroidism						
Syncope in the past year						
First degree relative with AF						
Heart palpitations in last year						
Severe aortic mitral valve disease						
Rheumatic heart valve disease						
Prosthetic heart valve						
Sleep Apnea						
Dialysis						
Chronic renal failure						
Prior cardiac surgery – CABG						
Prior cardiac surgery – valve sx						
Peripheral artery disease or know aortic plaque						
Carotid endarterectomy/ carotid stent						
Left atrial enlargement on echocardiogram						
Dementia						
Mild cognitive impairment						
Current smoker						
Prior smoker						
Independent in ADL						

Current Medications (at baseline and follow-up)

	Randomized (N=)					
	Overall (N=)		Intervention group (N=)		Standard care (N=)	
	n	%	n	%	n	%
Angiotensin receptor blocker (including ARNI)						
ACE Inhibitor						
Beta blocker						
Aldosterone inhibitor						
Diuretic						
Long acting nitrate						
Statins						
Insulin						
Oral hypoglycemic						
Aspirin						
Clopidogrel						
ASA / ER dipyridamole						
Ticagrelor						
Prasugrel						
ANY antiplatelet agent, i.e. aspirin OR clopidogrel OR ASA-ER dipyridamole OR ticagrelor OR prasugrel)						
Warfarin/Coumadin/Phenprocoumon						
Dabigatran						
Apixaban						
Rivaroxiban						
Endoxaban						
Oral anticoagulant therapy (include ANY oral anticoagulant, i.e. warfarin or dabi or apix or riva or edox)						
Low molecular weight heparin						
Reason anticoagulation started						
Atrial fibrillation/flutter						
Prevention of DVT or PE						
Other						

Compliance Summaries

BP Watch Compliance Summary

Intervention group (N=)					
	N	Median (IQR)	minimum	maximum	Average percent
BP Watch measurements					
Baseline**					
3months**					
Total*					

* Denominator is 28 measurements per person

** Denominator is 14 measurements/ person

ZIO Patch / BP Watch Non-Compliance Summary at Day 14 Monitoring visit

Intervention group (N=)		
	N	%
ZIO Patch monitoring stopped prior to 14 days		
ZIO patch fell off before 14 days		
Skin reaction to ZIO patch		
Early termination from study		
Poor compliance		
Other		
BP monitor stopped prior to 14 days		
BP monitor too difficult to use		
Early termination from study		
Poor compliance		
Other		

Analyses

Primary Outcome: ECG confirmed unrefuted AF at 6 months

	Crude Rates		Relative Risk	95% CI	P-value
Outcome	Intervention group (N=)	Standard Care Group (N=)			
ECG-confirmed unrefuted AF within 6 months	n/N (%)	n/N (%)			

Secondary Outcome Tables

T1: OAC use at 3 and 6 months

	Crude Rates		Relative Risk	95% CI	P-value
Outcome	Intervention group (n=)	Standard Care Group (n=)			
Oral anticoagulant use (for any reason) at 3 months					
Oral anticoagulant use (for any reason) at 6 months					
Oral anticoagulant use (for atrial fibrillation/flutter) at 3 months					
Oral anticoagulant use (for atrial fibrillation/flutter) at 6 months					

T2a: ECG confirmed unrefuted AF at 6 months (using original wording of the primary outcome definition).

	Crude Rates		Relative Risk	95% CI	P-value
Outcome	Intervention Group (n=)	Standard Care Group (n=)			
ECG-confirmed unrefuted AF within 6 months					

T2b: ECG confirmed unrefuted AF at 3 months (using both original and revised wording of the primary outcome definition).

	Crude Rates		Relative Risk	95% CI	P-value
Outcome	Intervention Group (n=)	Standard Care Group (n=)			
ECG-confirmed unrefuted AF within 3 months					

T3: ZIO Patch Compliance Summary

Intervention Group (N=)						
	N	Median	IQR	Maximum	Minimum	Percent time worn *
Time ZIO Patch worn (days) at baseline						
Time ZIO Patch worn (days) at 3 months						
Analyzable time recorded by ZIO Patch (days) at baseline						
Analyzable time recorded by ZIO Patch (days) at 3 months						

* Total time / 14 days

	Zio patch worn any time		Average percent time worn*
	N	%	
At baseline			
At 3 months			

* Denominator is the total number of patients who wore the zio patch x 14 days.

1st ZIO Patch/2nd ZIO Patch	+ve for AF n (%)	-ve For AF n (%)	Total
+ve for AF n (%)			
-ve For AF n (%)			
Total			

T4: Clinical Events at 6 months

	Intervention Group (n=)		Standard Care Group (n=)		HR	95 % CI	P-value
Outcome	N	%	N	%			
Ischemic stroke							
move this to the bleeding table below							
TIA							
Systemic embolism							
Death							
Composite of Ischemic Stroke, TIA or Systemic Embolism							
Composite of Ischemic Stroke or Death							

	Intervention Group (n=)		Standard Care Group (n=)		Relative Risk	95 % CI	P-value
Outcome	N	%	N	%			
Major bleeding at 6 months							
Intracranial hemorrhage at 6 months **							

**HR (95% CI), and Wald Chi-square p-value presented instead.

T5: Physician Visits and Hospitalizations at 6 months

	Intervention Group (n=)		Standard Care Group (n=)		Exp(estimate) = IRR	95 % CI	P-value
Outcome	N	%	N	%			
Physician visits at 6 months							
ED visits at 6 months							
Hospitalizations at 6 months							

IRR = incident rate ratio

T6: Potential Predictors of AF in the Intervention Group

Intervention Group vs Standard Care		
Variable	RR (95% CI)	p-value
Age		
Baseline Systolic blood pressure (at randomization)		
History of ischemic stroke or TIA		
History of MI or CAD (include if PMH CABG or coronary stent also)		
Diabetes		
APB during the first 24 hours of ZIO Patch recording		

And another Table with the 3 covariate model: with age, CHADS2 score, and APB count

T7: Agreement between ZIO Patch Monitor and Watch BP Monitor

		AF Detected by ZIO Patch		Total
		Yes	No	
AF detected by Watch BP	Yes			
	No			
Total				

Note: Total might be ># in the Intervention group.

T8: AF By Day, Intervention Group

	Patients in AF by day at Baseline													
ZIO Patch:	day1	day2	day3	day4	day5	day6	day7	day8	day9	day10	day11	day12	day13	day14
per day														
cumulative														

	Patients in AF by day at 3 months													
Zio Patch:	day1	day2	day3	day4	day5	day6	day7	day8	day9	day10	day11	day12	day13	day14
per day														
cumulative														

T9: Blood Pressure at 3 and 6 months

	Intervention group (n=)		Standard Care Group (n=)		t-test P-value
	N, Mean	SD	N, Mean	SD	
Systolic BP at 3 months Diastolic BP at 3 months Systolic BP at 6 months					
Diastolic BP at 6 months					

T10: AF Summaries, Intervention group

Intervention group (N=)			
Time to first detection of AF occurrence (days)	N, Median		IQR
Total AF burden (%)			
Total time in AF (hours, minutes)			
Number of AF episodes			
Time for the longest episode:			
≥ 30 seconds			
30 seconds – 5 minutes			
> 5 minutes			
> 24 hours			
	Total AF episodes	Median	IQR
Number of symptomatic AF episodes			
Duration of longest AF episode (hours, minutes)			

T11: Arrhythmia Summaries, Intervention Group

Intervention Group (N=)			
	N	Median number detected	IQR
Heart rate > 160 beats/ minutes for ≥ 30 seconds			
ventricular tachycardia (> 100 beats bpm for ≥ 30 seconds)			
polymorphic VT of VF			
Heart rate < 40 bpm for > 30 seconds			
third degree AV block or Mobitz type 2 second degree AF block pause ≥ seconds			

