Atrial Fibrillation Health Literacy and Information Technology Trial

NCT04076020

Document Date: April 30, 2023

Mobile Health Intervention for Rural Atrial Fibrillation

Study Protocol

April 2023

Funding Organization:	National Heart, Lung, and Blood Institute R01HL143010
Principal Investigator:	**Jared W Magnani, MD, MSc** Telephone: (412) 383 0611 E-mail: magnanijw@upmc.edu
Co-Investigator	**Bruce Rollman, MD, MPH** Telephone: (412) 692-2659 Email: rollmanbl@upmc.edu **Tim Bickmore, PhD** Telephone: (617) 373-5477 Email: bickmore@ccs.neu.edu **Michael Paasche-Orlow, MD, MA, MPH** Telephone: (617) 414-5877 Email: Michael.PaascheOrlow@bmc.org
Co-I/Data Coordinating Center:	**Samar R. El Khoudary, PhD, MPH** Telephone: (412) 624-5543 Email: sae25@pitt.edu **Maria Mori Brooks, PhD** Telephone: (412) 624-1618 Email: mbrooks@pitt.edu

List of Abbreviations

AE	Adverse Event
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on QualiTy of life
CDSM	Chronic disease self-management
DOAC	Direct oral anticoagulant
EDC	Epidemiology Data Center
EHR	Electronic Health Record
HCU	Health Care Utilization
HrQOL	Health-related Quality Of Life
IRB	Institutional Review Board
NVS	Newest Vital Sign
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PROMIS	Patient-Reported Outcomes Measurement Information System
QOL	Quality Of Life
UPMC	University of Pittsburgh Medical Center

1. ABSTRACT

Atrial fibrillation (**AF**) is a common, morbid condition. Anticoagulation to prevent thromboembolic strokes is a foremost priority in AF but adherence is challenging for patients and lapses in anticoagulation are common. Chronic disease self-management (**CDSM**) is a recognized program to enhance self-efficacy and improve adherence, quality of life, and patient-centered health outcomes. Rural patients with AF experience increased vulnerability to adverse outcomes due to geographic and social isolation, poor health care access, and limited health literacy. Study team will conduct a single-center parallel group randomized clinical trial to test the efficacy of a relational agent to improve patient-centered care in AF delivered by smartphone. The Principal Investigator and study team have used the agent – a computer character that simulates face-to-face conversation using voice, hand gesture and gaze cues to provide education, monitoring and problem-solving – to improve health behaviors and outcomes in individuals with limited computer and health literacy. Here, the team will expand its successful 30-day relational agent pilot to develop a novel CDSM program for AF. This study will combine the relational agent with the AliveCor Kardia smartphone heart rate and rhythm monitor. The team will implement a 4-month CDSM curriculum and assess its sustainability at 8 and 12 months. The trial randomizes 264 patients with AF who are receiving anticoagulation for stroke prevention to (1) the relational agent and Kardia intervention, accompanied by provider alerts for prespecified results; or (2) the control, consisting of an AF educational session and a smartphone with a general health application (WebMD). Our aims are: (1) To assess the effect of the relational agent and Kardia intervention on anticoagulant adherence, as determined by the proportion of days covered (PDC), and self-report. (2) To identify the effect of the intervention on health care utilization, hospitalizations, emergency visits, and AF-related procedures at 1-year follow up. (3) To determine the effect of the intervention on the patient-centered outcomes of quality of life and symptoms, as measured by the AF Effect on QualiTy of life (**AFEQT**) measure, specific to AF, and the general Patient-Reported Outcomes Measurement Information System-29 Profile at baseline, 4, 8 and 12 months. (4) To examine mechanisms for the effect of the intervention by symptom burden, AF classification, health literacy and intervention use. The trial will additionally follow the cohort through the study period for exploratory analyses of rurality and outcomes associated with AF. Expected Results: In this project we will evaluate a scalable patient-centered intervention to improve anticoagulation adherence, health care utilization and patient-centered outcomes in vulnerable rural individuals with chronic AF. If proven successful, this intervention can be broadly disseminated to improve the care of patients with AF.

BACKGROUND

Standard care is insufficient to address the combined challenges of AF, its complex symptoms and treatments, and the social determinant and health literacy obstacles that exacerbate outcomes with the condition. This study team has developed a novel, practical mHealth intervention that is accessible to high-risk patients such as those with limited social resources or health literacy.

2. STUDY RATIONALE AND SIGNIFICANCE OF THE RESEARCH

a) AF prevalence is estimated to reach 12 million US adults by 2030.[1,2] AF increases risks of stroke 5-fold,[3] heart failure 3-fold,[4,5] dementia 2-fold,[6,7] and death 1.5- to 2-fold.[8] Individuals with AF have 4.7-times greater annual days of hospitalization than those without,[9] and expenditures for Medicine beneficiaries with AF have increased 1.6-fold since 1999.[10] Among Medicare beneficiaries, the mortality rate following a diagnosis of AF is 19.5% at 1 year and 48.8% at 5 years.[11] Even on optimal therapy, patients experience a stroke rate of 1.5%, heart failure of 4-5%, and mortality of 3% per year.[12] This project aims to reduce the morbidity and social costs of AF.

b) Poor medication adherence results from the complex interaction between patients, their social environment, and the health care system and professionals.[13] Patient-level barriers to adherence have been characterized as limited health literacy and behavioral obstacles to successful medication management.[14] Rural individuals have additional risk for poor adherence because of limited health literacy, lower social resources, poverty, and geographic distance from care providers.[15,16] They also experience disparities in cardiovascular outcomes, attributable in part to social determinants of health.[17,18] Rural regions have higher unemployment and poverty rates, lower educational attainment,[19] higher rates of low health literacy, less access to health care services,[20] and worse control of cardiovascular disease and AF risk factors (hypertension, obesity, diabetes).[21,22] Our program promotes longitudinal, patient-centered strategies for rural patients to overcome adherence challenges.[23]

c) Chronic disease self-management (CDSM) provides a paradigm for patients to establish practical strategies to negotiate the long-term self- care required to succeed with a disease such as AF.[24-29] CDSM incorporates education and behavior change strategies. The general tenets of CDSM are: (1) patient-centered education on the causes and complications of chronic disease; (2) understanding medications; (3) managing common symptoms; (4) skills for partnership with physicians and the care team; and (5) self-assessment of goals for health-related quality of life (**HRQoL**). CDSM is available in only 8% of rural counties.[30] The relational agent addresses the limitations of prior interventions to provide virtual CDSM and bridge the rural health divide.

d) AF is a chronic disease with extensive symptoms, adverse outcomes, and resulting poor HRQoL. Anticoagulation is a mainstay of AF treatment but demands long-term – likely lifelong – daily adherence with concomitant monitoring for bleeding. AF symptoms are reported to diminish HRQoL, subjective health, and functional status. In our pilot intervention, patients described the effects of AF on general HRQoL: “It’s miserable…you never know when it’s going to hit…you’re physically drained…it scares me to death every day…I could have a stroke, it’s just a scary thing.” National and international guidelines emphasize improved social determinants exacerbate worse HRQoL and outcomes in AF. Our intervention addresses the poor HRQoL in AF that stems from symptoms, treatment burden, and clinical uncertainty. It is designed to empower patients, ameliorate health literacy related barriers to self-management, and improve patient-centered outcomes for vulnerable patients with AF.

e) The relational agent is a mobile health (mHealth) application for patient education, monitoring and problem-solving. It is a virtual agent that uses interactive conversation for health counseling and guidance. We have extensive experience developing health interventions delivered by relational agent to promote self-management and HRQoL (e.g.,

R01AG028669, 1R01HL081307, NCI 5R21CA127511, R01HL116448). The agent speaks with synthetic speech accompanied by animation to provide health education, empathic counseling, and monitoring. The patient engages by listening to didactic content or questions and selecting responses on the touch screen. Patients converse with the agent, develop an empathic therapeutic alliance, and report/record across domains of CDSM. The relational agent (a) elicits symptoms and (b) gestures to enhance educational content. The intervention here integrates the relational agent with the AliveCor Kardia (Mountain View, CA) smartphone heart rate and rhythm monitor to guide Kardia use and enhance CDSM in AF.

f) Our relational agent/Kardia intervention improves the current paradigm for rural AF care[24] by aiming to: (1) Enhance patient-centered resources. AF is a complex condition that requires long-term patient engagement[31-34] and the relational agent serves as an empathic coach to improve the patient experience of this chronic disease. We provide a non-pharmacologic, non-invasive approach that is accessible to patients, patient-centered, and disease-specific. (2) Synergize the relational agent/Kardia. Relational agent content prompts use of the Kardia when users report symptoms. The relational agent can correlate symptoms with heart rate and rhythm, improve symptom characterization, and guide CDSM to improve multiple patient-centered domains assessed by the Patient-Reported Outcomes Measurement Information System (**PROMIS**) instrument used here.[35] (3) Increase health-related attention. Rural individuals often have less access to resources for adherence support and disease-specific education.[36] Patients will benefit from AF-specific education, symptom monitoring, self-management content, and encouragement of engagement and activation.

3.0 STUDY AIMS

3.1 Aim 1

To assess the effect of the relational agent/Kardia intervention on anticoagulant adherence. We will quantify adherence to anticoagulation with (a) proportion of days covered (PDC) obtained from pharmacy data, and (b) self-report, at 4, 8, and 12 months. Hypothesis: Intervention participants will have better anticoagulant adherence than control arm participants as measured by objective and self-reported assessments of adherence.

