A Mobile Relational Agent to Enhance Atrial Fibrillation Self-Care

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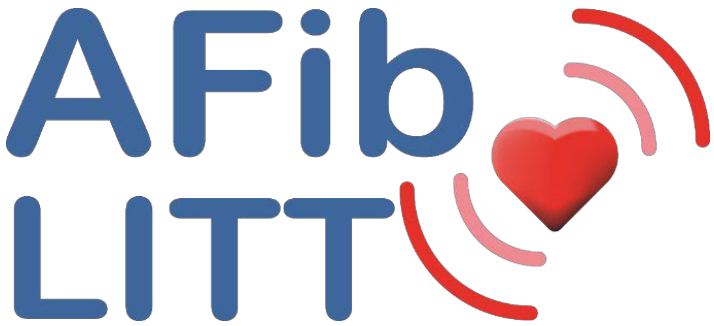

A Mobile Relational Agent to Enhance Atrial Fibrillation Self-Care

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List of Abbreviations

AE	Adverse Event
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on QualiTy of life
BPA	Best Practice Alert
CVD	Cardiovascular Disease
CCDC	Center for Clinical Trials and Data Coordination
DCC	Data Coordinating Center
DOCA	Direct oral anticoagulant
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
EHR	Electronic Health Record
HCU	Health Care Utilization
HrQoL	Health-related Quality of Life
IRB	Institutional Review Board
NHLBI	National Heart Lung Blood Institute
NIH	National Institutes of Health
NVS	Newest Vital Sign
OIT	Office of Information Technology
PDC	Proportion of Days Covered
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PM	Project Manager
QC	Quality Control
QOL	Quality of Life
RCT	Randomized Clinical Trials
SAE	Serious Adverse Event
SSL	Secure Socket Layering
UPMC	University of Pittsburgh Medical Center

1. ABSTRACT

Atrial fibrillation (**AF**) is a common, morbid condition. Symptoms, complex management, and significant adversity contribute to poor health-related quality of life (**HRQoL**). Social determinants of health exacerbate morbidity in AF, and limited health literacy compounds the poor patient experience of AF. We propose a single-center parallel group randomized clinical trial to test the efficacy of a relational agent to improve patient-centered care in AF. The relational agent is a computer character that simulates face-to-face conversation using voice, hand gesture, and gaze cues to provide education, monitoring and problem-solving. We have used the relational agent in multiple health contexts for self-care and demonstrated its success to improve health behaviors and outcomes in individuals with limited computer and health literacy. Here we propose to expand our successful 30-day pilot (n=31) of the relational agent in order to evaluate the effect of a 4-month self-care curriculum and assess its 8- and 12-month sustainability. All participants will receive an AliveCor Kardia smartphone heart rate and rhythm monitor. We will randomize 240 patients with AF who are receiving anticoagulation to either (1) the relational agent intervention provided by smartphone, a Kardia and accompanying EHR alerts, or (2) the control, consisting of an AF educational session, a Kardia, and a smartphone with a general health application for self-care (WebMD). Our trial will leverage the clinical infrastructure of the University of Pittsburgh Medical Center (**UPMC**) by recruiting at 8 UPMC clinics that share a common electronic health record. We will focus recruitment on individuals with limited socioeconomic resources, low health literacy, or racial/ethnic minorities. Our aims are: (1) To evaluate the effect of the relational agent and EHR alert intervention on anticoagulation adherence. We will quantify adherence using the Proportion of Days Covered (PDC) standard and pharmacy contact at 12 months, and complementary measures of self-reported non-adherence at baseline, 4, 8, and 12 months. (2) To determine the effect of the intervention on health care utilization at 4, 8, and 12 months using participant interview and the common EHR. (3) To examine the effect of the relational agent intervention on patient-centered outcomes. We will evaluate HRQoL with the AF-specific AF Effect on QualiTy of life (**AFEQT**) measure and general HRQoL with the Patient-Reported Outcomes Measurement Information System-29 Profile at baseline, 4, 8, and 12 months. Our trial will engage an 8-member patient advisory committee comprised of individuals with chronic AF to guide the intervention's cultural acceptability, recruitment, and presentation of results. Expected Results: In this project we will evaluate a scalable patient-centered intervention to improve HRQoL, improve anticoagulation adherence, and reduce health care utilization in vulnerable individuals with chronic AF. If proven successful, this intervention can be broadly disseminated to improve the care of patients with AF.

2. 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. We propose an innovative and accessible mHealth intervention to improve self-care for patients with this complex and chronic condition. We have developed a novel, practical mHealth intervention that is accessible to high-risk patients such as those with limited social resources or health literacy.

3. STUDY RATIONALE AND SIGNIFICANCE OF THE RESEARCH

a) AF prevalence is estimated to reach 6 to 12 million adults in the US 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] Even on optimal therapy, patients in randomized clinical trials (**RCT**) still

experience a stroke rate of 1.5%, heart failure 4-5%, and mortality 3% per year.[9] Individuals with AF have 4.7-times greater days of hospitalization compared to those without.[10] There has been a 1.6-fold increased expenditure per Medicare beneficiary with AF since 1999.[11] This project aims to reduce the morbidity and social costs of AF.

b) AF is a chronic disease with extensive symptoms, adverse outcomes, and resulting poor health-related quality of life (HRQoL). Anticoagulation is a mainstay of AF treatment but demands long-term – likely lifelong – daily adherence with concomitant monitoring for bleeding. We have reported that symptoms diminish HRQoL, subjective health, and functional status.[12] 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. (1) *Racial and ethnic minorities.* AF is reported as less prevalent in blacks but racial disparities in AF are well-evidenced. Blacks with AF have worse HRQoL, and we identified 1.5- to 2-fold greater rates of heart failure, coronary disease, stroke, and mortality in blacks with AF compared to whites in the community-based Atherosclerosis Risk in Communities Study. (2) *Income.* Lower income decreases access to health care and medications and increases Health Care Utilization (**HCU**) and likelihood of poor outcomes. Lower income in combination with limited health literacy challenges adherence, self-care, and patient activation. In our preliminary University of Pittsburgh Medical Center (UPMC) cohort (n=213), the association of lower income with significantly worse HRQoL was sustained following adjustment for demographics and comorbidities. (3) *Health literacy*. We have summarized the adverse relation of limited health literacy to outcomes, treatment access, symptom reporting, and adherence in AF.[13,14] Our intervention is designed to empower patients, ameliorate health literacy related barriers to self-care, and improve patient-centered outcomes for vulnerable patients with AF.