Subgroup analyses: outcome- AF at 6 months (primary outcome definition)

	Intervention Group		Standard Care Group		Intervention vs Standard Care	
Subgroup	Subgroup N	N(%)	Subgroup N	N(%)	Relative Risk (95% CI)	P for interaction
age ≥ 80						
age < 80						
Age>=85						
Age<85						
$CHADS_2$ 4-6						
$CHADS_2$ 2-3						
$CHADS_2$ 0-1						
History of ischemic stroke						
No history of ischemic stroke						

Intervention Arm only:

Subgroup	Total N	#Events N (%)
Frequent APB (>=30/hr)		
Infrequent APB (<30/hr)		
1st ZIO Patch for <=10 days		
1st ZIO Patch for > 10 days		
1st and 2nd ZIO Patch for <=10 days		
1st and 2nd ZIO patch for >10 days		
1st ZIO Patch for >10 days, 2nd ZIO Patch for <=10 days		
1st ZIO Patch<= 10 days and 2nd ZIO Patch for >10 days		

APPROVAL

Version #	**1.01**
Version Date	2019-10-25

By signing the below, I designate my approval of the above-named version of the SCREEN-AF Statistical Analysis Plan on behalf of all named authors.

Name	**Dr. David Gladstone**
Role	**Principal Investigator**
Signature	
Date (yyyy/mm/dd)	

By signing the below, I designate my approval of the above-named version of the SCREEN-AF Statistical Analysis Plan on behalf of all named authors.

Name	**Dr. Jeff Healey**
Role	**Co-Principal Investigator**
Signature	
Date (yyyy/mm/dd)	

By signing the below, I designate my approval of the above-named version of the SCREEN-AF Statistical Analysis Plan on behalf of all named authors.

Name	**Dr. Noah Ivers**
Role	**Co-Principal Investigator**
Signature	
Date (yyyy/mm/dd)	

By signing the below, I designate my approval of the above-named version of the SCREEN-AF Statistical Analysis Plan on behalf of all named authors.

Name	**Dr. Russell Quinn**
Role	**Co-Principal Investigator**
Signature	
Date (yyyy/mm/dd)	

By signing the below, I designate my approval of the above-named version of the SCREEN-AF Statistical Analysis Plan on behalf of PHRI Statistics.

Name	**Purnima Rao-Melacini**
Role	**Sr. Biostatistician**
Signature	
Date (yyyy/mm/dd)	

[i] Wilson JMG, Jungner G, eds. Principles and practice of screening for disease. Public Health Papers, No. 34: World Health Organization; 1968.

[ii] Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012;366(2):120-129.

[iii] Gladstone DJ, Spring M, Dorian P, et al.; EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med 2014; 26;370(26):2467-77.

[iv] Svennberg E. et al. STROKE-STOP Study. European Society of Cardiology (ESC) Congress 2013. Abstract 4382. Presented September 3, 2013.

[v] Hendrikx T, Hornsten R, Rosenqvist M, Sandstrom H. Screening for atrial fibrillation with baseline and intermittent ECG recording in an out-of-hospital population. BMC Cardiovascular Disorders 2013, 13:41.

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PROTOCOL SIGNATURE PAGE

Dr. David Gladstone Principal Investigator University of Toronto	_____ Name	_____ Date (YYYY-MM-DD)
Dr. Noah Ivers Co-Principal Investigator University of Toronto	_____ Name	_____ Date (YYYY-MM-DD)
Dr. F. Russell Quinn Co-Principal Investigator University of Calgary	_____ Name	_____ Date (YYYY-MM-DD)
Dr. Jeff Healey Co-Principal Investigator McMaster University	_____ Name	_____ Date (YYYY-MM-DD)

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PROTOCOL SIGNATURE PAGE

Dr. David Gladstone Principal Investigator University of Toronto	D Gladstone Name	2015-01-08 Date (YYYY-MM-DD)
Dr. Noah Ivers Co-Principal Investigator University of Toronto	Name	Date (YYYY-MM-DD)
Dr. F. Russell Quinn Co-Principal Investigator University of Calgary	Name	Date (YYYY-MM-DD)
Dr. Jeff Healey Co-Principal Investigator McMaster University	Name	Date (YYYY-MM-DD)

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PROTOCOL SIGNATURE PAGE

Dr. David Gladstone Principal Investigator University of Toronto	Name	Date (YYYY-MM-DD)
Dr. Noah Ivers Co-Principal Investigator University of Toronto	Name	9 JAN 2015 Date (YYYY-MM-DD)
Dr. F. Russell Quinn Co-Principal Investigator University of Calgary	Name	Date (YYYY-MM-DD)
Dr. Jeff Healey Co-Principal Investigator McMaster University	Name	Date (YYYY-MM-DD)

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Dr. F. Russell Quinn Co-Principal Investigator University of Calgary	 Name	2015-01-08 Date (YYYY-MM-DD)
Dr. Jeff Healey Co-Principal Investigator McMaster University	Name	Date (YYYY-MM-DD)

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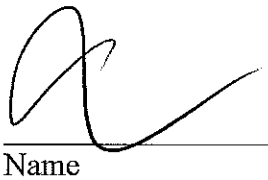
Dr. F. Russell Quinn Co-Principal Investigator University of Calgary	Name	Date (YYYY-MM-DD)
Dr. Jeff Healey Co-Principal Investigator McMaster University	 Name	2015/11/9 Date (YYYY-MM-DD)

CONTENTS

PROTOCOL SYNOPSIS

Study Title	Program for Identification of "Actionable" Atrial Fibrillation (PIAFF): Home-Based Screening for Early Detection of Atrial Fibrillation in Primary Care Patients Aged 75 Years and Older: the SCREEN-AF Randomized Trial
PIs	D. Gladstone, N. Ivers, F.R. Quinn, J. Healey
Sponsor	Hamilton Health Sciences through its Population Health Research Institute
Coordinating Centre	Population Health Research Institute, Hamilton, ON
Study Design	Phase 3 randomized controlled trial
Primary Hypothesis	Among primary care patients aged ≥75 years with hypertension and without known AF (but who would be potential candidates for oral anticoagulant therapy if AF were detected), we hypothesize that home-based AF screening with an ambulatory ECG patch monitor will be superior to standard care for AF detection. The anticipated AF detection rate at 6 months is 5% (intervention group) vs. 1% (control group), for a 4% absolute difference.
Sample Size/ Duration	N=822 (411 per group) enrolled over 12-24 months from Canadian primary care clinics, with a 6 month follow-up after the last patient enrolled; estimated total study duration 18-30 months.
Study Population	Primary care patients aged ≥75 years with hypertension without known AF, who are not taking oral anticoagulant therapy and have no contraindications to anticoagulation.
Inclusion Criteria	1. Age ≥75 years without known atrial fibrillation or atrial flutter. 2. The participant is clinically in sinus rhythm (both heart auscultation and 30-second pulse palpation have been performed by the enrolling physician and neither detects an irregular rhythm suggestive of atrial fibrillation). 3. History of hypertension requiring antihypertensive medication. 4. Written informed consent from the participant.
Exclusion Criteria	1. Any previously documented atrial fibrillation or atrial flutter ≥30 seconds. 2. Implanted pacemaker, cardiac defibrillator, cardiac loop recorder, or deep brain stimulator. 3. Likely to be poorly compliant or unreliable using home screening devices or with study follow-up requirements because of cognitive or other issues, or life expectancy <6 months due to concomitant disease. 4. Has a condition which in the opinion of the enrolling physician would not permit chronic treatment with oral anticoagulant therapy. 5. Patient already taking long-term oral anticoagulant therapy. 6. Known allergic reaction/intolerance to skin adhesives.
Intervention	• The intervention group receives AF screening with a 2-week ambulatory ECG patch monitor (ZIO XT Patch; iRhythm Technologies, Inc., San Francisco) worn at baseline and again at 3 months, in addition to standard care for 6 months (including a pulse check and heart auscultation by a physician at 6 months). The intervention group also receives a home BP monitor with automatic AF detection capability (WatchBP-Home A; Microlife Corporation, Taipei, Taiwan) to be used twice daily for 2 weeks during the ECG monitoring periods. • The control group receives standard care for 6 months (including a pulse check and heart auscultation by a physician at 6 months).