3.2 Aim 2

To identify the effect of the intervention on health care utilization (HCU). We will quantify 12-month HCU for intervention administration. Hypothesis: Intervention participants will have lower HCU events compared to control arm participants.

3.3 Aim 3

To determine the effect of the intervention on HRQoL and symptoms. We will compare HRQoL and symptoms between the intervention and control arms at 4, 8, and 12 months with the AF Effect on QualiTy of life (AFEQT) instrument (specific to HRQoL in AF) and the Patient-Reported Outcomes Measurement Information System (PROMIS)-29 Profile. Hypothesis:

Intervention participants will have superior HRQoL and lower symptom burden compared to control arm participants at 4, 8, and 12 months.

3.4 Aim 4

To examine mechanisms for the effect of the intervention. We will determine how patient-centered baseline factors including sex, race, health literacy, AF classification (paroxysmal versus chronic), and symptom burden moderate the intervention effect, and how intervention engagement and use, change in symptom burden, and AF therapies mediate the intervention effect on our primary and secondary outcomes.

4. STUDY DESIGN

4.1 Study Overview

This is a randomized clinical trial to evaluate the effect of a smartphone-based intervention on health outcomes in people with the heart disease called atrial fibrillation. The study will enroll 264 patients residing in rural municipalities (defined as "rural" by the Center for Medicaid and Medicare Services Rural Health Clinics Program) with this condition and randomize them to the intervention or control. Intervention participants will receive a smartphone with an application (or app) called a relational agent, which simulates conversation. In addition, they will receive an AliveCor Kardia for heart rate and rhythm monitoring, an FDA-approved, widely used instrument that pairs with the smartphone. Control participants will receive a smartphone with a general health application (WebMD) and they will not receive an AliveCor Kardia device. The intervention will last 4 months and participants will have visits at baseline, 4, 8 and 12 months. The study will evaluate the improvement in quality of life, medical adherence and health care utilization resulting from the intervention.

5.0 STATISTICAL CONSIDERATIONS

We propose a two-arm RCT to evaluate the efficacy of the relational agent and AliveCor Kardia heart rhythm monitor to improve patient-centered outcomes in patients with the debilitating chronic condition atrial fibrillation (AF). We will recruit 264 patients with AF receiving anticoagulation over a 30-month period, prioritizing recruitment in socioeconomically depressed regions in rural Northwest Pennsylvania. We will randomize participants 1:1 to receive the mobile relational agent and Kardia (n=132) or control (n=132) for 4 months, conducting randomization with a web- based data management system that we have used in prior RCTs. Randomization will be stratified by type of oral anticoagulant (warfarin or direct acting oral anticoagulant). We will assess the impact of our intervention at 4, 8 months and then at 12 months to determine sustainability. Our primary hypothesis will test whether the relational agent and Kardia intervention can improve adherence to anticoagulation as quantified by the PDC and by participant self- report. Our secondary hypotheses will evaluate 1) assessments of health care utilization between the intervention and control; 2) the improvement in health-related quality of life at 4, 8, and 12 months compared to the control, as measured by instruments specific to AF and general, validated quality of life assessments; and 3) the mechanisms for the effect of the intervention, as evaluated by assessments of moderation and mediation. All participants will have return visits at 4, 8, and 12 months. The outcomes will all be calculated without reference to intervention arm. We will use the intention-to-treat principle for all primary and secondary analysis. All analyses will be blinded to trial randomization arm.

Statistical approach for Aim 1. The primary outcome for Aim 1 is anticoagulant adherence as assessed by PDC. We will use the intention-to-treat principle for all primary and secondary

analyses. We will analyze PDC as continuous (range 0-1, higher ratio indicating better adherence) and binary (optimally adherent if ≥0.8) variables. We will assess differences between the 2 study arms in PDC at 12 months with linear regression (for continuous PDC) or logistic regression (for binary PDC) adjusting for trial stratification factor (as suggested by Kahan and Morris[37]). We will conduct our secondary assessments of adherence at 4 8, and 12 months similarly. We will categorize individuals scoring ≥2 on any of the 3 self-report adherence items (range 1-5, Voils et al.[38]) as nonadherent. To assess whether the effect of the intervention changes over time, we will use linear (for continuous measures) or non-linear (for categorical measures) mixed-effect models with random intercepts with adherence measures modeled as a function of study arm, study visit and their interaction. We calculated the statistical power to detect a range of difference in PDC (our primary outcome) between the intervention and control arms. After accounting for 10% attrition through 12 months (consistent with our prior RCTs), we determined that a sample size of 119 in each study arm will enable us to detect a minimum difference in PDC between the two groups as small as 11.7% with 85% power (assuming a SD=30%). Our power calculations assume use of 2-sided tests with 0.05 significance level. With an additional, unexpected 10% attrition (n=106 per arm, to accommodate for relocation, loss-to- follow-up, institutionalization, or death), we will be able to detect a minimum difference in PDC as small as 12.4% (0.41 standardized mean difference) with 85% power. Both are considered small effect sizes per Cohen's guidelines.[39]

Statistical approach for Aim 2. We will compare HCU across trial arms in models that again account for trial stratification factor.[37] We will use the electronic health record (**EHR**) in concert with 4-, 8-, and 12-month self-report to catalog events (hospitalization, emergency room and ambulatory visits, medications, and procedures) and classify them as related to AF. We will determine person-year of follow-up as starting from the date of randomization to the 12-month visit. We will then classify HCU in aggregate and by item as count outcomes. We will use generalized estimating equations (GEE) negative binomial regression models (chosen instead of Poisson regression due to expected over-dispersion in the data). Similar approaches will be used to assess counts for each HCU component. Based on preliminary data from an outpatient registry of individuals with chronic AF, we expect there will be 42.0 events for every 100 person-years in the control arm of the trial.[40]We estimate that we have 85% power to detect a minimum absolute reduction of 21 events per 100 person-years in the intervention group, assuming an equivalent number of events in the control group at 12 months with a sample size of 132 per arm. A 20% attrition in study participation (n=106 per arm) at 12 months will still allow us to detect a minimum of absolute reduction of 23 events per 100 person-years in the intervention group with 85% statistical power. As exploratory analyses, we will perform survival analyses to compare the time to event between the intervention and control arms for preselected outcomes: AF-related hospitalization, emergency visit, or procedure; myocardial infarction; heart failure; stroke; and all-cause mortality. Participants will contribute 18 to 51 months of follow-up; those without the event of interest will be censored at the end of follow-up. We will examine the assumption of proportional hazards and use Cox regression models to estimate the hazards ratio for assigned treatment for each outcome.

Statistical approach for Aim 3. We estimate that patients randomized to our intervention will have a clinically relevant improvement in HRQoL as demonstrated by AFEQT global score at 4-months follow-up vs. control. Our demonstration cohort (N=31) had a mean increase in AFEQT global score of 12±16 (from 64±23 to 76±19) over 30 days (range 0-100, greater scores indicating superior HRQoL). We will use linear regression adjusted for trial stratification factors and the baseline score as per Harrell[41] to evaluate the differences in AFEQT global and domain-specific scores between study arms at 4 months. We will similarly assess the effect of the intervention for

each of the 4 AFEQT domains and the 8 symptom and HRQoL domains measured by the PROMIS-29 at 4 months. Next, we will assess sustainability of the intervention effect at 8 and 12 months using linear mixed models. Our power calculations assume a 90% 4-month assessment completion rate (to accommodate for 10% attrition), 2-tailed α=0.05, and standard deviation of 17 (representing the upper limit of the 95% confidence interval for the SD and consistent with the data used to determine the minimum important difference[42]). Based on these assumptions, we expect our sample size (119 per arm) will enable us to detect a minimum difference in AFEQT between the two study arms at 4 months of at least 6.3, corresponding to 0.37 SD, a small effect size.[39] A 20% sample size attrition (n=106 per arm) at 12 months will allow us to detect a difference in AFEQT of at least 0.41 SD.

Statistical approach for Aim 4. Subgroup analyses will be performed to assess moderation of the intervention effect by baseline patient-centered factors: (1) sex; (2) race (white vs non-white); (2) health literacy, assessed using the Newest Vital Sign (**NVS**); (3) AF classification (paroxysmal vs permanent), (4) symptom burden, measured by the AFEQT; (5) anticoagulant type (warfarin or direct oral anticoagulant **(DOAC**)); (6) self-reported anticoagulant nonadherence (<2 or ≥2); and (7) duration of anticoagulation (<1 or ≥1 year). We will formally test for effect modification by creating a regression model for each outcome including the subgroup variable, the intervention assignment and the interaction between the subgroup variable and intervention and evaluating the significance of the interaction term. The false discovery rate[43] will be used to adjust for multiple comparisons. Causal mediation analyses will be used to determine the degree to which intermediate patient-level factors explain the intervention effect as potential mediators of the primary and secondary outcomes.[44-46] We will estimate the direct and indirect effects of the intervention on outcomes accounting for (1) changes in symptom burden during follow-up, measured by the AFEQT; (2) introduction of new AF therapies over 12-month study participation (antiarrhythmic, cardioversion or electrophysiologic study); (3) relational agent and Kardia usage; and (4) EHR alerts. Instead of emphasizing p-values, we will focus on estimation of mediation effect sizes.