c) Middle-range theory of self-care has articulated self-care as essential for individuals to promote health and manage chronic illness.[15,16] Self-care encompasses: (1) maintenance, disease-specific knowledge acquisition, adherence to treatments, and daily behavior to promote health; (2) monitoring, identifying and tracking common symptoms and disease-specific metrics; (3) management, the ability to distinguish symptom severity, follow and evaluate action plans, and initiate contact with health providers. The self-care model has been demonstrated to improve patient-centered and clinical outcomes in cardiovascular disease (**CVD**) such as heart failure, hypertension, coronary disease, and stroke.[15] Self-care research in AF has been limited by studies being short-term with poor patient retention, absence of a patient-centered approach, or lacking a self-efficacy focus. More successful self-care interventions for AF have had longitudinal and individualized, patient-facing content.[17-19] Accordingly, we propose to provide a longitudinal, patient-centered program that will engage patients and provide sustained improvement to self-care.

d) The relational agent is a mobile health (mHealth)[20] 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 for the relational agent to promote self-care HRQoL (e.g., R01AG028669, 1R01HL081307, NCI 5R21CA127511, R01HL116448).[21-24, 25-26] The relational 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 self-care. The relational agent (a) elicits symptoms and (b) gestures to enhance educational content. 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.

e) HRQoL as a benchmark goal for AF treatment.[13,14] Our intervention addresses the poor HRQoL in AF that stems from symptoms, treatment burden, and clinical uncertainty.

3.0 STUDY AIMS

3.1 Aim 1

To evaluate the effect of the relational agent intervention on adherence to anticoagulation. 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 determine the effect of the intervention on HCU. We will evaluate 4-, 8- and 12-month HCU (emergency visit, hospitalizations and number of days hospitalized) between the intervention and control arms by review of the EHR and participant interview. We hypothesize that intervention participants will have superior rates of HCU compared to control arm participants. As an exploratory analysis, we will compare the 12-month incidence of cardiovascular outcomes (myocardial infarction, heart failure, stroke) and mortality by trial arm.

3.3 Aim 3

To examine the effect of the relational agent intervention on patient-reported outcomes. We will compare patient-reported outcomes between the intervention and control arms at 4 months and assess sustainability at 8 and 12 months. We hypothesize that the intervention vs. the control at 4 months will produce improvement in: (1) AF-specific HRQoL (secondary outcome, measured by the AF Effect on QualiTy of life, or AFEQT[33,34] and (2) general HRQoL (secondary outcomes, measured by the Patient-Reported Outcomes Measurement Information System, PROMIS-29 Profile[35]).

4. STUDY DESIGN

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 240 patients at UPMC sites 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, intervention participants 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 also receive a smartphone with the application WebMD installed on the phone and the AliveCor Kardia. 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 adherence to anticoagulation, health care utilization, and patient-reported outcomes resulting from the intervention.

5.0 STATISTICAL CONSIDERATIONS

We propose a two-arm RCT to evaluate the efficacy of the relational agent to improve anticoagulation adherence in patients with the debilitating chronic condition AF. We will recruit 240 participants with AF receiving anticoagulation over a 30-month period, prioritizing recruitment in socioeconomically depressed regions in the Pittsburgh, PA, metropolitan area. We will randomize participants 1:1 to receive the intervention, a mobile Health relational agent (n=120) or control, an AliveCor Kardia device (n=120) 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 DOAC) and the Newest Vital Sign score. We will assess the impact of our intervention at 4, and then at 8 and 12 months to determine sustainability.

Our primary hypothesis will test whether the relational agent intervention can improve adherence to anticoagulation as measured by PDC and self-report. Our secondary hypotheses will evaluate whether the intervention can reduce rates of HCU and produce the recognized minimally important or greater improvement in HRQoL vs. the control, as measured by the AFEQT Instrument. Prespecified secondary analyses are listed in the approach and include the effect of the intervention by sex, race, income, and health literacy. All participants will have return visits at 4, 8, and 12 months. 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 is anticoagulant adherence as assessed by PDC. PDC will be analyzed as both continuous (range 0-1 with higher ratio indicating better adherence) and binary (optimally adherent if PDC ≥0.8) variables. Primary analysis to assess differences in PDC measures at 12 months between study arms will be adjusted for trial stratification factors (type of anticoagulant treatment)[36] using linear regression (for continuous PDC) or logistic regression (for binary PDC). For secondary assessments of adherence at 4, 8, and 12 months, we will analyze self-reported extent of non-adherence (Voils et al.[37]) as a binary variable, categorizing individuals with any of 3 items ≥2 (range 1-5) as reporting nonadherence. These models will be adjusted additionally for trial stratification factors.[36] We calculated the statistical power to detect a range of difference in PDC between the intervention and control arms. We determined that a sample size of 120 in the intervention group and 120 in the control group will enable us to detect a minimum difference in PDC between the two groups as small as 12.6% with 90% power. Our power calculations assume use of 2-sided tests with 0.05 significance level. With 15% attrition of the sample size (n=204), we will be able to detect a minimum difference in PDC between the 2 study arms as small as 14.1% (0.47 standardized mean difference) with 80% power.