Primary Outcome	New diagnosis of ECG-confirmed atrial fibrillation or flutter within 6 months post-randomization, defined as at least one episode of continuous AF >5 minutes (or AF documented on 2 separate 12-lead ECGs >5 minutes apart).
Secondary Outcomes	1. Oral anticoagulant therapy use at 3 and 6 months post-randomization. 2. Detection of the primary outcome at 3 months post-randomization. 3. Among intervention group patients with the primary endpoint detected by the ECG patch monitor: time to first detection of AF >5 minutes; daily and total AF burden; average duration per AF episode. 4. Among intervention group patients, detection of any AF episode ≥30 seconds, ≥30 seconds to 5 minutes, >5 hours, and >24 hours (to facilitate comparison with other studies in the literature). 5. Patient adherence with the screening devices (defined as the average number of monitoring days completed and reasons for non-adherence), patient satisfaction with the screening devices (as measured by user satisfaction surveys), and tolerability of the ECG monitor (defined as the incidence of adverse skin reactions related to the adhesive patch). 6. Clinical outcome events within 6 months post-randomization (ischemic stroke, TIA, systemic embolism, major bleeding, intracranial hemorrhage), physician visits, hospitalizations, and medication prescriptions. 7. Cost-effectiveness (cost per life year saved) and cost-utility (cost per quality adjusted life year (QALY) gained) of AF screening. 8. Detection of other potentially clinically important non-AF arrhythmias: atrial tachycardia, pause >3 seconds, high-grade atrioventricular block (Mobitz type II or third-degree AV block), ventricular tachycardia, polymorphic ventricular tachycardia/ventricular fibrillation. 9. Estimated sensitivity, specificity and false positive rate of a home AF-BP monitor (with ECG patch monitor as the gold standard). 10. Blood pressure control at 6 months post-randomization.

TABLE OF ABBREVIATIONS

AF	Atrial Fibrillation or Atrial Flutter
ASA	Acetyl Salicylic Acid
BP	Blood Pressure
CIHR	Canadian Institute of Health Research
CRF	Case Report Form
C-SPIN	Canadian Stroke Prevention Intervention Network
ECG	Electrocardiography
e-CRF	Electronic Case Report Form
GCP	Good Clinical Practice
HR	Heart Rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PHRI	Population Health Research Institute
PIAAF	Program for the Identification of "Actionable" Atrial Fibrillation
QALY	Quality Adjusted Life Year
TIA	Transient ischemic attack

FIGURE 1. TRIAL DESIGN

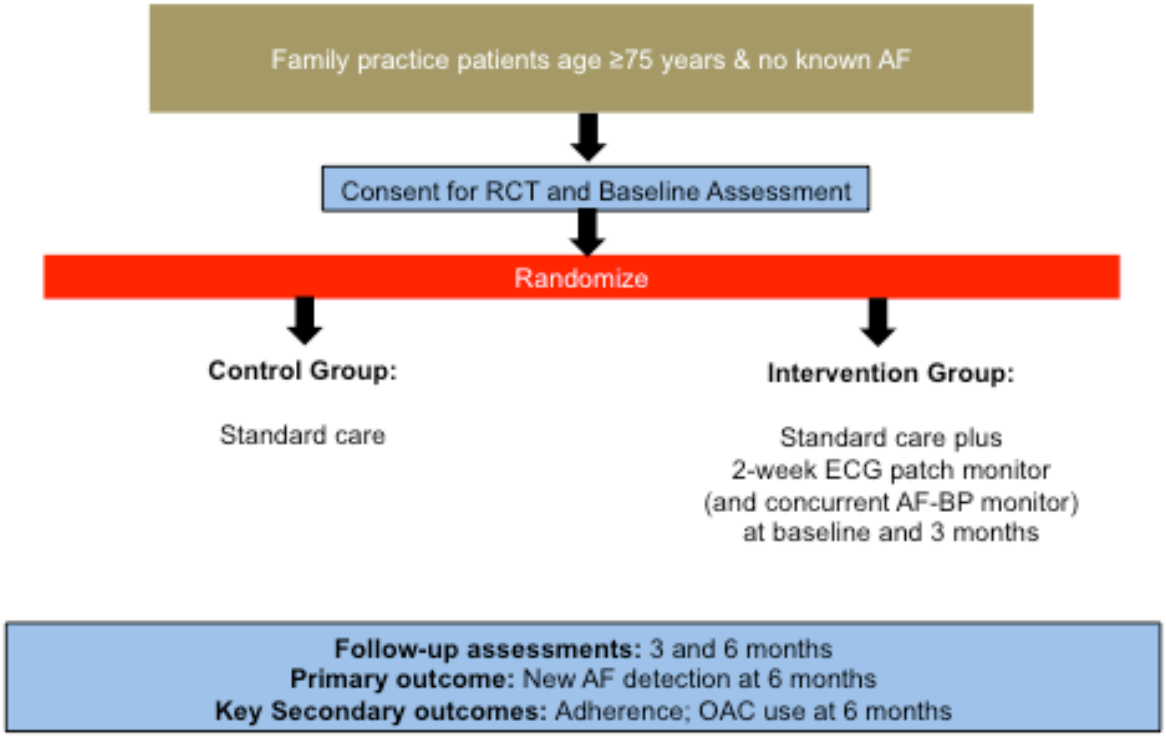


FIGURE 2. ECG PATCH MONITOR

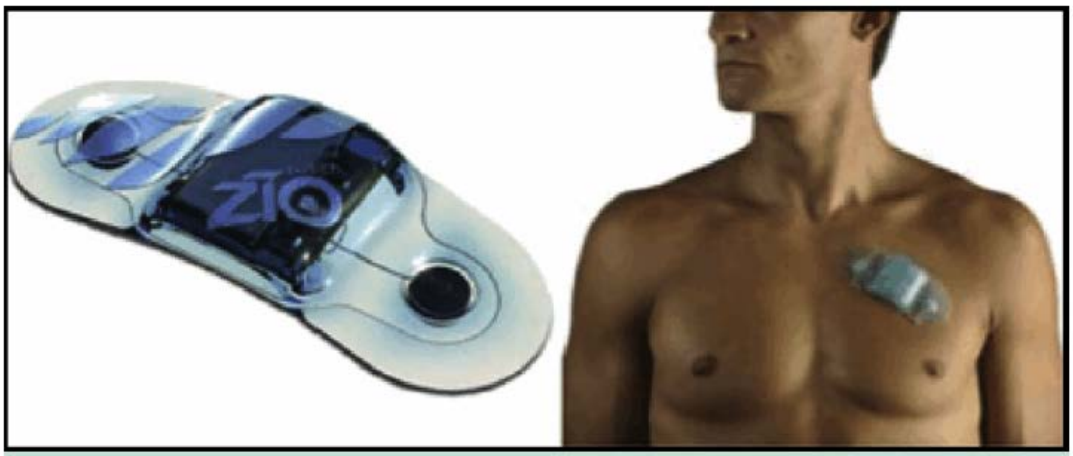


Figure 1 The Zio Patch (iRhythm Technologies, Inc, San Francisco, Calif) is an FDA-cleared, single-use, noninvasive, water-resistant, 14-day, ambulatory ECG monitoring adhesive patch.