Race and sex. We will ensure our study cohort is 50% women and 30% non-white race, of whom 80% (24% overall) will be black race. (1) We have reviewed[47] AF is less prevalent in blacks[48-50] but associated with worse outcomes[54] (2) Women have worse HRQoL and increased stroke risk than men.[51-53] (3) We have developed strategies to oversample participants of black race and female sex. Although the current trial is not specifically design to assess racial/sex variability in the intervention effect, since the overall effect has not yet been established, subgroups analyses among all race/sex groups will set the stage for further studies that focus on racial/sex effects. We note our statistical power for such trial participation: (1) if we randomize 64 study participants of black race, then we will have 85% power to detect a 22.8% PDC difference between trial arms. (2) Similarly, if we randomize 135 women, 51% of trial participants, then we will have 85% power to detect a 15.6% difference between trial arms.

6.0 SUBJECT SELECTION

6.1 Study Population and Recruitment

Individuals with a diagnosis of atrial fibrillation who meet the inclusion and none of the exclusion criteria will be eligible for participation in this study.

Study staff will promote awareness of our study through multiple ways. Recruitment will be conducted at numerous University of Pittsburgh Medical Center sites located in rural Pennsylvania counties. The PI and PM will contact cardiologist, admin staff, PCPs, nursing staff

and care managers at the UPMC clinics. They will visit these UPMC sites to introduce the study and present several educational discussions about the Atrial Fibrillation and the importance of this study for these patients as well as develop personal relationships with these clinic personnel. During these visits, the PI and PM will give the providers a newsletter which will briefly describe the study and will do a short presentation to clinicians and their staff.

Study team will also include the following recruitment strategies:

1) Study staff will screen the EHR to identify potentially eligible participants. Study staff will then notify clinic practice managers and/or clinicians which patients with upcoming appointments are potentially eligible for the study. On the day of scheduled appointment, clinic staff will notify potential participants that study staff will meet with them to introduce the study. After learning about the study, those wishing to participate will be consented and enrolled.

2) Study staff will mail recruitment letters to eligible participants. They will follow-up with a phone call and/or email these potentially eligible participants. If the eligible participants are interested, study staff will conduct the 6-item screening to ensure that the participant meets eligibility criteria. Those who meet all eligibility criteria will be mailed a hard copy of the consent form, medical and pharmacy release of information forms, and the baseline survey. Study staff will schedule their baseline visit phone call at a time that is preferred by the eligible participant. Those eligible patients who are interested will be informed about the current study, and for those wishing to participate, verbal informed consent will be administered by study staff.

3) Patient-centered brochures and posters will be placed in clinic waiting areas and in patient examination rooms. These materials will summarize the research study and will include study contact information so that participants will know how to reach the study team.

4) The study team will receive lists of potentially eligible patients from R3, which is a service of the Department of Biomedical Informatics. Potentially eligible patients will also be accumulated from a UPMC AFib diagnosis list, and will use those lists to screen the EHR of said patients for eligibility.

5) The study team will have a study website (https://aflitt.pitt.edu) which will provide a direct portal for candidate participants and referring providers to communicate with study staff. Individuals will have the opportunity via the website to receive an electronic survey for first-pass eligibility assessment.

6) Study team will leverage the web-based research portal of the University of Pittsburgh (Pitt+me, pittplus.com, https://www.facebook.com/pittplusme/)/ which provides an accessible listing of research studies accompanied by limited eligibility screening. The CTSI Pitt+Me team can screen candidate participants and direct them to study group if they are eligible. Participants who contact the study team via Pitt+Me will be scheduled for their baseline visit. Pitt+Me will also mail newsletters to candidates living in Pittsburgh by targeted zip codes.

Recruitment will be conducted by trained individuals serving as study research assistants and study staff.

6.2 Inclusion Criteria

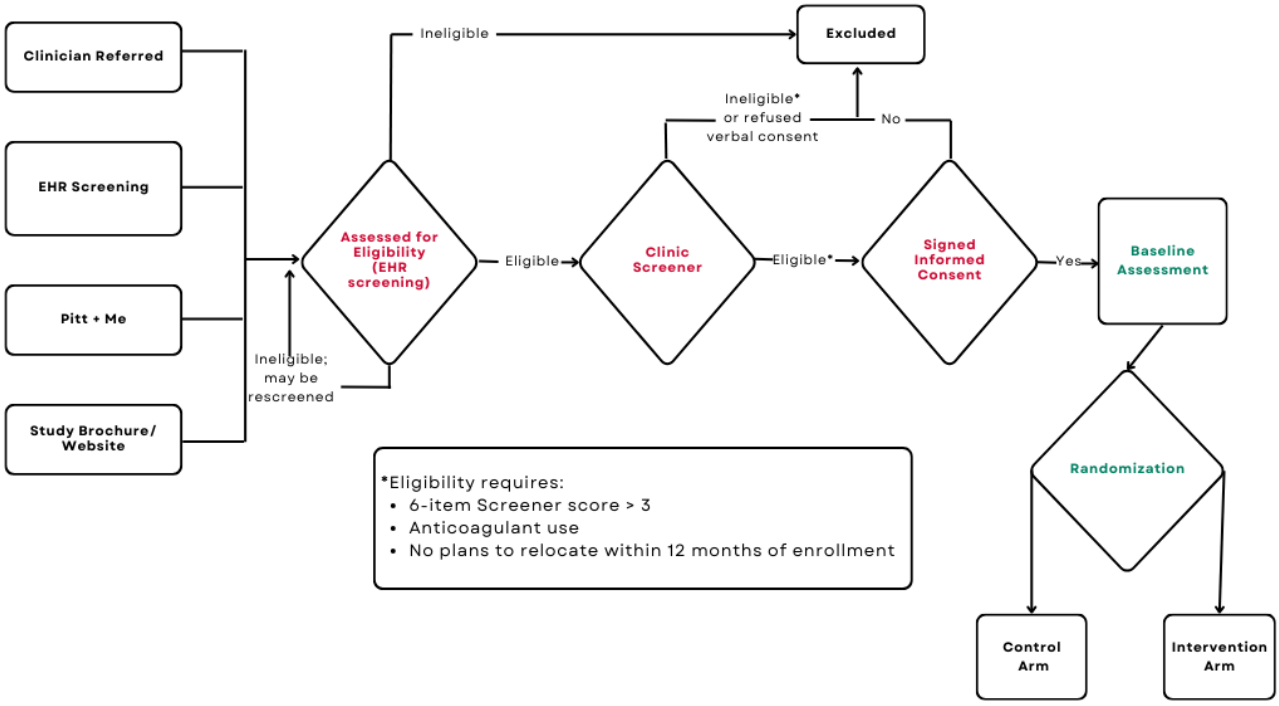
1. Adult, age ≥21.
2. Diagnosis of AF, identified from the EHR and confirmed by either an ECG, Holter, or a clinical note.
3. Resides in a municipality defined as rural by the Center for Medicaid and Medicare Services Rural Health Clinics Program.
4. Prescribed use of warfarin or DOAC (formerly NOAC) for AF stroke prevention.
5. English-speaking well enough to participate in informed consent and this study.
6. No plans to relocate from the area within 12 months of enrollment.

6.3 Exclusion Criteria

1. Previous catheter ablation procedure for treatment of AF (pulmonary vein isolation, AF ablation).
2. Previous AV nodal (atrioventricular nodal) ablation procedure.
3. Conditions other than AF that require anticoagulation, such as mechanical prosthetic valve, deep vein thrombosis, or pulmonary embolism.
4. Heart failure necessitating hospital admission ≤3 months prior to study inclusion.
5. Acute coronary syndrome (defined as at least 2 of the following: chest pain, ischemic electrocardiographic changes, or troponin ≥0.1 ng/mL) ≤3 months prior to study inclusion.
6. Untreated hyperthyroidism or ≤3 months euthyroidism before inclusion.
7. Foreseen pacemaker, internal cardioverter defibrillator, or cardiac resynchronization therapy.
8. Cardiac surgery ≤3 months before inclusion.
9. Planned cardiac surgery.
10. Presence of non-cardiovascular conditions likely to be fatal within 12 months (e.g., cancer).
11. Inability to comprehend the study protocol, defined as failing three times to answer correctly a set of questions during the consent process.[56]
12. PIs or study team's judgement as to the ability of the participant to comply and complete the study protocol.

7. STUDY DESIGN AND METHODS

Fig 1. Participant screening through Randomization Process



Red font = screening process (use EMPI or MRN); multiple screenings permitted
Green font = use Study ID

Screening process forms will be in "AF Screening" project with contact information etc. EDC will only export screening forms for research database.

"AFib-LITT" project after signed consent' Study ID assigned

7.1 Pre-Screening

To identify potentially eligible participants:

1) Screening for eligibility will be performed by using rosters and schedules of clinical visits. Study staff will screen the EHR to identify these potentially eligible participants.
2) The study may also use R3, which is a service of the Department of Biomedical Informatics. R3 will create a list of patients who meet the study's inclusion criteria and provide the list to study staff. Study staff will then verify the participant's eligibility by checking their medical history in EPIC and following the "EHR Screening Form" checklist.
3) Participants can also contact study staff directly (via phone call, email, Pitt+Me, study website) to express interest in participating in the study. Study staff will then screen the EHR to determine if the participant is eligible. Study staff can then schedule an appointment to talk with potential study candidate to provide more information about the study/consent participant.
4) If non-UPMC patients contact the study team and are interested in participating in the study, they will confirm with the patient that they will need to check the patient's eligibility by medical review. If the non-UPMC medical records are available in

"*EPIC Care Anywhere*" (an option in EPIC that links to other healthcare systems that are also using EPIC), study staff will check their medical history to confirm eligibility. However, if their medical records are not available in *EPIC Care Anywhere*, study staff will request the participant to sign a medical release form to receive the necessary medical information to determine eligibility.