Statistical approach for Aim 2. We will compare the difference in rate of HCU across trial arms. Person-year of follow-up will be calculated from the date of randomization to the 12-month visit date. The annualized rate of in-patient HCU will then be estimated by dividing the aggregate count of inpatient days by person-year of follow-up. Rates and rate ratios of HCU comparing intervention and control groups will be calculated. We will use generalized linear models with a Poisson distribution as our initial approach. If overdispersion is observed, we will utilize negative binomial distribution. Next, if observed data frequently display a higher relative frequency of zeros, then zero-inflated count models will be utilized. To better inform which model to use, we will conduct (1) a likelihood-ratio test for the overdispersion parameter α in the negative binomial specification against the Poisson model specification and (2) a Vuong test of the standard count model against the zero inflated count model.[38-41] Similar approaches will be used to assess counts for each HCU component. All models will account for trial stratification factors.[36] For the

exploratory analyses, we will compare the 12-month combined adverse cardiovascular outcomes and mortality rates by study arm using stratified Mantel-Haenszel Chi-square statistics accounting for trial stratification factors.[36] Our best estimates of HCU in AF patients are based on HCU rates observed in a community-based study that similarly ascertained HCU with health services claims.[10] The average number of days hospitalized was 13.2 days over 12 months. Given our sample size, we estimate that we have 80% power to detect a minimum of 9.7% reduction in HCU in the intervention group, assuming annual rates of 13.2 annual days of hospitalization in the control group. A 15% attrition in study participation (n=204) will allow us to detect a minimum of 10.6% reduction in HCU in the intervention group with 80% statistical power.

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 limited-sized AF pilot 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, with greater scores indicating superior HRQoL). We will use linear regression to model 4-month changes in AFEQT global score as a function of study arm, health literacy, and anticoagulation type. Similarly, we will assess the effect of the intervention for each of the 8 symptom and HRQoL domains measured by the PROMIS-29 at 4 months. Next, we will assess sustainability of the intervention effect at 12 months using linear mixed models. Our power calculations assume an 85% 4-month assessment completion rate (to accommodate for 15% attrition), 2-tailed α=0.05, and 19-point improvement in global AFEQT score between our intervention arm and control arm (consistent with the data used to determine the minimum important difference[34]) as well as standard deviation of 28 (representing the upper limit of the 95% confidence interval for the SD). The minimally important difference in AFEQT global scores has been determined elsewhere as a 19-point difference.[34] Based on these assumptions, we will have greater than 85% power to detect the minimally important difference in the 4-month improvement of the AFEQT global score, our primary outcome. We will have more than 85% power to detect similar effect sizes in our secondary outcome measures (e.g., AFEQT domains, PROMIS-29) between our intervention and control arms. A 15% sample size attrition (n=204) will allow us to detect the minimally important difference in AFEQT with 80% power.

Race and sex. We will ensure our study cohort comprises 51% women and at least 30% non-white race, of whom 80% (24% overall) will be black race. (1) These demographics reflect the Pittsburgh, PA, region. (2) We have reviewed[42] that multiple studies have reported AF as less prevalent in blacks.[43,44-46] Yet we and others have identified consistent data on racial disparities in AF. (3) There are sex-specific differences in AF, as women are more likely to present with atypical symptoms, report worse HRQoL than men, and have increased stroke risk in AF.[47-49] (4) Hence, we have developed strategies to oversample participants of black race and female sex, detailed in our Inclusion of Women and Minorities. We note our statistical power for such trial participation: (1) if we randomize 56 study participants of black race, then we will have 80% power to detect a 25.0-point difference in AFEQT between trial arms. (2) Similarly, if we randomize 122 women, 51% of trial participants, then we will have 80% power to detect a 17.0-point difference between trial arms.

Subgroup analyses. We will conduct secondary subgroup analyses for (1) health literacy (NVS <4 or ≥4); (2) type of anticoagulant (warfarin or DOAC); (3) sex; (4) race (white vs non-white); (5) self-reported anticoagulant nonadherence[37] (<2 or ≥2); (6) duration of anticoagulation (<1 or ≥1 year); (7) AF classification[13] as per the EHR at study enrollment (paroxysmal or persistent/permanent); and (8) introduction of new therapies for AF over 12-month study participation (antiarrhythmic, cardioversion or electrophysiologic study). We will test whether

each of these variables modifies the intervention effect on study outcomes in regression models. Our significance level will account for multiple comparisons.

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.

We will promote awareness of our study through multiple ways. Recruitment will be conducted at numerous University of Pittsburgh Medical Center sites located in Pittsburgh. The Principal Investigator (PI) and Project Manager (PM) will contact cardiologist, admin staff, primary care physicians, 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.

We 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 (with and without pull tabs) 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 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.

5) 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.

6) 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.

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

6.2 Inclusion Criteria

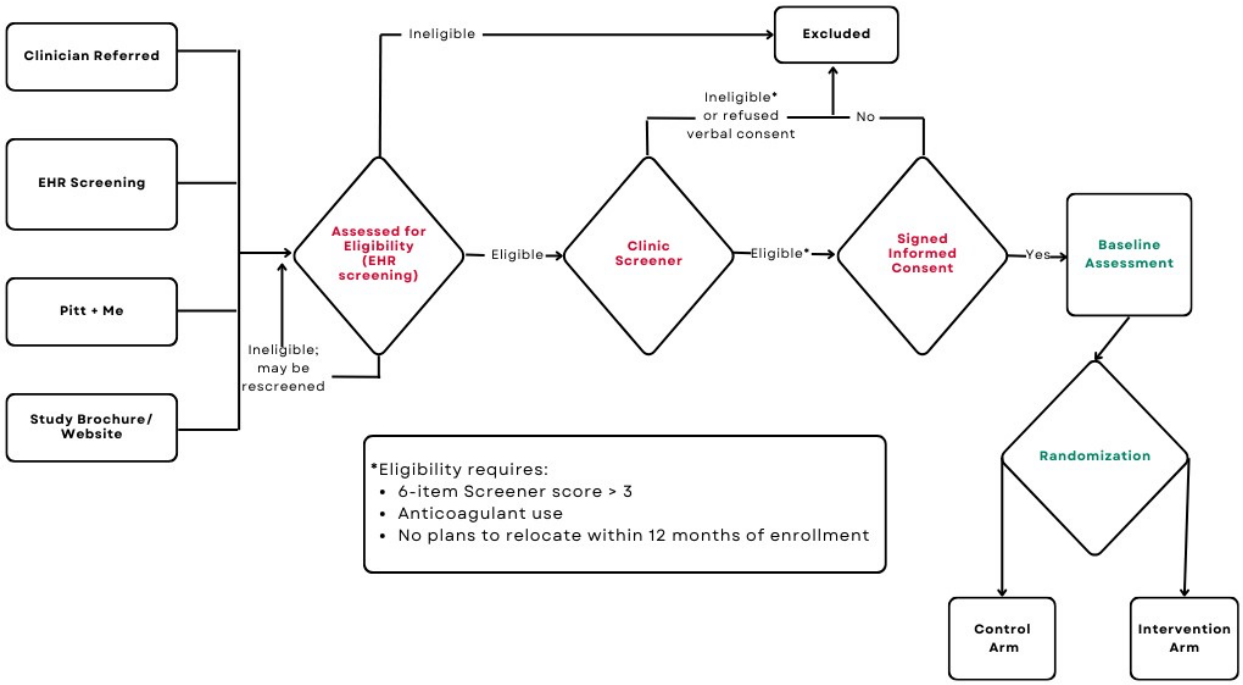
1. Adult, age ≥21;
2. Diagnosis of AF, identified from the EHR and confirmed by either an AF monitoring event (Electrocardiogram (**ECG**), Holter or event monitor) or a clinical note;
3. Prescribed use of warfarin or Direct Oral Anticoagulant (**DOAC**) (formerly NOAC) for AF stroke prevention;
4. English-speaking well enough to participate in informed consent and this study;
5. No plans to relocate from the area within 12 months of enrollment.