1.0 BACKGROUND AND RATIONALE

Atrial fibrillation (AF) is one of most common and treatable risk factors for stroke. Anticoagulant therapy for AF is highly beneficial for stroke prevention, but AF may go undetected and untreated because it is frequently paroxysmal and asymptomatic. The public health consequences of undiagnosed and untreated AF are enormous, and screening strategies for early detection and treatment of AF are widely considered to be part of the solution. Most guidelines do not contain recommendations for routine AF screening in primary care, and randomized evidence is lacking regarding which patients, if any, merit screening, with which devices, for how long, and at what cost. To improve patient care and outcomes, randomized trials are needed to determine the effectiveness and cost-effectiveness of AF screening interventions. Home-based self-diagnosis and remote health monitoring solutions are becoming the way of the future, and this trial investigates new technology devices that appear promising for AF screening in primary care. If more individuals with AF can be detected, then more individuals can be appropriately anticoagulated, and more strokes (including stroke-related deaths, disability and dementia) should be prevented.

There is considerable interest in investigating AF screening strategies for three key reasons: (1) recent advances in new portable device technologies are likely to make AF screening easier and more effective; (2) the availability of newer and safer oral anticoagulants means that it is more important than ever to improve the early detection of candidates who will benefit from such treatment; and (3) the prevalence of AF is rising significantly due to an aging population. The proportion of total strokes that are caused by AF is on the rise and likely will continue to increase in the future. AF is well-suited for screening to improve early detection and treatment and it fulfills the World Health Organization criteria for conditions that merit screening programs.[i]

Recent studies lend strong support for testing AF screening in primary care. In pacemaker patients, the ASSERT trial found that subclinical AF was present in nearly 40% of patients and increased the risk of stroke almost threefold.[ii] In patients with a recent cryptogenic ischemic stroke or transient ischemic attack, the EMBRACE trial demonstrated that ambulatory ECG monitoring for a target of 30 days with an external loop recorder was feasible (>80% patients completed at least 3 weeks of monitoring) and uncovered a substantial yield of subclinical AF (15%), with an incremental yield of monitoring over 30 days.[iii] In a Swedish population-based screening study of healthy community-dwelling seniors aged 75 or 76 years (STROKE-STOP), a 2-week intermittent AF screening intervention using a handheld ECG (twice daily 30-second ECG recordings) detected new AF in 3% of participants.[iv] In another Swedish study of patients with $CHADS_2$ score ≥1 attending family practice or hospital outpatient clinics (mean age 71 +/- 8 years; range 53-85), newly-detected AF was found in 35/928 (3.8%) with a 4-week screening intervention (10-second handheld ECG recordings twice daily and if palpitations).[v] Most of the AF detected in this study was asymptomatic (88%) and paroxysmal (83%). Only one-third of AF diagnoses were detected on day 1 of screening; the rest were detected on days 2-28. Most (82%) AF detected was found within the first 14 days of screening, and the mean time to first AF detection was 7 +/- 8 days (range 1-28). A limitation of the intermittent screening studies is the very short recording duration; with this approach, the duration of AF episodes and total AF burden remain uncertain, and the indication for anticoagulant therapy is unclear for those who may have only <30 seconds of AF detected.

Therefore, a continuous ECG monitoring strategy, rather than intermittent ECG, is advantageous as it is expected to detect a substantially greater prevalence of paroxysmal AF and also document total AF burden that is important for anticoagulant decision-making. To maximize AF detection, the present trial

is investigating a more intensive non-invasive screening protocol than has been tested in previous studies.

2.0 AIM AND OBJECTIVES

2.1 Overall Aim

The overall aim is to establish a practical and cost-effective screening strategy that could be applied in primary care for early detection of AF in patients who would benefit from anticoagulant therapy if AF were detected. The ultimate goal of this primary prevention initiative is to prevent more strokes (and the resulting deaths, disability, dementia, costly hospitalizations and institutionalization, through the early detection and treatment of AF. This trial investigates novel technologies for home-based AF screening that will estimate the prevalence of subclinical paroxysmal AF in individuals aged ≥75 years. The data generated from this study should inform future research and have the potential to contribute to evidence-based primary care practice guidelines for AF screening.

2.2 Objectives

Primary Objective

To investigate the yield of a novel ambulatory ECG patch monitor for early detection of AF in primary care patients aged ≥75 years with hypertension.

Secondary Objectives

1. To determine whether the ambulatory ECG screening intervention significantly increases the proportion of participants who are prescribed oral anticoagulant therapy.
2. To assess patient tolerability and adherence with home AF screening devices.
3. To assess the incremental yield of screening according to monitoring duration.
4. To explore predictors of AF.
5. To estimate the cost-effectiveness (cost per life year saved) and cost utility (cost per quality adjusted life year (QALY) gained of AF screening by combining cost and intermediate outcome data collected during the trial with an AF prediction economic model developed to estimate longer term costs and effects.
6. To evaluate the yield of intermittent AF screening using a home AF-BP monitor, and calculate its sensitivity, specificity and false positive rate with a simultaneous continuous ECG monitor used as the gold standard.

2.3 Hypotheses

Primary Hypothesis

Among primary care patients aged ≥75 years without known AF (but who would be potential candidates for oral anticoagulant therapy if AF were detected), we hypothesize that home-based AF screening with an ambulatory ECG patch monitor will be superior to standard care for AF detection. The anticipated AF detection rate at 6 months is 5% (intervention group) vs. 1% (control group), for a 4% absolute difference.

Secondary Hypotheses

1. The ECG patch monitor will result in significantly more patients treated with oral anticoagulant therapy at 6 months compared with standard care. The anticipated treatment rates are: 4.5% (intervention group) vs. 1% (control group) at 6 months, for a 3.5% absolute difference.
2. The screening strategies will be feasible to implement in this patient population with acceptable rates of patient adherence, satisfaction, and tolerability.
3. There will be an incremental yield of AF detection by the ECG patch monitor with increasing duration of screening, as measured at 24h, day 7 and up to day 14 of monitoring, and by comparing the yield of a repeat monitor vs. a single monitor.
4. Baseline variables including age, number of atrial premature beats, number of episodes of non-sustained atrial tachycardia, longest duration of non-sustained atrial tachycardia, number of episodes of brief AF (30 seconds to 5 minutes), history of hypertension, $CHADS_2$ score, or left atrial enlargement will be predictors of the outcome of AF >5 minutes at 6 months.
5. The AF screening intervention will be cost saving overall (i.e. 'up-front' screening costs will be more than offset by 'down-stream' health care cost savings) with improved patient outcomes. In other words, AF screening is anticipated to be dominant compared to no screening. If not dominant, it is anticipated that AF screening will be cost-effective, having a low cost-effectiveness ratio ($/life year saved) and low cost-utility ratio ($/QALY gained). Cost-effectiveness and cost-utility will have prespecified subgroups: older individuals (age ≥80 vs. <80 years), history of hypertension vs. no hypertension, high vs. low $CHADS_2$ scores (4-6 vs. 1-3), frequent vs. infrequent atrial premature beats (e.g. baseline APB counts of ≥500/24 hours vs. <500/24 hours).
6. Continuous screening with an ECG patch monitor for 2 weeks will be superior to intermittent screening with an AF-BP monitor for detection of paroxysmal AF, and the AF-BP monitor will have a false-positive screen rate >10%.