In-person recruitment: Study staff will then notify clinic practice managers and/or clinicians which patients with upcoming appointments are potentially eligible for the study. On the day of scheduled appointment, clinic staff will notify potential participants that study staff will meet with them to introduce the study. After learning about the study, those wishing to participate will be consented and enrolled.

Virtual recruitment: Study staff will also mail recruitment letters to these potentially eligible participants and will follow up with call and/or email. If they are interested, they will provide their verbal consent and complete the 6-item screening item to confirm eligibility. Study staff will then mail hard copies of the consent forms, medical and pharmacy release forms, and the baseline survey. Study staff will then schedule their baseline visit phone call at a time that is preferred by the eligible participant. Those eligible patients who are interested will provide their verbal consent and complete the baseline survey.

7.2 Screening at Baseline

Participants who are screened to be eligible will be scheduled to either meet with a study recruiter (Research Assistant/ Project Manager) or have a scheduled phone call with a study recruiter. Individuals who agree to participate will provide their verbal agreement and this will be noted in the "**Clinic Screening Form**" and will undergo a 6-item screener consisting of being asked to repeat and remember 3 words, and to state correctly the day of the week, month, and year. Implementation of basic memory assessment for screening is a standard component of clinical research studies.

7.3 eConsent Process

The Investigator will prepare the informed consent form and the authorization of medical release form and submit to Institutional Review Board (**IRB**) for approval. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. ***The informed consent will be completed online using a tablet that is provided by the research team, or will be given by the participant verbally over the phone to a study team member during their baseline call.*** However, if a paper version will also be made available for use only when the online version cannot be accessed (e.g. no available tablets, no internet access, unable to access the REDCap system, etc.). Or, if a participant gives verbal consent over the phone to a study team member, they will sign and return a paper version of the consent for to the study team. If a paper version is completed, either in place of a virtual consent or if given verbally, then this paper consent form will be scanned and saved as a PDF and attached to the participant's record. The paper version of the form will also be stored in a locked filing cabinet, behind two locked office doors.

In-person consent: The informed consent will be conducted in a private location to respect subject privacy. Following the briefing of the research study, the study recruiter will provide the subject ample time to read the consent and study recruiter will answer any of their questions regarding the document. Prior to the subject's participation in the study, the study recruiter will ensure that the participant understand the research study and their role in the study. They will be made aware of their responsibilities during the baseline visit, after randomization assignment, and

throughout the study period. The importance of continued follow-up should be stressed and balanced with a discussion of the effect of withdrawal on the study. The participant will sign and date the econsent in REDCap using their finger or stylus on the study tablet, include their first and last name, as well as DOB and a security question. Designated study staff member will then e-sign and date the consent form. The copy of the signed econsent will be saved in REDCap and a copy of it will be provided to the participant, upon request. Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

Verbal consent: Potentially eligible participants who are interested in participating in the study but unable to meet with a study recruiter, will be able to complete the consent and the baseline survey over the phone. Study staff will mail the consent form prior to calling the participant so that the participant will have ample time to read the consent form and understand the research study.

Medical Release Form

After the participant has e-signed the informed consent form, the study staff will review the *Authorization to Use and Disclose Health Information* form with the participant (in person or over the phone). This form is to be signed by the participant for permission to obtain pharmacy records from their preferred pharmacy during the course of their study participation. This *Authorization to Use and Disclose Health Information* form has an expiration date of 12 months. Therefore, we will ask participants to sign 2 copies of the *Authorization to Use and Disclose Health Information* forms (one with the current date and another post-dated) to ensure that we get a whole year of pharmacy record information.

The study participant will also be asked to sign two copies of the *Authorization for Release of Protected Health Information* form, in the event that the participant is admitted to a non-UPMC hospitals during the study period.

7.4 Survey Process

Once the participant has provided their written or verbal consent, the participant will complete the survey. The surveys are to be completed at baseline, 4-, 8-, and 12-months after randomization. The surveys are to be completed online using the study tablet or over the phone with a study staff. Paper versions of the surveys (see **Table 1** for assessments completed at each visit) will be mailed to participants who prefer to complete the surveys over the phone with a study staff. Each survey will have a "Q by Q" guide (specifying responses to sample questions participants may have for each question/item) for staff to refer to if participants raise questions during form completion supporting consistency.

7.5 Randomization

Participants meeting all of the inclusion and none of the exclusion criteria will be randomized to one of 2 groups, a control and an intervention group. To ensure flexibility in achieving the proposed allocation of patients between study arms, permuted block randomization will be used. Additionally, randomization will be stratified by type of anticoagulant, (warfarin or DOAC) as DOACs do not require monitoring and are associated with fewer major bleeding events compared to warfarin.

If the participant is randomized to the treatment group, he or she will receive the ECA+Kardia app/hardware that will come pre-loaded onto a study iPhone that will be returned at the end of

the study. These study iPhones will either be mailed or provided to the participant in person.

Participants randomized to control will receive an educational session (over the phone or in person) and a brochure published by the American Heart Association that describes AF and the relevance of anticoagulation. Control participants will receive an Apple smartphone (identical to that received by intervention participants) with the WebMD (www.webmd.com/mobile) application installed and directions for its use. The WebMD app provides general health content and can be used for enhanced self-care. We will inform control participants that they may use the WebMD app to track symptoms and record and learn about their medications for AF and other conditions.

7.6 Blinding

This is a parallel-arm, randomized clinical trial. Neither the study participants nor the study staff will be blinded to assignment to intervention or control arm. The baseline and 4-follow-up visits will be completed either in person or over the phone with a study staff member.

7.7 Intervention

FIG 2. RELATIVE AGENT
An example of a screen shot of the relational agent and a clinical encounter menu

Relational Agent

The relational agent is a mobile health (mHealth)[57] application for patient education monitoring and problem-solving. It has had extensive use in multiple contexts and has been developed in the lab of Timothy Bickmore, PhD, Northeastern University. Dr. Bickmore has developed over 25 health interventions in which the relational agent is designed to foster a sense of therapeutic alliance. The relational agent speaks with synthetic speech accompanied by animation to provide health education, emphatic counseling and monitoring. The patient engages by listening to didactic content or questions and selecting responses on the touch screen (**FIG 2**). Patients thereby converse with the agent, develop empathic therapeutic alliance, and report/record across domains of self-care. To adapt the relational-agent intervention specifically to this study population, in-depth interviews will be conducted with potential study participants prior to the start of recruitment. The interviews will capture anecdotal evidence regarding clinical encounters, barriers to care and medication adherence, and general experience living with atrial fibrillation that will inform content development and delivery. In addition, preferences for the relational agent's physical persona will be queried.

We integrate the relational agent with the AliveCor Kardia (Mountain View, CA) smartphone heart rate and rhythm monitor to guide Kardia use and enhance AF self-care monitoring.

Kardia

The AliveCor (Kardia) is a FDA-approved, heart-rhythm monitor that is accessed via smartphone application. The device is attached to the smartphone and provides a lead I ECG rhythm strip with 30 seconds of finger placement on two poles (**FIG 3**), like metallic buttons (there is no electric current and participants have an experience analogous to the performance of a standard 10-second, 12-lead electrocardiogram used in routine clinical practice). The tracings are uploaded to a secure web-based portal with time stamps of use, duration of use, and heart rate and rhythm (sinus of AF). The Kardia has been principally used for AFib detection. The Kardia app will be downloaded to the participant's study provided iPhone from the App Store. Study staff will create their Kardia account using the the participant's first name, and substituting their last name with "**####**" (where #### represents the participant's assigned study ID). The date of birth, height and weight for every participant will be the same information (to ensure that study staff won't enter identifying information). The study staff will assist the participant in running a sample EKG on their smartphone by asking the participant to place the Kardia device close to their smartphone and then to lightly place the index and middle fingers on the pads for 30 seconds (pictured below). They will also explain to the participant that he/she will not be able to see the first results immediately; however, the results of all other EKGs taken forward will be recorded immediately. We will instruct participants to use the Kardia a minimum of once daily. Kardia use is tracked automatically and review of the results will be completed by the PI, who is a cardiologist and has the expertise to oversee Kardia interpretation (**FIG 4**).

FIG 3. KARDIA

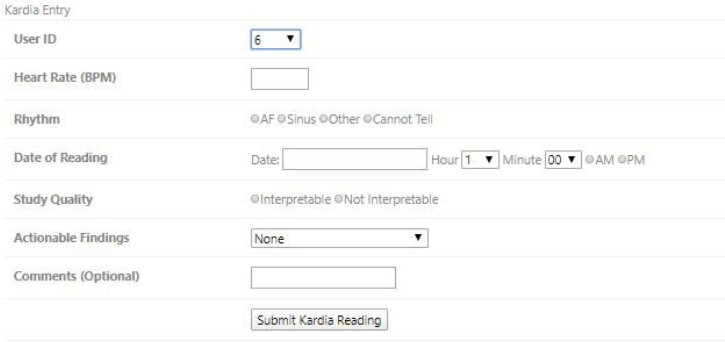


FIG 4: DATA from KARDIA

8. STUDY PROCEDURES

8.1 Assessments

Study team will conduct research assessments with each study subject at baseline, and then at 4, 8 and 12 month follow up visits. Sociodemographic, clinical and outcome information will be obtained directly from subjects and through review of their medical records including hospital databases, outpatient records, and insurance records. Study team will administer the assessments as portrayed in table below.