6.3 Exclusion Criteria

1. Prior catheter ablation procedure for treatment of AF (pulmonary vein isolation, AF ablation);
2. Prior 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;[51]
12. A medical disorder, condition, or history that would impair the participant's ability to participate or complete the study.

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

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 meet 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 meet with a study recruiter (Research Assistant/ Project Manager). 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 correctly state 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 Consent 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, 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 tracking system, etc.). If a paper version is completed, then this 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 tracking 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 Forms

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. 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 the following factor that may influence outcomes with AF: (1) Health literacy (low versus higher) based on the NVS (<4 or ≥4), because of the prevalence of limited health literacy in lower income individuals, its relevance to health outcomes and disparities, and necessity for success as a patient with AF. (2) 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), Kardia 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) and Kardia applications 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 recruitment study staff will be blinded to assignment to intervention or control arm.

7.7 Relational Agent

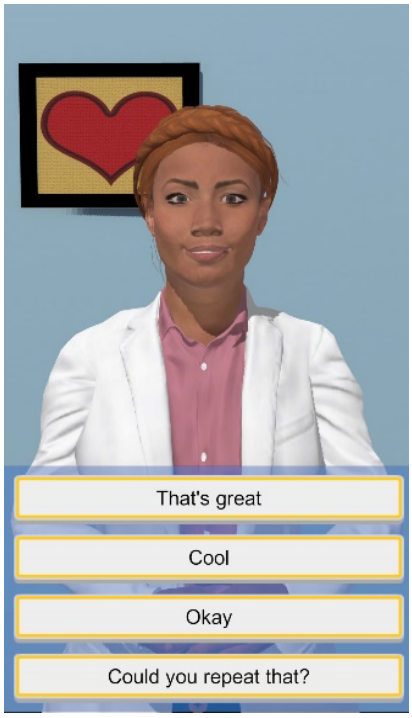


FIG 2. RELATIVE AGENT
An example of a screen shot of the relational agent and a clinical encounter menu

The relational agent is a mobile health (mHealth)[20] application for patient education monitoring and problem-solving. It has had extensive use in multiple contexts and has been developed in the lab of Dr. Timothy Bickmore, Northeastern University. Dr. Bickmore has developed over 25 relational agent -based 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.

7.8 Kardia

The AliveCor (Kardia) is an 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 smartphone (or study provided iPhone) from the App Store or Play Store. Study staff will create their Kardia account using the participant's first name and substituting their last name with "**XXXX**" (where XXXX 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

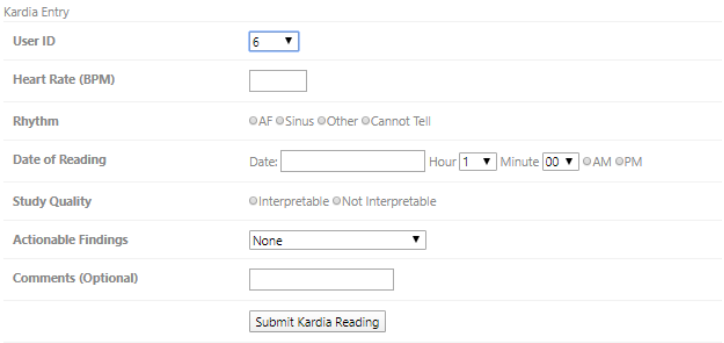


FIG 4: DATA from KARDIA

8. STUDY PROCEDURES

8.1 Assessments

We will conduct research assessments with each study subject at baseline, 4mth, 8mth and 12mth 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. We will administer our 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.

8.1.1.2 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.

8.1.11 History 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:

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

8.1.14 Medical History

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

8.1.14.1 Congestive heart failure
8.1.14.2 Hypertension
8.1.14.3 Diabetes
8.1.14.4 History of stroke or TIA
8.1.14.5 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.
8.1.14.6 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.

We will maintain relational agent and Kardia results daily on a web-based dashboard developed with the help of the Center for Clinical Trials and Data Coordination (**CCDC**). Relational agent dashboard results will consist of use statistics, reported symptoms, and adherence anticoagulation. Kardia results include date and time of use and heart rate and rhythm.

Dashboard results will be reviewed every weekday except federal holidays. Particular attention is given to the fact that this intervention does not replace or preclude usual and routine care. Hence the dashboard does not preclude urgent or emergency assessments as would be obtained were an individual not participating in this study. The informed consent documents that individuals should pursue care as they would if not participating in this study and participants are likewise instructed of this when they enter the study.

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 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). If the participant used his or her personal phone for the study, study apps will be removed. If the participant used sponsor-supplied smartphones, the devices will be returned. 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

Medical records will be reviewed to assess health care utilization (emergency visit, hospitalization, and number of days hospitalized). Medication fill data, for purposes of calculating medication possession ratio, a common measure of medication adherence, will also be extracted from the EHR and from the pharmacist(s). We will assess the EHR for incidence of adverse cardiovascular event and mortality. We 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

The study team will recruit subjects at the University of Pittsburgh Medical Center (UPMC) who have a chronic heart rhythm disease, atrial fibrillation, and are receiving anticoagulation for stroke prevention. Participants are expected to constitute a high-risk population, as they will have limited socioeconomic resources, low health literacy, and/or be racial/ethnic minorities. The study will consist of 240 adults who will be randomized to an intervention or control cohort.