3.0 METHODS

3.1 Trial Design

The design is an investigator-initiated, multicentre, open-label, two-group randomized controlled trial investigating non-invasive, home-based AF screening. The trial targets patients aged 75 years and older without known AF who would be potential anticoagulant candidates if AF were detected. Eligible participants will be recruited from primary care practices and randomly allocated (1:1) to one of two groups:

- The control group will receive standard care for 6 months (including a pulse check and heart auscultation by a physician at 6 months); or

- The intervention group will undergo ambulatory screening for AF with a 2-week continuous ECG patch monitor (ZIO XT Patch) worn at baseline and again at 3 months, in addition to standard care for 6 months (including a pulse check and heart auscultation by a physician at 6 months). The intervention group will also receive a home BP monitor with automatic AF detection capability to be used twice daily for 2 weeks during each of the ECG monitoring blocks.

Study assessments for both groups are at randomization, 3 months, and 6 months following randomization. Total patient participation is 6 months. The protocol will have Health Canada and

research ethics board approvals, and written informed consent will be obtained from participants prior to any study procedures being performed.

As the ZIO XT Patch is an investigational device, this study has been designed to be compliant with ISO 14155. Further details on the ZIO XT Patch can be found in the Application for Investigational Testing, as submitted to Health Canada. If new information about the ZIO XT Patch becomes available that would affect participants, they will be notified, informed of the issue(s) and either re-consented or removed from the trial. If they were to be terminated early from the trial, the level of medical care they received would not be affected.

3.2 Randomization

The randomization schedule will be computer-generated using variable block randomization and administered to sites via telephone.

3.3 Patient Population

3.3.1 Inclusion Criteria

1. Age ≥75 years without known atrial fibrillation or atrial flutter.
2. The participant is clinically in sinus rhythm (both heart auscultation and 30-second pulse palpation have been performed by the enrolling physician and neither detects an irregular rhythm suggestive of atrial fibrillation).
3. History of hypertension requiring antihypertensive medication.
4. Written informed consent.

3.3.2 Exclusion Criteria

1. Any previously documented atrial fibrillation or atrial flutter ≥30 seconds.
2. Implanted pacemaker, cardiac defibrillator, cardiac loop recorder, or deep brain stimulator.
3. Likely to be poorly compliant or unreliable using home screening devices or with study follow-up requirements because of cognitive or other issues, or life expectancy <6 months due to concomitant disease.
4. Has a condition which in the opinion of the enrolling physician would not permit chronic treatment with oral anticoagulant therapy.
5. Patient already taking long-term oral anticoagulant therapy.
6. Known allergic reaction/intolerance to skin adhesives.

Justification of Eligibility Criteria

The target population selected is one that is at risk for AF based on older age and hypertension (the two strongest risk factors for development of AF) and eligible for anticoagulant therapy if AF were detected, according to guidelines. At the time of enrolment, participants will have a virtual $CHADS_2$ stroke risk stratification score between 2 and 6 points, which is associated with an annual predicted stroke risk of 4%-18% without anticoagulation if AF is present. Anticoagulant therapy can substantially reduce this risk (64% average relative stroke risk reduction with warfarin vs. placebo; 63% stroke risk reduction with apixaban vs. ASA). The population prevalence of clinically overt AF is highly age-dependent: <1.7% for individuals aged <65 years, 1.7%-3.0% for ages 65-69 years, 3.4%-5.0% for ages

70-74 years, 5.0%-7.3% for ages 75-79 years, 7.2%-10.3% for ages 80-84 years, and 9.1%-11.1% for age ≥ 85 years.[vi] The prevalence of subclinical AF is currently uncertain in a general primary care population, but is also believed to be age-dependent. While screening individuals under age 75 years may be important, it is expected to have a lower yield for AF detection and lower cost-effectiveness for the type of interventions being studied. The eligibility criteria are intentionally broad to facilitate recruitment within busy primary care clinics and maximize external validity and potential future applicability of the screening interventions in practice. We are targeting patients who do not already have an indication for chronic oral anticoagulant therapy but would be potential candidates for anticoagulant therapy if AF were detected. Thus, detection of new AF by the screening interventions would be likely to have a clinically meaningful treatment impact, i.e. resulting in an evidence-based change in management in terms of initiation of long-term oral anticoagulation.

3.4 Study Interventions

3.4.1 ECG Patch Monitor

The ZIO XT Patch (iRhythm Technologies, San Francisco, California; http://www.irhythmtech.com/zio-solution/zio-patch/) is an ultra-portable wearable adhesive patch monitor that provides continuous single-lead ECG recording for up to 14 days. It has been cleared by the FDA for arrhythmia detection and is in current clinical use in the U.S.[vii] It will be used in this trial under an investigational testing authorization by Health Canada. The ZIO XT Patch is a single-use device worn over the left pectoral region with a skin adhesive (see Appendix). Its small, lightweight, water-resistant, patch-based design has advantages for patients compared with traditional ECG screening methods (e.g. Holter, event loop recorders, mobile outpatient telemetry systems), which are all more cumbersome and require detachable wired leads, two or more removable skin contact electrodes, plus separate recording units (+/- smartphone attachment).

The ZIO Patch has been shown to have excellent agreement with simultaneously acquired Holter recordings for the detection of AF (k=1.0) and quantification of AF burden (r=0.96).[viii] [ix] In a study of 146 patients referred for outpatient evaluation of cardiac arrhythmia underwent simultaneous monitoring with a conventional 24-hour Holter monitor and ZIO Patch, the prolonged monitoring afforded by the ZIO Patch detected significantly more arrhythmia events than Holter (96 vs. 61, $p<0.001$) and no AF episodes detected by Holter went undetected by the ZIO Patch.[x]

The ZIO Patch appears well tolerated. In Rosenberg et al.'s study,[8] 74 patients were instructed to wear the patch as long as possible up to 14 days and it was worn for a mean duration of 10.8 days +/- 2.8 (range 4-14); 16 patients had premature discontinuation of monitoring because the patch fell off. In the study by Barrett et al.[10] of 146 patients, the median wear time was 11.1 days (range 0.9-14.0). When surveyed, 81% of patients preferred the ZIO Patch over Holter monitor and 94% rated the ZIO Patch as comfortable to wear vs. 52% for the Holter monitor; only 11% reported that the ZIO Patch affected their daily activities vs. 76% for Holter monitor.

In the present trial, the device will be provided to participants in the ECG patch monitor group by the enrolling site at the time of enrolment or couriered to participants' homes within a target of one week post-randomization. Participants will receive verbal and written instructions on the use of the patch monitor as per the ZIO Patch Clinical Reference Manual, supplemented by telephone support/troubleshooting provided by the Study Coordinating Centre. Participants are instructed to wear the monitor continuously day and night (uninterrupted) for up to 14 consecutive days, including during sleep and showering. Participants are instructed to press a button on the device to document the timing

of any palpitations or other arrhythmia symptoms. At the completion of each monitoring period, participants return the ZIO XT Patch and ZIO XT Patch Diary via mail to iRhythm Technologies, Inc. for central interpretation and reporting. At 3 months, participants will receive a second ZIO XT Patch by mail and instructed to complete another 2 weeks of monitoring.

3.4.2 Home AF-BP Monitor

The WatchBP-Home A device (Microlife Corporation, Taipei, Taiwan; http://www.watchbp.com/) is a portable home BP monitor with automatic AF detection capability. It is commercially available and Health Canada approved for clinical use.