Table 1

Assessment (In order of study procurement)	Screening/ Consent (in clinic or by phone)	Baseline (in clinic or by phone)	4mth Follow-up (in clinic or by phone)	8mth Follow-up (by phone)	12mth Follow-up (by phone)	Role to assessment
Clinic Screening Form (includes 6-item screener)	X					
Consent	X					
Sociodemographic Characteristics						***Exploratory Outcome***
Demographics		X				
Transportation		X				
Kaiser: Your Current Living Situation		X				
Smoking		X				
Alcohol Use		X				
Montreal Cognitive Assessment		X			X	
Quality of Life Assessment						***Secondary Outcome***
AFEQT		X	X	X	X	
PROMIS-29 Profile v2.0		X	X	X	X	
Anticoagulant Adherence						***Primary Outcome***
VOILS: Medication Nonadherence		X	X	X	X	
VOILS: Medication - Reasons for nonadherence		X	X	X	X	
Self-Efficacy						***Exploratory Outcome***
PROMIS Self-Efficacy for Managing Medications &Treatments		X	X	X	X	
PROMIS Self-Efficacy Managing Symptoms		X	X	X	X	
Social Measures						***Exploratory Outcome***
BRIEF Health Literacy Screener		X				
Newest Vital Sign (NSV)		X				
Connor-Davidson Resilience Scale (CD-RISC-10)			X			
Berkman-Syme Social Network Index			X			
Psychiatric Symptoms						***Covariate***
Patient Health Questionnaire (PHQ-8)		X	X	X	X	
Medical Co-Morbidity Variables						***Covariate***
AF History		X				
Vital Signs (BMI)		X				
Antiarrhythmic Medications		X	X	X	X	
Other Medications		X				
Other Medical History		X				
New AF Therapies (Cardioversion, pacemaker)			X	X	X	
Proportion of Days Covered (PDC)					X	***Primary Outcome***
Health care utilization (events)			X	X	X	***Secondary Outcome***
RELATIONAL AGENT/Kardia Information						***Exploratory Outcome***
Relational Agent usage			X			
Study team Kardia review time			X			
AliveCor Tracking			X			
Satisfaction in using Relational Agent and Kardia			X			
Clinical events **Cardiac hospitalizations** (heart failure, myocardial infarction, hospitalization for AF)			X	X	X	
AS NEEDED FORMS:						
Adverse Event and Serious Adverse Event monitoring						
Protocol Deviations						
Unanticipated Problems						
Withdrawal						
Death notification						

8.1.1. Sociodemographic Characteristics

Demographic information (date of birth, sex) will be recorded at screening. Race/ethnicity, education, employment, marital status, insurance, financial resources and transportation status will be determined by self-report.

8.1.1.1 Your Current Living Situation
Five items from Kaiser's Your Current Living Situation Questionnaire.

8.1.1.2 Smoking
Six items from the NHANES Smoking questionnaire.

8.1.1.3 Alcohol
Five items from the NHANES Alcohol questionnaire.

8.1.1.4 Montreal Cognitive Assessment (added June 2021)
The entire Montreal Cognitive Assessment (telephone version).

8.1.2 Symptoms of Atrial Fibrillation
The 20-item AF Effect on QualiTy of life (AFEQT) is a validated instrument for measuring AF quality of life (**QOL**).

8.1.3 PROMIS-29 Profile v2.0
A generic health-related quality of life survey ranked on a 5-point Likert Scale. There is also 11-point rating scale for pain intensity.

8.1.4 Medication Nonadherence
Voils two-part scale of self-reported measure of medication non-adherence.

8.1.5 PROMIS Self-efficacy Managing Medications and Treatments
An eight-item tool to assess confidence in managing medication schedules of different complexity. Managing medication and other treatments in challenging situations such as when travelling, when running out of medication, and when adverse effects are encountered.

8.1.6 BRIEF Health
Validated 4-item instrument for quantifying health literacy.

8.1.7 Newest Vital Sign Health Literacy
Validated 6-item instrument for quantifying health literacy.

8.1.8 Connor-Davidson Resilience Scale (CD-RISC-10) (added June 2021)
A validated 10-item social factors quality of life survey ranked on a 5-point Likert Scale.

8.1.9 Berkman-Syme Social Network Index (added June 2021)
A validated 11-item social factors quality of life survey.

8.1.10 Patient Health Questionnaire-8 (PHQ-8)
An 8-item validated self-administered instrument to measure symptoms of depression in primary care settings and has been used in heart failure populations.

8.1.11History of Atrial Fibrillation
Six items describing individual history of AF.

8.1.12 Anthropometrics

Anthropometrics will consist of weight, height, and BMI as determined from the most recent data available in the electronic health record. Data recorded >1 year prior to study enrollment will not be used.

8.1.13 Medications

Medications will be obtained from the electronic health record. Specific medications recorded will be:

8.1.13.2 Warfarin
8.1.13.3 Novel oral anticoagulants
8.1.13.4 Medications for blood pressure
8.1.13.5 Medications for cardiovascular disease, e.g. beta blockers, ACE inhibitors, ARBs, dihyropyridine and non-dihydropyridine calcium channel blockers.
8.1.13.6 Other antiplatelet agents, e.g. clopidogrel, prasugrel, ticagrelor
8.1.13.7 Medications for diabetes (insulins and oral agents)

8.1.14 Medical History

Medical history will be obtained from EHR problem lists and include:

8.1.14.2 Congestive heart failure
8.1.14.3 Hypertension
8.1.14.4 Diabetes
8.1.14.5 History of stroke or TIA
8.1.14.6 Vascular disease, as determined by history of myocardial infarction as a clinical event; coronary angiography with stenosis documented as >50%; peripheral arterial disease, as documented by symptomatic claudication, ankle-brachial index documented as ≤0.90, carotid stenosis >80%, or abdominal aortic aneurysm measured at ultrasound by >5 cm.
8.1.14.7 Cardioversion procedures, including electrical cardioversion, pharmacologic cardioversion, and pulmonary vein isolation (AF ablation)

8.1.15 Health Care Utilization

Information on health services utilization, including hospitalizations, outpatient visits, and other specialty referrals, and medication usage by abstracting patients' medical records. We will also advise patients to report any hospitalizations or other medical events (especially those that occur at non-UPMC locations) to our research team by telephone any time. All reports of utilization will be investigated using hospital records.

9 Follow-up Visit Schedule

<u>Throughout the duration of baseline to 4 months</u>

All participants will receive scheduled check-in calls at study day 7, 14, 30, 60 and 90. These calls will serve to support participants and attend to any difficulties they may be experiencing with the study protocol and/or device(s) they are asked to use daily. Participants who haven't mailed back their medical release forms will be reminded to do so during these calls.

Study staff will maintain relational agent and Kardia results daily on a web-based dashboard developed by our collaborators at Northeastern University with the help of the Epidemiology Data Center (**EDC**). Agent dashboard results will consist of use statistics, reported symptoms, and self-

reported adherence to anticoagulation. Kardia results include date and time of use and heart rate and rhythm. Dashboard results will be reviewed daily.

2nd Study follow-up: - +~4 months

Participants will complete the 2nd visit at 4 months in person or over the phone if the participant is unable to meet with study staff. Study staff will send reminder cards/e-cards to the participants prior to their follow-up visit. Participants will complete a feedback survey as well as assessments and questionnaires identical to several of those done at the baseline visit. Medical records will be reviewed to assess health care utilization (emergency visit, hospitalization, and number of days hospitalized). Study iPhones will be returned during the 4-month visit, either in person or mailed back to the study team in a postage prepaid box provided to the participant. This visit will take participants 45-60 minutes to complete.

3rd Study follow-up: - +~8 months

The 3rd follow up will be conducted over the phone by trained interviewers.

Medical records will be reviewed to assess health care utilization (emergency visit, hospitalization, and number of days hospitalized). Participants will complete assessments and questionnaires identical to several of those done at the baseline and month 4 visits.

4th Study follow-up: - +~12 months

The 4th follow up will be conducted over the phone by trained interviewers. Participants will complete assessments and questionnaires identical to several of those done at the baseline and month 4 and 8 visits. Medical records will be reviewed to assess health care utilization (emergency visit, hospitalization, and number of days hospitalized).

At time- +~12 months

Medication fill data, for purposes of calculating the proportion of days covered (PDC), a common measure of medication adherence, will also be extracted from the EHR and from the pharmacist(s). Study staff will assess the EHR for incidence of adverse cardiovascular event and mortality. Study staff will also use the National Death Index to identify participant deaths and their dates.