The intervention cohort will receive a smartphone with a relational agent application and an 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, a Kardia device and a smartphone with the WebMD application installed. Participants will use the apps and Kardia 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 control participants will also use the Kardia to check their heart rates and rhythm. The study team will follow up on the results of the smartphone agent and/or 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 National Heart Lung Blood Institute (**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 4 individuals and chaired by Leslie McClure, PhD, MS. The remaining members of the DSMB have a combination of expertise in clinical trials, health services research, and biostatistics. 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 Dr. McClure, 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

An AE is any untoward medical occurrence, which does not necessarily have a causal relationship with the trial intervention, after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of the study intervention.

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.

All AEs will be reported with an event diagnosis (including the term and grade based on CTCAE grading), start/stop dates, action taken, any corrective measures taken, outcome, and other possible causes. For all events, the relationship to study intervention and the attrition of the event will be determined by the investigator. Attribution is an assessment of the relationship between the AE and the medical intervention. After naming and grading the event, the clinical investigator or study staff must assign an attribution to the AE using the following attribution categories:

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to the study intervention	Unrelated	The AE is clearly **NOT** related to the intervention
	Unlikely	The AE is **doubtfully related** to the intervention
Related to the study intervention	Possible	The AE **may be related** to the intervention
	Probable	The AE **is likely related** to the intervention
	Definite	The AE **is clearly related** to the intervention

For each AE, the seriousness will be determined according to the criteria given below.

Definition of serious adverse event (SAE)
An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (1–6):

1. Results in death.
2. Is life-threatening.
3. Requires inpatient hospitalization or prolongation of existing hospitalization. A planned hospitalization or prolongation of hospitalization for a pre-existing condition will not be regarded as an SAE.
4. Results in persistent or significant disability / incapacity.

5. Is a congenital anomaly / birth defect.
6. Is another medically important serious event as judged by the investigator.

The SAE form will capture information on the setting where the event occurred, the intensity (mild, moderate, severe), relevant lab results and other tests, and the concomitant medications. Study staff will also record a detailed description of the event, evaluation, assessment and any applicable treatment.

Each serious adverse event will be followed up until resolution or stabilization, by submission of updated reports to the designated person.

Relatedness of the adverse event to the research study
The study team will make a determination as to the relatedness of an AE to the intervention. AEs will be categorized as one of the following (1-6):

1. Unrelated (would have occurred regardless of the study and/or intervention)
2. Unlikely related (likely to have occurred regardless of the study and/or intervention)
3. Possibly related (may have occurred due to the study and/or intervention)
4. Probably related (likely to have occurred due to the study and/or intervention)
5. Definitely related (would not have occurred outside of the study and/or intervention)
6. Indeterminate

Unanticipated Problems (UAP)

An unanticipated problem is any incident, experience, or outcome that meets each of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The Unanticipated Problem form captures information about the date of the event and when the site became aware of the event, subject(s) affected, if the event was expected or unexpected, whether it is related to the research study, if it places the subject(s) or others at greater risk of harm, type of unanticipated problem. Study staff will also include a general description of the problem, and corrective actions taken. This form will be completed for each unique event.

Reporting of adverse events, serious adverse events and unanticipated problems
All serious adverse events will be reported to the Data Coordinating Center (DCC), which will regularly summarize their frequency and quantity. The DSMB, all investigators, and IRB will also be promptly notified in accordance with the respective policies and procedures.

The study team will learn of AE, SAE, and unanticipated problems by participant interview at the 4-, 8- and 12-month assessments; direct contact with participants during the 4-month intervention phase of the study or following; 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. We will follow guidelines set forth by the University of Pittsburgh's Institutional Review Board (**IRB**) and the Human Research Protection Office. The Center for Clinical Trials and Data Coordination, serving as the Data Coordinating Center (**DCC**) 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, as defined above);
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. In accordance with the University of Pittsburgh IRB, all internal AEs which are (1) unexpected, fatal or life-threatening, and (2) related (as per criteria above, defined by being possibly, probably, or definitely related to the study and intervention) to the relational agent and/or Kardia will be reported to the IRB within 24 hours of learning of the event. All other reportable AEs will be reported to the IRB within 10 working days 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 (possibly, probably, or definitely) to the study procedure (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. Those SAEs that meet such criteria will also be reported to the NHLBI within 7 calendar days of initial receipt of information. SAE that are (1) non-fatal or non-life-threatening, (2) unexpected, and (3) determined as related to the study procedure will be reported to the IRB and NHLBI within 15 calendar days of the receipt of information. Any unanticipated adverse effect related to the study procedure will be reported to the IRB and NHLBI within 10 working days of the receipt of information.

The project manager, co-investigators, PI, and statistician will review aggregate data on AEs and SAEs regularly. SAEs that merit reporting to the IRB and NHLBI will also be reported to the DSMB, which 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.

Data and safety monitoring for continuation, modification, or termination of participation or the clinical trial. The DSMB will regularly 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.

Expected events. Participants in this study have atrial fibrillation, a chronic heart condition associated with significant morbidity. Individuals are likely to be older age, have multiple additional conditions, and have frequent hospitalizations. The following items are categorized as expected events given their high likelihood of occurring in this population:

- Chest pain or stable angina
- New unstable angina, requiring clinical evaluation such as stress testing with or without accompanying hospitalization
- New or suspected myocardial infarction
- Cardiac catheterization of the left or right heart
- Percutaneous Coronary Intervention (PCI)
- Coronary Artery Bypass Graft (CABG)
- Mechanical complications of MI (e.g., rupture of intraventricular septum, left ventricular free wall, mitral valve papillary muscle or left ventricular aneurysm)
- Signs, symptoms or treatment suggestive of heart failure, either preserved or reduced ejection fraction
- Cardiomyopathy, i.e. new onset heart failure
- Cardiogenic shock, requiring vasopressor or circulatory support
- Transient Ischemic Attack (TIA)
- Stroke, ischemic or hemorrhagic
- Bleeding event, identified as cerebral or gastrointestinal
- Mobitz type 1 AV block
- Mobitz type 2 AV block
- Complete (3rd degree) AV block
- Right bundle branch block
- Left bundle branch block
- Bifascicular block
- Pacemaker or defibrillator implantation
- Electrophysiologic procedure (pulmonary vein isolation or other ablation electrical cardioversion)
- Admission for initiation of antiarrhythmic medication requiring in-patient monitoring (e.g., sotalol, dofetilide)
- Asystole
- Syncope
- Fall with traumatic injury (e.g., concussion, fracture)