This device has been validated for AF detection and endorsed as an AF screening tool in primary care according to the National Institute for Health and Care Excellence (NICE) guidelines.[xi] Preliminary evidence indicates that its use in primary care for patients aged 65 years and older could be cost saving for the health care system.[xii]

In 4 studies of patients attending cardiology/hypertension clinics (n=1430), the device showed excellent accuracy for AF detection when compared to 12-lead ECG.[xiii] For most accurate AF detection, 3 sequential measurements are recommended. When 2 or 3 out of 3 readings are positive for AF, the sensitivity is 97% (95% CI: 94-100%) and specificity is 89% (95% CI: 86-92%); when all 3 readings are positive, specificity increases to 97%. These results are for a single clinic-based assessment, however. Another study investigated home screening with daily AF-BP readings for one month, and results were compared with a handheld ECG recording as a gold standard performed just prior to the AF-BP monitor readings.[xiv] In this study, daily AF-BP monitor status was considered positive for AF if 3 of 4 readings on a given day were positive (if 2 of the first 3 readings were positive, then a fourth reading was taken one hour later and required to be positive). Based on an analysis of daily AF-BP monitor status among the 117 patients who complied with the protocol of taking multiple readings, all 8 patients with ECG documented AF had true-positive AF-BP monitor status and 8 patients had false positive status, for a sensitivity of 100% and specificity of 93%. However, because of missing data from additional patients who were not fully compliant with the protocol, the specificity was estimated at 90% (range 87% to 92%).

In the present trial, participants randomized to the intervention group will receive an AF-BP monitor to use concurrently with the ECG patch monitor. Verbal and written instructions will be provided regarding the use of the device and proper technique for home BP measurement as per the Canadian Hypertension Education Program guidelines (with references to online video demonstrations). Participants are instructed to take home BP measurements twice daily (morning and evening) only on the days that they are wearing the ECG patch monitor. During this time, additional recordings are recommended at the time of any palpitations or arrhythmia symptoms. The timing of any screen positive results on the AF-BP monitor will be correlated with the concurrent ECG monitor results (participants will document the time of each AF-BP monitor assessment on a Home AF-BP Diary, and are advised to press the ZIO XT Patch notification button right away if there is a screen positive result on the AF-BP monitor for a time-stamp of this occurrence). Each AF-BP assessment consists of 3 sequential measurements. Participants are given a Home AF-BP Diary (a modified version of the CHEP home BP diary) with instructions to document the date/time and results of all AF-BP readings (systolic BP, diastolic BP, AF status + or -) and to bring this diary to each follow-up visit for physician review and submission to the Study Coordinating Centre.

All AF screen positives on the AF-BP monitor will be recorded. For this study, we have defined AF-BP monitor status as being a "screen positive" for AF in a given day only if all 6 of 6 readings indicate AF (i.e., all 3 of the 3 consecutive recordings are positive for AF on two separate assessments performed 5 minutes apart). This approach is designed to further maximize specificity for AF detection and minimize false positives compared with the methods used in previous studies. That is, participants whose monitors indicate AF on all 3 recordings must repeat the AF-BP assessment 5 minutes later; if the 5-minute assessment also indicates AF on all 3 readings, then it is classified as an AF screen positive day.

Daily AF-BP monitor status is classified as either:
1. screen negative (if AF not indicated on all 3 measurements), or
2. screen positive (if AF indicated on all 3 of 3 measurements and confirmed all 3 of a second set of 3 measurements performed 5 minutes later)
3. uninterpretable/missing data (if participants did not perform any measurements that day)

3.4.3 ECG Interpretation and Results

Recorded ECG data from the ZIO XT Patch will be analyzed centrally at the iRhythm National Clinical Center, Chicago, a commercial data processing center that adheres to Medicare Independent Diagnostic Testing Facility Performance Standards. Data will be analyzed as per standard operating procedures for clinical reporting, blinded to clinical details of the participants. A results report will be generated and sent to the Study Coordinating Centre, the participant, and the participant's family physician within a target of 14 days after completion of ECG monitoring.

The referring family physician will be responsible for any clinical decision-making.

For study analysis, ECG patch monitor results reports will be classified into the following categories:
1. No episodes of AF ≥30 seconds
2. Any AF episode lasting ≥30 seconds to 5 minutes
3. Any AF episode lasting >5 minutes
4. Any AF episode lasting >5 hours
5. Any AF episode lasting >24 hours
6. Other potentially significant arrhythmia, defined as: atrial tachycardia (>4 beats, not including AF), pause >3 seconds, high-grade atrioventricular block (Mobitz type II or third-degree atrioventricular block), ventricular tachycardia (> 4 beats), polymorphic ventricular tachycardia/ventricular fibrillation.

The Study Coordinating Centre will notify all participants of their results by telephone as soon as possible within 2 business days of receiving the results report, and those with abnormal results will be advised to follow-up with their family physician immediately for clinical management. The Study Coordinating Centre will notify the referring family physician of all abnormal results by FAX or email within a target of 2 business days after receiving the results report. If the local family physician is unavailable, the Study Coordinating Centre will assist in referring participants with abnormal test results to the most appropriate medical centre (e.g. local AF clinic, specialist, or emergency department).

Regardless of the results of the first ECG patch monitor, participants in the intervention group will remain in the trial to complete a second 2-week ECG patch monitor at 3 months post-randomization and follow-up assessments at 3 months and 6 months post-randomization. The purpose of the second

ECG patch monitor is to screen further for a new diagnosis of AF >5 minutes in those with no AF or AF <5 minutes detected on the first monitor, and to further assess the AF burden in those with AF detected on the first monitor.

3.5. Central Adjudication

All ZIO XT Patch ECG tracings of events reported as AF ≥30 seconds or potentially significant non-AF arrhythmias will be over-read and adjudicated by a central study committee of at least 2 arrhythmia experts blinded to clinical details of participants, with any disagreements resolved by a third cardiologist. This committee will also adjudicate all ECGs that participants may receive clinically (outside the study protocol) where AF is reported or suspected. The decisions of the central adjudicators will be used for all statistical analyses. An event adjudication charter will be developed and govern all details, definitions, and activities of this central review. Similarly, all clinical stroke/TIA/systemic embolism outcome events will be adjudicated by a central committee blinded to randomization group assignment.

3.5.2 Study Outcomes

Primary Outcome

The primary outcome of the trial is ECG-confirmed detection of new AF (atrial fibrillation or atrial flutter) within 6 months post-randomization, defined as at least one episode of continuous AF lasting >5 minutes (or AF documented on two separate12-lead ECGs performed >5 minutes apart).

Although the minimum clinically important AF duration is currently uncertain, the duration criterion of AF >5 minutes chosen for this trial is considered a potentially clinically significant and actionable finding based on the literature. In the MOST study, any atrial high rate episode >5 minutes predicted clinical AF (HR 5.9) and stroke or death (HR 2.8).[16] In the ASSERT study, any subclinical atrial tachyarrhythmia >6 minutes predicted clinically-evident AF (HR 5.6) and ischemic stroke or systemic embolism (HR 2.5).[2] Shorter AF episodes (<5 minutes) will likely be more prevalent than longer episodes in this screening study, but their clinical significance is less certain; we will separately analyze the prevalence of brief AF episodes (30 seconds to 5 minutes) as a secondary outcome, in addition to runs of non-sustained atrial tachycardia.

The primary outcome includes AF detected by any means (detected by the study devices or detected clinically outside the study). Sites must document any new diagnosis of AF detected outside of the study as part of clinical care and send all source documentation to the coordinating centre for adjudication. We will separately report AF detection by each of the study devices.

The timing of the primary outcome assessment at 6 months is chosen to maximize the yield of screening in the intervention group (given the known incremental yield of AF monitoring over time from studies of implantable loop recorders and pacemakers), and also to maximize the opportunity for AF detection in the control group, i.e. to assess how much AF may manifest clinically during 6 months of follow-up. Shorter follow-up durations were considered for the primary endpoint but would not enable a sufficiently long period to determine whether or not AF would declare itself clinically anyways as part of routine care. Secondary outcomes will assess if significant between-group differences emerge earlier (e.g. after the first 2 weeks of monitoring or at 3 months post-randomization) and will determine the magnitude of any additional AF detection from 3-6 months post-randomization.