10 Clinical Trial Oversight and Monitoring

10.1 Data Safety Monitoring

This study will recruit subjects at the University of Pittsburgh Medical Center (UPMC) who have a chronic heart rhythm disease, atrial fibrillation (AF), and are receiving anticoagulation for stroke prevention. Participants are expected to constitute a high-risk population, as they will live in rural settings, have limited socioeconomic resources, and likely have low health literacy. The study will consist of 264 adults who will be randomized to an intervention or control cohort. The intervention cohort will receive (1) a smartphone with a relational agent application, described in the application as an embodied conversational agent, and (2) the AliveCor Kardia heart rate and rhythm monitor (described here as *Kardia* for simplicity). Topics and content provided by the relational agent will focus on selfcare in AF, including symptom monitoring, maintenance, and health-promoting behaviors. The relational agent will also provide education about AF and its treatments and outcomes, and health-related quality of life. The Kardia is an FDA-approved device that also uses the smartphone. It provides 30 continuous seconds of ECG monitoring similar to a Lead I rhythm strip of a 12-lead ECG. Both devices are non-invasive and may be described as smartphone applications, or apps. Participants randomized to the control arm will receive an educational session about AF and a smartphone with the WebMD application installed. participants will use the intervention for 4 months and have return visits at 4-, 8- and 12-months with assessments as documented in the application. Intervention participants will use the smartphone in order to have interactive exchanges with the relational agent and to check their heart rates and rhythm with the Kardia. The study team will follow up on the results of the smartphone agent and the Kardia, as these mobile health applications can provide important information that can be used to guide and enhance patient care. If results meet specified criteria, then the study team will send alerts through the electronic health record to the physicians and care teams that provide care for intervention participants. The research questions being investigated by this study consequently have direct implications for clinical care and patient management.

10.2 Data Safety Monitoring Board

To ensure the safety of the participants and the validity and integrity of the data, the clinical trial will have a Data and Safety Monitoring Board (DSMB). The DSMB will be charged with evaluating the quality of trial administration, monitoring safety issues, and providing guidance on scientific, methodological and ethical issues. As its first priority, the DSMB will approve and codify the DSMB charter. Following approval by the DSMB, the charter will be submitted to the NHLBI for review and approval. The DSMB charter will describe the study protocol, data and safety monitoring plan, operation and format of DSMB meetings, Adverse Event (**AE**) definitions, AE reporting templates and case report forms, stopping rules for the trial, and a schedule for conducting blinded assessments of study benefit and safety.

The DSMB will be valuable for ensuring the quality and scientific validity of the study. It will be comprised of 3 individuals. Members will adhere to the University of Pittsburgh's policy on conflict of interest and are expected to participate for the duration of this clinical trial. The DSMB will have scheduled meetings every 6 months to evaluate and review safety, review any potential breaches in protocol, and discuss summaries of the interim AE and serious adverse event (**SAE**). The DSMB will make recommendations concerning (1) participant safety, (2) the benefit and risk ratio of the study, (3) the efficacy of the study intervention, (4) any possible amendments to the study protocol or consent, and (5) proposed ancillary studies and their impact on participant burden. Following each meeting, the DSMB will make recommendations on continuation, modification, or

termination of this trial. The DSMB will further evaluate adherence to the protocol and the recruitment and retention of participants. DSMB meeting format will be open or closed session, as determined by DSMB Chair with regard to NHLBI participation. Additional meetings will be arranged as per the charter for the need to review events or issues arise (such as an unexpected number or severity of AE). For safety monitoring, discussion will take place on whether or not any reported incident is unanticipated and/or places subjects or others at greater risk of harm, and if protocols or consent processes need to be modified. The DSMB will review the annual progress report on (1) confirmation of adherence to the data and safety monitoring plan, (2) a summary of data and safety monitoring issues for the since the last report, (3) changes in the research protocol or data and safety monitoring plan, and (4) IRB status and approvals.

10.3 Adverse events

Individuals enrolled in this trial will have a chronic disease, atrial fibrillation. This trial will use standard definitions for adverse events that accord with Federal mandates for human subjects' protection and adverse event reporting.

Identification of AE, SAE, and unanticipated problems. The study team will learn of AE, SAE, and unanticipated problems by participant interview at the 4-, 8- and 12-month assessments; direct contact by participants during the scheduled check-in calls; review of the electronic health record; communication from referring physicians or participants' providers; or contact with the study team initiated by family or other participant surrogates.

Responding to AE, SAE, and unanticipated problems. Study staff will follow guidelines set forth by the University of Pittsburgh's Institutional Review Board (IRB) and the Human Research Protection Office. The University of Pittsburgh Epidemiology Data Center, serving as the Data Coordinating Center (EDC) for the trial, will develop AE case report forms specific to this trial. The project manager and PI will prospectively record all incidents that meet any of the above definitions, and then classify AE within 24 hours of identification using the following criteria:

1. Severity (mild, moderate, severe, life threatening);
2. Relationship to study intervention (not related, unlikely, possibly, probably, or definitely related);
3. Action take regarding study intervention (none, medical intervention, hospitalization, intervention discontinued, or other);
4. Outcome of AE (resolved, recovered with minor sequelae, recovered with major sequelae, ongoing or continuing treatment, condition worsening, death, or unknown);
5. Expected AE (yes or no); and
6. Whether the AE constitutes an SAE.

All AEs and classification according to these criteria will be maintained in a log and signed by the PI. In accordance with the University of Pittsburgh IRB, all internal AEs which are (1) unexpected, fatal or life-threatening, and (2) related or possibly related to the relational agent /Kardia intervention will be reported to the IRB within 24 hours of learning of the event.

For this clinical trial, an example of an AE that would merit classification as an SAE would be hospitalization. AEs that are classified as SAEs will be further reviewed to determine if (1) they are unexpected, and (2) related or possibly related to the study procedure (relational agent relational agent and AliveCor). SAEs meeting these criteria will be reported to the IRB within 2 business days (48 hours) of learning of the event. In accordance with NHLBI regulations, SAEs

will be reported within 7 days of initial receipt of information to the NHLBI. SAE that are non-fatal and non-life-threatening will be reported to the NHLBI within 15 days of the receipt of information.

The project manager, co-investigators, PI and statistician will review aggregate data on AEs and SAEs regularly. The DSMB will be notified simultaneously with the IRB and NHLBI and will receive case report forms and documentation with a request for timely response to the SAE.

Unanticipated problems will likewise be reported to the IRB within 24 hours of the PI learning of the incident if they are fatal or life-threatening. The report will explain why the incident is considered an unanticipated problem and how the protocol will be modified. Incidents that do not meet the three criteria for unanticipated problems (unexpected, given the research procedures; related or possibly related to participation in the research; and suggest that the research places participants at a greater risk of harm than previously known or recognized) will be considered as either potential AE or classified as SAE as defined above. Unanticipated problems that are not SAEs will be reported to the IRB and the NHLBI within 14 days of the PI becoming aware of the problem.

Risk assessment. Participation in the proposed research may be considered moderate risk. This is because (1) the investigation may have direct implications for clinical care; (2) findings identified by use of the relational agent and Kardia may enter the electronic health record and thereby result in modified care; and (3) recruitment of high-risk populations (i.e., individuals with limited socioeconomic resources, low health literacy, and/or racial/ethnic minorities). As stated in the **Informed Consent**, use of the relational agent does not replace routine, urgent, or emergent clinical care. Participants in this trial will be instructed NOT to delay seeking care because they are using the relational agent to address a medical problem, question, concern or issue. All AE will be closely evaluated in order to ascertain if the AE is related or possibly related to participation in this research. Participant use of the relational agent and Kardia in proximity to the AE will be scrutinized for whether or not use of the intervention delays participants from seeking care. If necessary, participants will be directly interviewed to appreciate their understanding of the relation of their participation in this research and the occurrence of the AE. The project manager, co-investigators, and PI will review the AE and evaluate for their association with the intervention. The results of such examination will be recorded on a unique report form as prepared by the **Epidemiology Data Center** and submitted routinely for review to the DSMB.

An additional risk for participants is loss of confidentiality. The risk of breach of confidentiality is best addressed by appropriate study procedures. The PI will be responsible for assuring that study procedures are adhered to regarding data security, transfer, and communications in tracking participants by meeting regularly with study staff, reviewing procedures and performing quality control reviews of study forms.

Data and safety monitoring for continuation, modification, or termination of participation or the clinical trial. The DSMB will review summaries of AEs, SAEs, and Unanticipated Problems and make recommendations for the continuation, modification or termination of the trial. The trial is not expected to have an early termination.

Data Management and Security to Protect Privacy. The University of Pittsburgh Epidemiology Data Center (EDC) has extensive experience with supervising the conduct and data management of clinical trials and will serve as the data coordinating center (DCC) for this study under the direction of Dr. El Khoudary. Study data will be maintained on University of Pittsburgh servers. Security and integrity of study resources will be achieved via strictly enforced policies, standards and guidelines which are compliant with federal regulations and guidelines including the Health Insurance Portability and Accountability Act (HIPAA), the Federal Information Security

Management Act of 2002 (FISMA) and Department of Health and Human Services (HHS). Access to the data system requires training and certification with respect to protocol, procedure and security. Access to data on EDC servers is managed by EDC server administrators via Active Directory and Windows Authentication. Study data will be stored on an EDC SQL Server that is behind the University of Pittsburgh enterprise firewall system and is protected in a server VLAN. Direct access to this database server is restricted and is only available to authorized EDC personnel with appropriate credentials and data privileges. Regularly scheduled backups and archives protect central and local information from hard disk failures. Permanent archives of critical project files are created and are stored in a secure off-site facility to prevent data loss due to catastrophic events.

Data collection forms. The EDC will support the research team to develop required protocols, data collection forms and venues for the data collection (e.g., telephone interview, clinic visit). Data collection forms will be designed to ensure protocol compliance, optimize interview flow with branching logic, reduce missing data elements, minimize participant burden in self-reports, and support efficient data collection and analysis processes.