11 Data Management and Quality Monitoring Plan

Data Management and Security to Protect Privacy. The Center for Clinical Trials and Data Coordination will serve as the DCC at the University of Pittsburgh will supervise the

data management plan for this study. The DCC will employ procedures for data management that have been established and validated by other studies. The DCC will assure high quality forms, monitor data quality, and track and link the multiple data sources. The DCC will develop data collection forms, design the database management system for data entered and for subject tracking, implement procedures for quality control, and provide statistical programming and collaborate in report writing and presentation of study results. The DCC will devise a system such that data from all sources are linked and entered using multiple checks.

DCC databases are located on secure, password-protected servers, behind the University of Pittsburgh firewalls. The web and database servers use Secure Socket Layering (**SSL**) to ensure data security and confidentiality. Servers incorporate RAID hard drives for data redundancy. A separate web server dedicated for Cold Fusion applications is also available. The servers are part of the UPMC network, only connections from users authenticated from the domain controller are accepted, thus providing a secure environment for all data. Specifically, the policies for computer systems security implemented at UPMC are as follows:

- Provide physical security of data. The server resides in the same building as the UPMC Office of Information Technology (**OIT**) servers. The lobby of the building in which the systems reside is under the security purview of the University of Pittsburgh General Services Security Office and is under surveillance. All central systems are physically secured behind two card-access doors with access to the primary door restricted to key personnel in the OIT. Access through the primary door is also protected by a keypad alarm system that is tied directly into the on-site central emergency response security control center. Written policies exist for contingencies to provide access to the room to those not explicitly authorized.

- Provide virtual security via connectivity. Internal access to all systems is done via MicroSoft Challenge Handshake Authentication Protocol. With the exception of internet provider-based services, external client access must first gain access to the internal network before connecting to the systems. This connection is initiated via a Virtual Private Network connection using Point-to-Point Tunneling Protocol or through the University's modem pool which require Kerberos authentication. All web-based mail is encrypted with high-encryption domestic SSL.

All data are protected with disaster recovery via several methods:

- Hardware redundancy: Several stages of redundancy exist at the hardware level to minimize failure: Dual-redundant power supplies exist on each disk array; hot-spare disk is configured to automatically self-heal in the event of a disk failure in the array; emergency power generators ensure a 100% electrical uptime; and uninterrupted power supplies present the systems with conditioned steady-state power.

- Data backup: Backups are completed daily over the UPMC network using both on-site and off-site disk-based backup devices.

- Data Security: All data are stored on servers that are password-protected. To protect against security breaches, data will be electronically encrypted so that only the intended recipient can decode.

Creation of analytic datasets for statistical programming. The Statistical Analyst of the data management team will be responsible for cleaning the datasets, construction of the analytical

variables, and writing the computer code to format and label each variable in the datasets. Documentation will be developed that will include data dictionaries defining the field names, location, and formats of all variables, the data collection forms, coding manuals, and documentation for computed variables and scale construction. Data will be cleaned in "batches" and cleaned batches appended to the master database. Statistical summaries will be provided.

Data collection and form development. The CCDC supports the research team in designing, piloting, and implementing data collection forms by ensuring that the data fields are unambiguous, and the systems for recording information function smoothly.

Each case report form (CRF) has been developed by the CCDC in conjunction with the clinical study team. In order to make sure that important study forms are not overlooked, CRFs will be considered across the following categories: 1) screening & baseline information; 2) 4-, 8- and 12- month follow up visits and their blinded assessments; 3) 7-, 14-, 30-, 60-, and 90- day check in calls with the participants; 4) results and adherence to the ECA and Kardia; 5) electronic health record alert and alert tracking to resolution; 6) modifications to medications and interventions specific to AF during the 12-month study participation; 7) medication possession ratio; 8) health care utilization; and 9) clinical endpoints and vital status. This approach facilitates CRF development for each of the categories and prevents particular forms from being missed.

Database tracking system. The tracking system will generate a schedule of data collection for each participant and, where applicable, automatically send reminders to the study team when a data collection visit or call is due. The study coordinator or research assistant will log into the data entry and tracking system, enter the participant's study ID, then choose the visit to be viewed; the appropriate set of forms will be generated for that participant based on the visit number. The CCDC has a primary goal to minimize missing data, so all of the study forms will have certain key fields that are required before form submission. Pop-up windows upon form submission will remind the study team that particular fields are empty and give reasons as to why incomplete data was submitted. Each CRF will be made available on the study website for review and download by study personnel at any time.

A subset of the CRFs will include the ability for the study team to electronically "sign off" on the submitted information. These CRFs include those that are a part of the screening visit, and CRFs at baseline and beyond that are deemed critical enough (i.e., concomitant medications, symptoms, adverse events, etc.). Select study personnel will have log-in credentials for a separate "PI Portal," which facilitates this process.

Data entry. Study data will be entered electronically via a password-protected Web-based data entry system. However, study team members will have paper versions of forms for manual entry in case of technical issues. The system will be created using ASP.NET programming, with the data stored using MS SQL Server. When the study team logs in and enters the participant study ID for which data are being entered, the screens generated will match the paper form(s) most recently created for that study ID. The study staff member will not be able to enter data for forms not generated for that study ID or visit. Similarly, the Web-based data entry screens will have out-of-range and other limits that will not permit the entry of inappropriate data.