Secondary Outcomes

1. Oral anticoagulant therapy use at 3 and 6 months post-randomization.
2. Detection of the primary outcome at 3 months post-randomization.
3. Among intervention group patients with the primary endpoint detected by the ECG patch monitor: time to first detection of AF >5 minutes; daily and total AF burden; average duration per AF episode.
4. Among intervention group patients, detection of any AF episode ≥30 seconds, ≥30 seconds to 5 minutes, >5 hours, and >24 hours (to facilitate comparison with other studies in the literature).
5. Patient adherence with the screening devices (defined as the average number of monitoring days completed and reasons for non-adherence), patient satisfaction with the screening devices (as measured by user satisfaction surveys), and tolerability of the ECG monitor (defined as the incidence of adverse skin reactions related to the adhesive patch).
6. Clinical outcome events within 6 months post-randomization (ischemic stroke, TIA, systemic embolism, major bleeding, intracranial hemorrhage), physician visits, hospitalizations, and medication prescriptions.
7. Cost-effectiveness (cost per life year saved) and cost-utility (cost per quality adjusted life year (QALY) gained) of AF screening.
8. Detection of other potentially clinically important non-AF arrhythmias: atrial tachycardia, pause >3 seconds, high-grade atrioventricular block (Mobitz type II or third-degree AV block), ventricular tachycardia, polymorphic ventricular tachycardia/ventricular fibrillation.
9. Estimated sensitivity, specificity and false positive rate of a home AF-BP monitor (with ECG patch monitor as the gold standard).
10. Blood pressure control at 6 months post-randomization.

3.6 Study Procedures and Assessments

Site investigators and staff will be trained on study procedures through one of the following: investigator meetings, webinars, or site initiation visits.

3.6.1 Screening for Eligibility

All consecutive patients aged ≥75 years attending participating primary care clinic sites will be screened for study eligibility.

At sites participating in the C-SPIN PIAFF-FP Study (a primary care office-based AF screening study for patients aged ≥65 years), participants who enrol in PIAFF-FP are eligible for enrolment into the SCREEN-AF trial only if they are aged ≥75 years and screen negative for AF on the PIAFF-FP Study office-protocol.

3.6.2 Enrolment and Randomization

Eligible patients will be offered study participation and written informed consent will be obtained. Participants are considered enrolled in the study at the time that written informed consent is signed. Randomization should take place as soon as possible following enrolment. The participating site will phone the SCREEN-AF study hotline to reach the Central Study Coordinator who will provide the randomization allocation. The study monitoring interventions should commence as soon as possible, with a target of one week after randomization.

3.6.3 Baseline Assessment

The baseline assessment at the time of enrolment will collect data on patient demographics, medical history, AF risk factors, stroke risk factors, $CHADS_2$ and CHA_2DS_2-VASc score, bleeding history, functional status, medications, and history of palpitations. Pulse and blood pressure will be recorded in accordance with recommended methods.

3.6.4 Follow-Up Assessments

Scheduled study follow-ups consist of a telephone assessment at 3 months and an in-person assessment at 6 months (+/-14 days for each visit). Data will be collected and entered into a CRF regarding any new diagnosis of AF, stroke or systemic embolism, and current medications. A telephone follow-up will be required if an in-person visit is not possible at 6 months. Unscheduled in-person study visits with the local site physician will be required as soon as possible for participants with an abnormal test result from the ECG patch monitor. For any AF detected outside of the study monitors, and for any stroke or systemic embolism events, original source documentation (ECG tracings, hospital records, etc.) are to be collected by sites and submitted to the Study Coordinating Centre for adjudication purposes. Every effort must be made by sites to avoid patients being lost to follow-up. The follow-up schedule of appointment dates should be planned with participants at the time of randomization and sites are to maintain accurate contact information (phone numbers, email and mailing addresses). Patients using the AF-BP monitor will submit their home BP diaries to their family physician for review. All anticoagulant treatment decisions, arrhythmia management, and hypertension management will be at the discretion of the local enrolling Investigator.

Adherence with Study Procedures

The total duration of ECG monitoring will be automatically recorded (time-stamped) by the ZIO Patch monitor. Adherence with the AF-BP monitoring will be documented according to participant completion of the home BP diary.

4.0 STATISTICAL CONSIDERATIONS

4.1 Sample Size

Sample size calculations are based on estimated rates of AF detection from previous studies (see below) and an assumption that detection of a 4% absolute difference between groups in the primary outcome of AF would be clinically meaningful. Given the major efficacy of anticoagulation, even small increases in AF detection and anticoagulant treatment rates are considered important given the potential large implications for stroke prevention at a population level.

We hypothesize that the 6-month rate of AF detection will be 5% (intervention group) vs. 1% (control group), for a 4% absolute difference between groups. To detect this difference with 90% statistical power at a two-sided alpha of 5%, the required sample size is 390 per group. This sample size will be able to detect at least a 3.5% between-group difference in the secondary outcome of anticoagulant treatment at 6 months (4.5% vs. 1%) with 83% power. A total of 370 patients without AF will provide about 80% power to detect a 4.1% increase in AF detection by the ECG monitor vs. the AF-BP

monitor, given an hypothesized 10% false positive rate by the AF-BP monitor. To compensate for attrition, we increased the total sample size by 5%, yielding 822 participants (411 per group).

In a large Swedish population-based screening study of healthy community-dwelling seniors aged 75 or 76 years (STROKE-STOP), newly-detected AF was found in 3% of 6496 individuals using an intermittent home-based screening intervention consisting of 30-second handheld ECG recordings twice daily for 2 weeks.[3]

Engdahl et al. invited inhabitants of Halmstad, Sweden aged 75 to 76 years to attend a screening program.[xv] Screening with a 12-lead ECG detected previously unknown AF in 10/848 patients (1.2%; 95% CI, 0.5–1.9). Among patients in sinus rhythm on 12-lead ECG and CHADS2 score of ≥2, 2-week handheld ECG event recording (20 or 30 seconds twice daily or with any palpitations) detected new paroxysmal AF in 30/403 (7.4%; 95% CI, 5.2–10.4).

In another Swedish study of patients with CHADS2 score ≥1 attending family practice or hospital outpatient clinics (mean age 71 +/- 8 years; range 53-85), newly-detected AF was found in 35/928 (3.8%) with a 4-week screening intervention consisting of a 10-second handheld ECG recording twice daily and if palpitations.[5]

The yield of the intermittent ECG intervention used in these studies is comparable to what we anticipate the AF-BP monitor could detect in the present trial during 2-4 weeks of screening. We expect the ECG patch monitor to have a higher detection rate because it employs continuous rather than intermittent monitoring. Therefore, in the present trial we anticipate the ECG patch monitor will have an AF detection rate >3% because we are targeting an older cohort than the studies cited above and screening at two separate time points 3 months apart. We expect the majority of AF detected in this trial will represent prevalent cases of subclinical paroxysmal AF, but 6 months of follow-up will also enable the opportunity to detect new incident cases of AF that develop during this time period.

4.2. Statistical Analysis

A general description of the planned analyses is outlined below. A detailed statistical analysis plan will be provided in a separate document. All analyses will be performed using SAS 9.2 (Cary, NC). The analysis population will consist of all randomized participants, unless otherwise specified.

4.2.1 Primary Analysis

The primary analysis will test whether the ECG patch monitor intervention is superior to standard care for the primary outcome of AF detection at 6 months. The results will be summarized by the intervention vs. control group. This will be an “intention-to-screen” analysis that compares the proportion of participants achieving the primary outcome among all randomized participants.