Data Management Manual of Operations. The EDC will assist in developing a Manual of Operations (MOP) to document all data collection and management procedures for the study. The MOP will include an overall description of the project, the study protocol, data collection procedures (including question by question instructions), and detailed descriptions of all other procedures required to conduct the study. In addition, an internal DCC Manual of Operations (DCC MOP) will be developed. The DCC MOP will provide documentation of the internal procedures, such as the creation of analytic data sets, the generation of reports, and the data freeze. The MOPs will facilitate consistency in protocol implementation and provide some protection against potential disruptions due to personnel turnover.

Quality control/Data Collection Monitoring. The DCC will monitor all aspects of study performance and protocol compliance and will be responsible for monitoring the data from all study entities as well as adherence to established adverse event reporting. Electronic data capture methods will be implemented for this study. Study data will be subjected to extensive checks for completeness, accuracy, and consistency including data validations to verify the authenticity of participant IDs, prohibit duplicate record entries, and incorporate range, format, data type checks and alert values. To facilitate monitoring of study performance, data status reports will be generated and reviewed by study leadership on a regular basis. These reports will include recruitment and retention, protocol adherence, data quality, and study participant characteristics. **Creation of analytic datasets for statistical programming.** The statistical programmer and analyst of the data management team will be responsible for cleaning the datasets and preparing the corresponding codebooks and statistical summaries. These datasets will be used to carry out the full range of data analysis activities needed to prepare monitoring reports, abstracts and manuscripts. This will include planning and developing methods for data analysis, statistical programming, and interpreting and summarizing data for internal and DSMB reports.

10.0 Archival of data

Throughout the study, data will be predominantly recorded and stored electronically. Sources of data include screening records, assessments, summaries from the electronic health record, and compilation from web sites such as the relational agent dashboard. All such tangible electronic data will be archived for a minimum of seven years following the publication of the primary

analysis. We will upload the full data set to BioLINCC prior to study closure.

11.0 Costs and payments

Each study subject will be provided $25 for the baseline visit, $50 for the 4-month follow-up visit, $25 for the 8-month follow up telephone assessment and $50 for the last 12-month telephone assessment as compensation for his/her time. This totals $150 of participant compensation if the entire study is completed.

12.0 Qualifications of Investigators

Jared W. Magnani, MD, MSc (Principal Investigator) is an Associate Professor of Medicine in the Division of Cardiology, Department of Medicine, University of Pittsburgh School of Medicine. Dr. Magnani is a clinical cardiologist and cardiovascular epidemiologist with a focus on health services research. He has served as a Framingham Heart Study investigator, having completed a clinical research fellowship in that study and received a Master of Science in epidemiology from Boston University. He has led multiple investigations of novel atrial fibrillation risk factors in the Framingham Heart Study and other cohorts, and been supported by the American Heart Association, the Doris Duke Foundation, and the NIH. Dr. Magnani is responsible for initiating and developing the study. He will develop and supervise content for the smartphone-based intervention. He will establish study infrastructure, develop a manual of operations, meet routinely with study staff, and supervise all aspects of study administration. He will have overall responsibility for implementing and monitoring all phases of the proposed research plan.

Bruce L. Rollman, MD, MPH (Co-Investigator) is a Professor of Medicine, Psychiatry, Biomedical Informatics, and Clinical and Translational Science. He is the UPMC Endowed Chair in General Internal Medicine and the Director of the Center for Behavioral Health and Smart Technology. Dr. Rollman has expertise and leadership in the development and implementation of randomized clinical trials at UPMC. He has been principal investigator on six NIH-funded R01 clinical trials, which have used multidisciplinary approaches to improve outcomes for mood disorders and cardiovascular disease. Dr. Rollman serves as local mentor for Dr. Magnani's Doris Duke Clinical Scientist Development Award, and has guided the completion of the preliminary data concerning this project as presented in the proposal. He will provide guidance and expertise for the development and successful implementation of this trial. As such, Dr. Rollman will provide senior level advisement on trial execution and implementation. Dr. Rollman will attend regular study meetings, meet monthly with the study PI, and participate in the abstracts and manuscripts presenting study results.

Samar R. El Khoudary, PhD, MPH, BPharm (Co-Investigator; Study Statistician) is an Associate Professor of Epidemiology and Clinical and Translational Science Institute and a core faculty member of the Epidemiology Data Center (EDC). She has extensive experience in multi-center longitudinal studies and statistical methodologies to analyze longitudinal data and clinical trials. She will provide primary statistical leadership of the study and oversee the routine operations of the EDC as pertinent to this study. Dr. El Khoudary will lead the Data Coordinating Center (EDC) of this study and will supervise the data management and statistical organization of this study. Dr. El Khoudary will supervise the preparation of all data reports and will work closely with the statistical programmer regarding on-going analysis. Dr. El Khoudary will collaborate with Dr. Magnani and the other study investigators in manuscript writing and abstracts' preparation for scientific meetings. She will work with study investigators to frame hypotheses, propose appropriate analytic methods, interpret the analytic results, and formulate appropriate conclusions.

Maria M. Brooks, PhD (Co-Investigator; Study Statistician) is a Professor of Epidemiology and Biostatistics and a director of the Epidemiology Data Center (EDC). Dr. Brooks has an extensive portfolio of experience in the statistical design and analysis of clinical trials. She will provide robust, high-level input on clinical trial design, study implementation, the study protocol, and she will interface with our DSMB. Dr. Brooks provides senior oversight on statistical and analytical issues. She will collaborate on manuscript writing and presentations at scientific meetings.

Timothy W. Bickmore, Ph.D. (Co-Investigator) is a Professor of Computer and Information Science at Northeastern University. His background is in artificial intelligence, natural language processing and health communications. He has over 20 years' experience managing advanced software technology R&D projects and has spent the last ten years developing natural language dialogue systems for health education, counseling and behavior change. Dr. Bickmore will be responsible for all technical development on the project and all aspects of the project conducted at Northeastern University.

Michael Paasche-Orlow, MD, MA, MPH (Co-Investigator) is Professor of Medicine at Boston University School of Medicine. He is a primary care clinician and a nationally recognized expert in the field of health literacy. He has served as primary mentor for Dr. Magnani's Doris Duke clinical Scientist Development Award, and has an extensive contribution to investigations of health literacy and interactive behavioral informatics programs. He has collaborated extensively with Drs. Magnani and Bickmore (co-investigator, Northeastern University) to develop the relational agent system used in this trial. Dr. Paasche-Orlow will participate in the development and implementation of the relational agent and its content as relevant for doctor-patient communication. He will oversee the assessment and implementation of health literacy throughout the study, spanning the agent development, participant recruitment, and interpretation of study results.

References

1. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119-125.
2. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults. *JAMA*. 2001;285:2370.
3. Wolf PA, Dawber TR, Thomas HE, Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham study. *Neurology*. 1978;28:973-977.
4. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley Study. *Am J Med*. 2002;113:359-364.
5. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: Incidence, risk factors, and prognosis in the Manitoba Follow-up Study. *Am J Med*. 1995;98:476-484.
6. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke*. 1997;28:316-321.
7. Santangeli P, Di Biase L, Bai R, Mohanty S, Pump A, Cereceda Brantes M, Horton R, Burkhardt JD, Lakkireddy D, Reddy YM, Casella M, Dello Russo A, Tondo C, Natale A. Atrial fibrillation and the risk of incident dementia: A meta-analysis. *Heart Rhythm.* 2012;9:1761-1768.
8. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. *Circulation*. 1998;98:946-952.
9. Bengtson LG, Lutsey PL, Loehr LR, Kucharska-Newton A, Chen LY, Chamberlain AM, Wruck LM, Duval S, Stearns SC, Alonso A. Impact of atrial fibrillation on healthcare utilization in the community: The Atherosclerosis Risk In Communities Study. *J Am Heart Assoc*. 2014;3:e001006. PMCID: PMC4338687.
10. Freeman JV, Wang Y, Akar J, Desai N, Krumholz H. National trends in atrial fibrillation hospitalization, readmission, and mortality for Medicare beneficiaries, 1999-2013. *Circulation*. 2017;135:1227-1239.
11. Piccini JP, Hammill BG, Sinner MF, Hernandez AF, Walkey AJ, Benjamin EJ, Curtis LH, Heckbert SR. Clinical course of atrial fibrillation in older adults: The importance of cardiovascular events beyond stroke. *Eur Heart J.* 2014;35:250-256. PMCID: PMC3896863.
12. Kirchhof P, Breithardt G, Camm AJ, Crijns HJ, Kuck KH, Vardas P, Wegscheider K. Improving outcomes in patients with atrial fibrillation: Rationale and design of the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial. *Am Heart J.* 2013;166:442-448.
13. Sabaté E, World Health Organization. *Adherence to long-term therapies : Evidence for action*. Geneva: World Health Organization; 2003.
14. Bosworth HB. Causes of medication nonadherence. *Enhancing medication adherence: The public health dilemma.* Tarporley: Springer Healthcare Ltd.; 2012:9-16.