Participant eligibility & randomization. The data entry process will begin during the online participant enrollment into the clinical trial. Study team personnel will generate a participant ID,

which will unlock screening forms that will be completed to assess the study inclusion and exclusion criteria detailed in the protocol. The CCDC will utilize an “eligibility checklist” which is pre-populated with information from all questions that directly relate to inclusion and exclusion criteria. By not having a separate form with checkboxes for each criterion, this will prevent any data entry errors which may result in ineligible randomizations.

Study design tracking. An important function of any data management system is its ability to track the progress of study participants through the various phases of the study. Given the richness of our cohort, it is critical to retain all participants in the study for the duration of the trial. The tracking and reporting systems are integrated within our web-based data management system. The tracking system includes programmed follow-up time periods so that the study team can ascertain which participants are due for milestone visits or contacts. In addition, we will create a calendar so that study staff can schedule follow-up visits. Study staff will be able to maneuver through the tracking system for individual participants. The CCDC team tracks hits to the tracking system to monitor how frequently study staff are using the tracking system and to monitor the overall performance of study staff members and determine individual use and concomitant effects on study follow-up, retention, and tracking system use. This enables the CCDC to partner with the study team to better coordinate study staffing to ensure recruitment and follow-up rates remain consistent. The tracking system will further permit the CCDC to generate reports to monitor study progress and for presentation at steering committee meetings. These reports will include detailed recruitment numbers, SAEs, and reports of outstanding forms.

Quality control procedures for data collection and data entry. The CCDC has several systems programmers and data managers who design and maintain the data entry/checking programs as well as maintain the databases, generate reports, and provide on-site support for the all levels of study personnel. In addition, CCDC staff generate appropriate documentation and other training materials that will be made available on the study website for data entry personnel. Being located in close proximity to the study team, the CCDC staff are able to have regular meetings to review any problems with CRF, data entry, or troubleshoot use of the website.

The CCDC institutes multiple strategies to ensure data is high quality: use of standard methods of data collection and recording, careful programming of the data management system, detailed documentation of computer operations and data editing procedures, and regular meetings with project staff to review any changes in procedure. The CCDC will verify all data, program out-of-range data checks into data entry fields and evaluate the full data process within and across forms.

A typical variable may be subjected to two kinds of range checking: impossible values (e.g., negative blood pressure) and suspicious values (e.g., SBP > 300). The former will be coded into the data entry system, restricting such values from being entered. CCDC personnel check suspicious values from the enrollment of the first participant to the data-cleaning phase, at which point logical checks will be performed, and outliers will be analyzed.

Audit logs track changes to information previously submitted and recorded on electronic forms and will be used to ensure data integrity. Information on the person responsible for the change, the date of the change, the previous entry in the data field, the new entry in the data field, and the reason for the change are recorded and displayed in the electronic forms audit trail.

Database backup. The EWI (Enterprise Web Infrastructure) employed by the CCDC is backed up with the Symantec NetBackup system. The backup images are processed through an IBM ProtectTier appliance and stored on IBM DS8870 storage arrays. All EWI servers receive daily operating system backup with a retention period of 60 days. Server content is replicated to a secondary IBM DS8870 storage array located at Posvar Hall on the main campus of the University of Pittsburgh. This protects the backup images in the event of a catastrophic event at the data center.

EWI sites with a back-end database server also receive a daily backup. All EWI database servers have a daily full backup and daily log backups. EWI database servers running MS SQL Server utilize a specialized NetBackup SQL backup agent. Any EWI database server running MySQL has a daily backup in the form of daily local dump. The exported database files are then backed up during the daily operating system backup with replication again in the Posvar Hall site on the University of Pittsburgh's main campus. The backup methods described here have been tested and demonstrated to provide comprehensive successful recovery of data.

The CCDC is compliant with FDA 21 CFR part 11 protocols. Access to data is controlled through password and authentication policies. Only approved individuals have access to data. Password policies control the length and variability of the user password selection. Audit trails are implemented to log date, time, individual, changed values, and rationale for all data changes.

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. Second, the paper format informed consents from the study will likewise be stored for seven years. We will upload the full data set to BioLINCC prior to study closure. Finally, the web-based relational app will continue to be available for public download for at least a year after study closure.

12.0 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.

13.0 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 National Institutes of Health (**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, serve on the Steering Committee, meet monthly with the study PI, and participate in the abstracts and manuscripts presenting study results.

Kaleab Abebe, PhD (Co-Investigator; Study Statistician) is an Associate Professor of Medicine, Biostatistics and Clinical and Translational Science at the University of Pittsburgh. Dr. Abebe directs the CCDC located within the Center for Research on Health Care in the Department of Medicine. Dr. Abebe's collaborative research focuses on design, conduct, and analysis of multicenter, randomized, controlled trials. As founding director of the CCDC, Dr. Abebe has contributed to the design, conduct, and analysis of multiple trials. He has an extensive portfolio of experience in the statistical design and analysis of clinical trials. Accordingly, he will provide input on clinical trial design, study implementation, and statistical analyses over the course of the trial. He will participate on the Steering Committee for the trial and will collaborate on manuscript writing and presentations at scientific meetings.

Timothy W. Bickmore, PhD (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 relational agent development, participant recruitment, and interpretation of study results. Dr. Paasche-Orlow will serve on the Steering Committee.

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. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: The Anticoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *JAMA*. 2001;285:2370-2375.
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. 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.
10. 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. PMC4338687.
11. 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.
12. Rienstra M, Lyass A, Murabito JM, Magnani JW, Lubitz SA, Massaro JM, Ellinor PT, Benjamin EJ. Reciprocal relations between physical disability, subjective health, and atrial fibrillation: The Framingham Heart Study. *Am Heart J*. 2013;166:171-178. PMC3701157.
13. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, Members AATF. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of