4.2.2 Secondary Analyses

Secondary Analyses in the Intervention Group vs. Control Group

Secondary analyses will be conducted in a similar fashion to compare the proportion of patients in each group with the primary endpoint detected within the first 24 hours, 7 days, and 14 days after the start of monitoring, as well as the secondary endpoints of AF ≥30 seconds, AF >5 hours, AF >24 hours, other (non-AF) arrhythmias, and oral anticoagulant use at 3 months and 6 months.

Secondary Analyses in the Intervention Group

We will compare patient characteristics among those with AF vs. without AF detected. Among those in the intervention group with any AF ≥30 seconds detected within 6 months, we will perform a descriptive analysis of daily and total AF burden per patient and the proportions of asymptomatic vs. symptomatic AF. Adherence to the screening intervention will be assessed by the average wear time of the ECG patch monitor and average number of days using the AF-BP monitor, and the proportion of participants who complete at least 75% of the target number of monitoring days. Questionnaires will assess patient self-reported tolerability with each device after completion of each monitoring period.

AF Predictors (Intervention Group Only)

We will explore predictors of AF including the following prespecified variables: age; APB count during the first 24 hours of ECG patch monitoring; number of runs of atrial tachycardia during the first 24 hours of ECG monitoring; $CHADS_2$ score; hypertension history; left atrial size (in subset of patients who have had a clinical echocardiogram). We hypothesize higher AF detection rates in the following prespecified subgroups: age ≥80 years vs. <80 years; frequent APBs (≥500/24h) vs. infrequent APBs (<500/24h); frequent vs. infrequent runs of atrial tachycardia during the first 24 hours of ECG patch monitoring; $CHADS_2$ score 4-6 vs. 1-3; history of hypertension vs. no hypertension; known left atrial enlargement vs. no enlargement.

AF-BP Monitor Validation (Intervention Group Only)

We will assess the performance of the AF-BP monitor as an AF screening tool by evaluating the per-patient results and individual and daily readings against the simultaneously-acquired ECG patch monitor recordings as the gold standard diagnostic test. For study analysis, each positive AF-BP screen will be classified as either a true positive or true negative and each negative AF-BP screen will be classified as a true negative or false negative for each subject. In addition, similar results will be summarized on the basis of daily AF-BP monitor readings for exploratory purposes. Sensitivity and specificity will be estimated based on subject-level AF-BP screens.

4.2.3 Health Economics

The short-term cost and outcome data from this trial will be used in a longer-term AF cost and outcome prediction model. In addition to determining whether the 'up-front' cost of the screening intervention is offset by 'down-stream' cost savings through reduction in health care costs, incremental cost-effectiveness and cost-utility ratios will be calculated showing the cost per life year saved and cost per QALY gained. A preliminary AF model has already been developed for this study, and further enhancements to the model will be implemented based on the trial data. The economic model will be generic to allow for the consideration of different patient characteristics, risk factors, and detection rates. This will permit the cost-effectiveness to be determined based on the type and cost of the screening device, the screening duration, and patient characteristics (e.g. age, excessive atrial ectopic activity, $CHADS_2$ score).

4.2.4 Long-Term Clinical Outcomes

A follow-up study will assess 2-year and 5-year outcomes via linkages to provincial administrative databases, including rates of death or hospitalizations for ischemic stroke or systemic embolism, new diagnosis of AF, and oral anticoagulant use.

5.0 ADHERENCE TO STUDY PROTOCOL

All patients enrolled will be followed until 6 months post-randomization. Adherence to the requirements for the protocol will be monitored by the Study Coordinating Centre and significant protocol deviations will be documented.

6.0 TRIAL ORGANIZATION

6.1 Coordinating Centre

The study is coordinated at the Population Heath Research Institute (PHRI) of the Hamilton Health Sciences Corporation and McMaster University. PHRI will be responsible for the overall conduct of the study.

6.2 Operations Committee

The Operations Committee will be responsible for the design, execution, analysis, and reporting of the study, and will assign appropriate responsibilities to the other committees when required. The Operations Committee will hold the primary responsibility for publication of the study results. This committee will convene regularly by teleconference meetings to address policy issues and monitor study progress, execution and management. The Operations Committee includes the Principal Investigators, other investigators, and PHRI project team personnel.

7.0 ETHICAL, SAFETY CONSIDERATIONS AND REGULATORY STANDARDS

7.1 Ethical Considerations

Ethics Approval

This study will be conducted in compliance with the protocol, principles laid down in the Declaration of Helsinki, Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH), and ISO 14155:2011 where applicable. Before study initiation, the Investigator must have written and dated approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the protocol, consent form, subject recruitment materials/process. Amendments to the protocol will also require IRB/IEC and/or Competent Authority approval where applicable and in accordance with local laws and regulations. Amendments developed to address immediate and potential safety hazards to the patients may be implemented immediately with subsequent notification to local IRB/IEC.

Regulatory Approval

As the ZIO XT Patch is not approved for use in Canada, an exemption for research will need to be obtained. No exemption is required for the WatchBP device as it has full approval for use in Canada.

Informed Consent

Prior to patient participation, written informed consent must be obtained from each participant and comply with the Declaration of Helsinki, ISO 14155:2011, and applicable local regulations. The original signed consent must be retained on file by the Investigator and a copy given to the patient.

Risk/Benefit Analysis

There are minimal potential risks to participating in this study. There is a reasonable expectation that some participants may benefit from participating in the study through early detection of AF that could lead to improved treatment and outcomes. A control group is justified in this trial given that home-based AF screening is not part of current clinical practice and, although promising, is not supported by level 1A evidence or guidelines. The control group receives current standard of care.

Patient Confidentiality

All participant information will be stored on a high security computer system and kept strictly confidential. Participant confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computerized files. Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited except for the following reason; Medical information may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare.

7.2 Safety and Adverse Event Reporting

For the purpose of this study, safety reporting will consist of adverse device reactions related to the ZIO XT Patch only, specifically related to the device tolerability. It is not anticipated that there will be any Serious Adverse Device Events, however, if there are, they will be reported to the Principal Investigator, iRhythm Technologies Inc. and Health Canada.
Drug related Serious Adverse Drug Reactions will be collected in an unsolicited manner. If they occur, they will not be reported in the study database, but will be sent directly to the pharmaceutical company that markets the drug, as per standard practice in accordance with ICH-GCP guidelines (4.11 Investigator responsibilities Safety Reporting) and applicable regulatory requirements. Other non-drug related SAEs will not be collected in the database.

8.0 DATA HANDLING, MONITORING AND RECORD KEEPING

Data will be collected using an electronic data capture system called iDataFax. Along with data entry, the system will assist in data management, report generation and quality control. Source documentation supporting the trial information reported on the e-CRF will be filed at the Investigator's site and made available for trial related monitoring, audits, IRB/IEC review, and any regulatory inspections if required. The Investigator must retain all study records/files in accordance with applicable regulatory requirements. A Data Management Plan will be developed by the Population Health Research Institute and outline the detailed strategies to ensure quality in data collection and reporting. Data monitoring will be done through "Quality by Design" risk based strategy. The database will be programmed with pre-defined risk indicators and thresholds. If one of these risk indicators or thresholds are met, the study team will be alerted and the appropriate actions can be taken.

Appendix 1. Study Schedule

Assessments/Procedures	Enrolment	14 days post enrollment	3 months (+/-14 days)	6 months (+/-14 days)
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Demographics/Past Medical History Checklist	X			
Medications	X		X	X
Telephone Follow-up and Patient Instructions Re: Study Procedures		X		
ZIO Patch Monitoring Results			X	X
Follow-up Visits			X	X
Study Monitor Tolerability/Patient Satisfaction Survey				X
Termination and Death Report			(X)	X
Adverse Events (intervention group only)			X	X

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