15. Quarells RC, Liu J, Davis SK. Social determinants of cardiovascular disease risk factor presence among rural and urban black and white men. *J Men's Health.* 2012;9:120-126. PMCID: PMC3418704.
16. Hayden K, Schweinle W. Demographic considerations in anticoagulation therapy for atrial fibrillation. *S D Med*. 2015;68:116-119.
17. Havranek EP, Mujahid MS, Barr DA, Blair IV, Cohen MS, Cruz-Flores S, Davey-Smith G, Dennison-Himmelfarb CR, Lauer MS, Lockwood DW, Rosal M, Yancy CW. Social determinants of risk and outcomes for cardiovascular disease: A Scientific Statement from the American Heart Association. *Circulation.* 2015;132:873-898.
18. Institute of Medicine (U.S.). Committee on the Future of Rural Health Care. *Quality through collaboration : The future of rural health.* Washington, D.C.: National Academies Press; 2005.
19. Kusmin L. US Department of Agriculture Rural America at a Glance, 2016 edition. https://www.ers.usda.gov/webdocs/publications/80894/eib-162.pdf?v=42684. Accessed on October 19, 2018.
20. Aneja S, Ross JS, Wang Y, Matsumoto M, Rodgers GP, Bernheim SM, Rathore SS, Krumholz HM. Us cardiologist workforce from 1995 to 2007: Modest growth, lasting geographic maldistribution especially in rural areas. *Health Aff (Millwood).* 2011;30:2301-2309. PMCID: PMC3332098.
21. Kim JI, Sillah A, Boucher JL, Sidebottom AC, Knickelbine T. Prevalence of the American Heart Association's "ideal cardiovascular health" metrics in a rural, cross-sectional, community-based study: The Heart of New Ulm Project. *J Am Heart Assoc.* 2013;2:e000058. PMCID: PMC3698762.
22. Matthews KA, Croft JB, Liu Y, Lu H, Kanny D, Wheaton AG, Cunningham TJ, Khan LK, Caraballo RS, Holt JB, Eke PI, Giles WH. Health-related behaviors by urban-rural county classification - United States, 2013. *MMWR Surveill Summ.* 2017;66:1-8.
23. Mainous AG, 3rd, King DE, Garr DR, Pearson WS. Race, rural residence, and control of diabetes and hypertension. *Ann Fam Med.* 2004;2:563-568. PMCID: PMC1466748.
24. Holman H, Lorig K. Patient self-management: A key to effectiveness and efficiency in care of chronic disease. Public Health Rep. 2004;119:239-243. PMCID: PMC1497631.
25. Lorig KR, Holman H. Self-management education: History, definition, outcomes, and mechanisms. *Ann Behav Med.* 2003;26:1-7.
26. Holman HR, Lorig KR. Patient education: Essential to good health care for patients with chronic arthritis. *Arthritis Rheum.* 1997;40:1371-1373.
27. McCorkle R, Ercolano E, Lazenby M, Schulman-Green D, Schilling LS, Lorig K, Wagner EH. Self-management:Enabling and empowering patients living with cancer as a chronic illness. *CA: Can J Clin*. 2011;61:50-62. PMCID: PMC3058905.
28. Lorig K. Partnerships between expert patients and physicians. *Lancet.* 2002;359:814-815.
29. Fischer D, Stewart AL, Bloch DA, Lorig K, Laurent D, Holman H. Capturing the patient's view of change as a clinical outcome measure. *JAMA*. 1999;282:1157-1162.
30. Smith ML, Towne SD, Herrera-Venson A, Cameron K, Kulinski KP, Lorig K, Horel SA, Ory MG. Dissemination of Chronic Disease Self-Management Education (CDSME) programs in the United States: Intervention delivery by rurality. I*nt J Environ Res Public Health*. 2017;14. PMCID: PMC5486324.
31. Benzo R, Vickers K, Ernst D, Tucker S, McEvoy C, Lorig K. Development and feasibility of a self-management intervention for chronic obstructive pulmonary disease delivered

with motivational interviewing strategies. J Cardiopulm Rehabil Prev. 2013;33:113-123. PMCID: PMC3586298.
32. McCabe PJ, Schumacher K, Barnason SA. Living with atrial fibrillation: A qualitative study. *J Cardiovasc Nurs.* 2011;26:336-344.
33. Reynolds MR, Morais E, Zimetbaum P. Impact of hospitalization on health-related quality of life in atrial fibrillation patients in Canada and the United States: Results from an observational registry. *Am Heart J.* 2010;160:752-758.
34. Lane DA, Langman CM, Lip GY, Nouwen A. Illness perceptions, affective response, and health-related quality of life in patients with atrial fibrillation. *J Psychosom Res.* 2009;66:203-210.
35. U.S. Promis: *Dynamic tools to measure health outcomes from the patient perspective.* http://www.healthmeasures.net/explore-measurement-systems/promis. Accessed on October 21, 2018.
36. Pathman DE, Ricketts TC, Konrad TR. How adults' access to outpatient physician services relates to the local supply of primary care physicians in the rural Southeast. *BMC Health Serv Res.* 2006;41:79-102. PMCID: PMC1681540.
37. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. *Stat Med.* 2012;31:328-340.
38. Voils CI, Maciejewski ML, Hoyle RH, Reeve BB, Gallagher P, Bryson CL, Yancy WS, Jr. Initial validation of a self report measure of the extent of and reasons for medication nonadherence. *Med Care.* 2012;50:1013-1019. PMCID: PMC3494794.
39. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, N.J.: L. Erlbaum Associates; 1988.
40. Steinberg BA, Kim S, Fonarow GC, Thomas L, Ansell J, Kowey PR, Mahaffey KW, Gersh BJ, Hylek E, Naccarelli G, Go AS, Reiffel J, Chang P, Peterson ED, Piccini JP. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J.* 2014;167:735-742 e732. PMCID: PMC4006943.
41. Biostatistics for biomedical research. http://www.fharrell.com/doc/bbr.pdf. Accessed on September 27, 2018.
42. Dorian P, Burk C, Mullin CM, Bubien R, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A, Spertus J. Interpreting changes in quality of life in atrial fibrillation: How much change is meaningful? *Am Heart J.* 2013;166:381-387.
43. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B* (Methodological). 1995;57:12.
44. VanderWeele TJ. Mediation analysis: A practitioner's guide. *Annu Rev Public Health.* 2016;37:17-32.
45. VanderWeele TJ, Lantos JD, Siddique J, Lauderdale DS. A comparison of four prenatal care indices in birth outcome models: Comparable results for predicting small-for-gestational-age outcome but different results for preterm birth or infant mortality. *J Clin Epidemiol.* 2009;62:438-445.
46. Vansteelandt S. Estimating direct effects in cohort and case-control studies. *Epidemiology.* 2009;20:851-860.
47. Amponsah MK, Benjamin EJ, Magnani JW. Atrial fibrillation and race - a contemporary review. *Curr Cardiovasc Risk Rep.* 2013;7. PMCID: PMC3815541.

48. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African Americans: The Atherosclerosis Risk In Communities (ARIC) Study. *Am Heart J*. 2009;158:111-117. PMCID: PMC2720573.
49. Golwala H, Jackson LR, 2nd, Simon DN, Piccini JP, Gersh B, Go AS, Hylek EM, Kowey PR, Mahaffey KW, Thomas L, Fonarow GC, Peterson ED, Thomas KL. Racial/ethnic differences in atrial fibrillation symptoms, treatment patterns, and outcomes: Insights from Outcomes Registry for Better Informed Treatment of Atrial Fibrillation. *Am Heart J.* 2016;174:29-36.
50. Rodriguez CJ, Soliman EZ, Alonso A, Swett K, Okin PM, Goff DC, Jr., Heckbert SR. Atrial fibrillation incidence and risk factors in relation to race-ethnicity and the population attributable fraction of atrial fibrillation risk factors: The multi-ethnic study of atherosclerosis. *Ann Epidemiol.* 2015;25:71-76, 76 e71. PMCID: PMC4559265.
51. Ball J, Carrington MJ, Wood KA, Stewart S, Investigators S. Women versus men with chronic atrial fibrillation: Insights from the standard versus atrial fibrillation specific management study (SAFETY). *PLoS One.* 2013;8:e65795. PMCID: PMC3667075.
52. Scheuermeyer FX, Mackay M, Christenson J, Grafstein E, Pourvali R, Heslop C, MacPhee J, Ward J, Heilbron B, McGrath L, Humphries K. There are sex differences in the demographics and risk profiles of Emergency Department (ED) patients with atrial fibrillation and flutter, but no apparent differences in ED management or outcomes. *Acad Emerg Med.* 2015;22:1067-1075.
53. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, Howard VJ, Lichtman JH, Lisabeth LD, Pina IL, Reeves MJ, Rexrode KM, Saposnik G, Singh V, Towfighi A, Vaccarino V, Walters MR. Guidelines for the prevention of stroke in women: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:1545-1588.
54. Magnani JW, Norby FL, Agarwal SK, Soliman EZ, Chen LY, Loehr LR, Alonso A. Racial differences in atrial fibrillation-related cardiovascular disease and mortality: The Atherosclerosis Risk In Communities (ARIC) Study. *JAMA Cardiol.* 2016;1:433-441. PMCID: PMC5347977.
55. Rural Health Information Hub (funded by the Federal Office of Rural Health Policy). https://www.ruralhealthinfo.org/am-i-rural. Accessed on 12/11/2019
56. Taub HA, Baker MT. The effect of repeated testing upon comprehension of informed consent materials by elderly volunteers. *Exp Aging Res.* 1983;9:135-138.
57. Kumar S, Nilsen WJ, Abernethy A, Atienza A, Patrick K, Pavel M, Riley WT, Shar A, Spring B, Spruijt-Metz D, Hedeker D, Honavar V, Kravitz R, Lefebvre RC, Mohr DC, Murphy SA, Quinn C, Shusterman V, Swendeman D. Mobile health technology evaluation: The mHealth evidence workshop. *Am J Prev Med.* 2013;45:228-236. PMCID: PMC3803146.