Cardiology/American Heart Association Task force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:e199-267. PMC4676081.
14. H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace*. 2016;18:1609-1678.
15. Riegel B, Moser DK, Buck HG, Dickson VV, Dunbar SB, Lee CS, Lennie TA, Lindenfeld J, Mitchell JE, Treat-Jacobson DJ, Webber DE. Self-care for the prevention and management of cardiovascular disease and stroke: A scientific statement for healthcare professionals from the American Heart Association. *J Am Heart Assoc*. 2017;6PMC5634314.
16. Riegel B, Jaarsma T, Stromberg A. A middle-range theory of self-care of chronic illness. *ANS*. 2012;35:194-204.
17. Lane DA, Barker RV, Lip GY. Best practice for atrial fibrillation patient education. *Curr Pharm Des*. 2015;21:533-543.
18. Hendriks JM, Vrijhoef HJ, Crijns HJ, Brunner-La Rocca HP. The effect of a nurse-led integrated chronic care approach on quality of life in patients with atrial fibrillation. *Europace*. 2014;16:491-499.
19. Stewart S, Ball J, Horowitz JD, Marwick TH, Mahadevan G, Wong C, Abhayaratna WP, Chan YK, Esterman A, Thompson DR, Scuffham PA, Carrington MJ. Standard versus Atrial Fibrillation-spEcific managemenT strategY (SAFETY) to reduce recurrent admission and prolong survival. *Lancet*. 2015;385:775-784.
20. 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.PMC3803146.
21. Wang C, Bickmore T, Bowen DJ, Norkunas T, Campion M, Cabral H, Winter M, Paasche-Orlow M. Acceptability and feasibility of a virtual counselor (VICKY) to collect family health histories. *Genet Med*. 2015;17:822-830. PMC4503525.
22. Sequeira SS, Eggermont LH, Silliman RA, Bickmore TW, Henault LE, Winter MR, Nelson K, Paasche-Orlow MK. Limited health literacy and decline in executive function in older adults. *J Health Commun*. 2013;18 Suppl 1:143-157. PMC3807941.
23. Bickmore TW, Silliman RA, Nelson K, Cheng DM, Winter M, Henault L, Paasche-Orlow MK. A randomized controlled trial of an automated exercise coach for older adults. *J Am Geriatr Soc*.2013;61:1676-1683.
24. Bickmore TW, Schulman D, Sidner C. Automated interventions for multiple health behaviors using conversational agents. *Patient Educ Couns*. 2013;92:142-148.PMC3727973.
25. Bickmore T, Schulman D, Yin L. Maintaining engagement in long-term interventions with relational agents. *Appl Artif Intell*. 2010;24:648-666. PMC3035950.

26. Bickmore TW, Mitchell SE, Jack BW, Paasche-Orlow MK, Pfeifer LM, Odonnell J. Response to a relational agent by hospital patients with depressive symptoms. *Interact Comput*. 2010;22:289-298.PMC2901553.
27. Bickmore TW, Pfeifer LM, Byron D, Forsythe S, Henault LE, Jack BW, Silliman R, Paasche-Orlow MK. Usability of conversational agents by patients with inadequate health literacy: Evidence from two clinical trials. *J Health Commun*. 2010;15 Suppl 2:197-210.
28. Puskar K, Schlenk EA, Callan J, Bickmore T, Sereika S. Relational agents as an adjunct in schizophrenia treatment. *J Psychosoc Nurs Ment Health Serv*. 2011;49:22-29.
29. Bickmore TW, Paasche-Orlow MK. The role of information technology in health literacy research. *J Health Commun*. 2012;17 Suppl 3:23-29.
30. Edwards RA, Bickmore T, Jenkins L, Foley M, Manjourides J. Use of an interactive computer agent to support breastfeeding. *Matern Child Health J*. 2013;17:1961-1968.
31. Gardiner P, Hempstead MB, Ring L, Bickmore T, Yinusa-Nyahkoon L, Tran H, Paasche-Orlow M, Damus K, Jack B. Reaching women through health information technology: The GABBY preconception care system. *Am J Health Promot*. 2013;27:eS11-20. PMC3779885.
32. King AC, Bickmore TW, Campero MI, Pruitt LA, Yin JL. Employing virtual advisors in preventive care for underserved communities: Results from the Compass Study. *J Health Commun*. 2013;18:1449-1464.
33. Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A, Burk C. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) questionnaire in patients with atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2011;4:15-25.
34. 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 e388.
35. U.S. Promis: Dynamic tools to measure health outcomes from the patient perspective. http://www.healthmeasures.net/explore-measurement-systems/promis. Accessed on May 21, 2017.
36. Jonassaint CR, Gibbs P, Belnap BH, Karp JF, Abebe KK, Rollman BL. Engagement and outcomes for a computerised cognitive-behavioural therapy intervention for anxiety and depression in African Americans. *BJPsych open*. 2017;3:1-5. PMC5204129.
37. Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M. Effect of a self-management program on patients with chronic disease. *Eff Clin Pract*. 2001;4:256-262.
38. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. *Stat Med*. 2012;31:328-340.
39. Cameron AC, Trivedi PK. *Regression analysis of count data*. Cambridge, UK ; New York, NY, USA: Cambridge University Press; 1998.
40. Greene WG. *Economic analysis*. Upper Saddle River: Prentice Hall; 2003.
41. Winkelmann R. *Econometric analysis of count data*. Berlin: Springer; 2003.
42. Horton NJ, Kleinman KP. Much ado about nothing: A comparison of missing data methods and software to fit incomplete data regression models. *Am Stat*. 2007;61:79-90. PMC1839993.
43. 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. PMC2720573.

44. Amponsah MK, Benjamin EJ, Magnani JW. Atrial fibrillation and race - a contemporary review. *Curr Cardiovasc Risk Rep*. 2013;7. PMC3815541.
45. 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. PMC3896863.
46. 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, Outcomes Registry for Better Informed Treatment for Atrial Fibrillation R. Racial/ethnic differences in atrial fibrillation symptoms, treatment patterns, and outcomes: Insights from Outcomes Registry for Better Informed Treatment for atrial fibrillation registry. *Am Heart J*. 2016;174:29-36.
47. 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. PMC4559265.
48. 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. PMC3667075.
49. 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.
50. Watson A, Bickmore T, Cange A, Kulshreshtha A, Kvedar J. An internet-based virtual coach to promote physical activity adherence in overweight adults: Randomized controlled trial. *JMIR*. 2012;14:e1.PMC3374543.
51. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro heart survey on atrial fibrillation. *Chest*. 2010;137:263-272.

APPENDIX A: **CONSENT FORM**

APPENDIX B: **MEDICAL RELEASE FORM_PHARMACY**

APPENDIX C: **MEDICAL RELEASE FORM_NON-UPMC**