

**Keep it SIMPLE: Improving Anti-Coagulation Medication Adherence  
for Patients with non-valvular atrial fibrillation**

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## **Keep it SIMPLE: Improving Anti-Coagulation Medication Adherence for Patients with non-valvular atrial fibrillation**

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## PROTOCOL SYNOPSIS

<b>Protocol Title</b>	Keep it SIMPLE: Improving Anti-Coagulation Medication Adherence for Patients with non-valvular atrial fibrillation
<b>Protocol ID</b>	PRC15-0709
<b>Study Site</b>	Parkview Research Center
<b>Study Design</b>	Interventional; Longitudinal
<b>Patient Participation</b>	Approximately six months
<b>Study Duration</b>	Approximately twenty-four months
<b>Purpose</b>	<p>This study is designed to develop patient focused strategies that improve adherence to anticoagulant medication in patients with non-valvular atrial fibrillation (AF). There are two phases to the study: Intervention Development and Intervention Trial. The intervention to be developed during Phase 1 includes tailored health education messaging delivered through a personal health record, MyChart. During the development of the intervention in Phase 1 we will use a patient-centered, iterative design process that includes interviews, prototype development and testing. One trigger for health education messaging will be failure to take, fill, or refill anticoagulant medication prescription – information obtained from an e-prescribing data feed to the electronic medical record (Surescripts) and use of a smart pill bottle (AdhereTech – HIPAA compliant, FDA-registered Class I medical device) that sends notification in real time when participants open or fail to open their pill bottle. The intervention trial in Phase 2 will be comprised of two groups, control and experimental. Both the control and experimental group will receive standard care, which includes access to MyChart. In addition to standard care, both groups will receive training on the use of MyChart and the AdhereTech smart pill bottle, and medication adherence for both groups will be monitored with Surescripts e-prescribing software and AdhereTech smart pill bottle use. The experimental group will receive the intervention: tailored health messaging delivered via MyChart pertinent to AF and oral anticoagulant use. Outcomes of this work include a novel intervention, as well as information regarding patient preferences for tailored education.</p> <p><b>Specific Aims:</b> <i>Aim 1:</i> Determine AF patient preference for content, timing, and delivery mode of tailored educational information about AF and anticoagulant therapy; <i>Aim 2:</i> Determine the impact of tailored messaging via personal health record on adherence to anti-thrombotic therapy and health outcomes in people living with AF; <i>Aim 3:</i> Determine the feasibility of measuring medication adherence with queries to electronic prescribing software and use of ‘smart’ pill bottles.</p>

## STUDY BACKGROUND

The proposed—Keep it SIMPLE, Study—will focus on promoting safe and prescribed use of anticoagulant medication in patients living with non-valvular atrial fibrillation (AF). The risk of thromboembolism (primarily stroke) is a key factor resulting in emergency room visits, re-hospitalization and death in AF patients. The non-adherence to oral anticoagulation therapy is a frequent causative factor.<sup>1</sup> There are many factors that contribute to the complexity of medication non-adherence among the AF patient population, including patient knowledge about AF and related therapies, the patient's health beliefs and concerns, patient-provider communication, and the particular reminder systems and habits that patients develop to help them consistently and correctly take medication. Therefore, education aimed at changing behavior related to medication adherence must be tailored to the patient's specific needs. Typically, physicians provide brief advice to patients and their families during their outpatient visits. However, the impact of this advice on lifestyle changes and medication compliance has been limited.<sup>2</sup> The evolution of electronic health tools (e.g. patient portals to personal health records, web-based tools, and mobile applications) has created an opportunity to provide additional tailored education and coaching to patients, which may result in increased patient engagement and improved health outcomes.

According to a report issued by the U.S. Department of Health and Human Services (HHS) Office of the National Coordinator (2014), there is potential for health information technology (IT) to improve medication adherence by supporting consumer decision-making and coordination between patients and health care providers.<sup>3</sup> The goal of this research study is to evaluate the effectiveness of electronic health tools on engagement and health literacy of patients with AF and to evaluate the resultant effect on medication adherence and health outcomes. The proposed project combines new innovations and applications to Parkview's previous work evaluating the impact of personal health records (PHRs) on patient engagement, which has yielded promising results.<sup>4,5,6,7,8</sup>

Parkview Research Center, under the direction of Dr. Michael J Mirro, recently completed a two-arm randomized, prospective 6-month pilot study to explore the impact of a PHR on medication adherence and patient engagement in patients with AF who were taking the novel oral anticoagulant medication, dabigatran. Patients in that study were provided access to a PHR, Epic's MyChart. The intervention group (N=44) received one-on-one training on MyChart use and received educational newsletters about dabigatran at 4, 6 and 10 weeks via MyChart. The control group (N=41) received the standard care and PHR access without any training or health education. A survey, comprising 54 questions pertaining to technology acceptance, medication knowledge, medication adherence, and patient activation measure (PAM), was sent to both groups at the baseline and the end of study. Medication dispensing data collected from the

pharmacy where patients filled their prescriptions were used for calculating the medication possession ratio (MPR).

Results from that study revealed that knowledge of dabigatran and MPRs increased significantly in the intervention group, but not in the control group. Self-reported medication adherence also increased by 10% in the intervention group, compared to 4% in the control group. In the proposed project, we plan to develop a more robust approach to impact medication adherence with ALL types of oral anticoagulants- vitamin K antagonists (VKAs) and novel oral anticoagulants (NOACs) - that includes tailored messaging to patients via MyChart during key transitions in care such as new AF diagnosis or changes in medication. The proposed study provides an opportunity to further explore the utilization of health information technology tools in relation to self-management of AF and adherence to anticoagulation therapy.

### **Study Hypothesis:**

Our hypothesis is that tailored messaging delivered via a personal health record will enhance patient engagement and health literacy related to atrial fibrillation and anticoagulant therapy, which in turn will improve medication compliance and health outcomes.

### **Specific Aims:**

*Aim 1:* Determine AF patient preference for content, timing, and delivery mode of tailored educational information about AF and anticoagulant therapy.

*Aim 2:* Determine the impact of tailored messaging via personal health record on adherence to anti-thrombotic therapy and health outcomes in people living with AF.

*Aim 3:* Determine the feasibility of measuring medication adherence with queries to electronic prescribing software and use of 'smart' pill bottles.

## **RATIONALE AND OBJECTIVES**

Medication safety and adherence, especially at transitions across the continuum of care, is a primary concern for healthcare providers, the U.S. Food and Drug Administration, as well as the Centers for Medicare & Medicaid Services. A key target for improvement in adherence regimens related to medication is the AF population receiving anticoagulation therapy due to the prevalence of the disease and the devastating impact of non-adherence. Estimates of the prevalence of AF in the United States ranged from ~2.7 million to 6.1 million in 2010, and AF prevalence is expected to rise to between ~5.6 and 12 million in 2050<sup>9</sup>. The risk of AF increases with age, with over 70% of cases occurring in adults over the age of 65. People with AF are twice as

likely to die and almost 5 times more likely to have a stroke than those without AF.<sup>10</sup> AF also contributes a substantial economic burden. In the US, the direct cost of treating patients with AF is reported to be about \$6 billion<sup>11</sup> and the direct cost of AF-related stroke is approximately \$8 billion each year.<sup>12</sup>

The American College of Cardiology, Heart Rhythm Society and the American Heart Association guidelines for managing patients with AF recommended oral anticoagulation (OAC) therapy to prevent thromboembolism for the majority of patients. Historically, warfarin (Coumadin) has been the gold standard for managing thromboembolic risk in AF. The use of Coumadin requires intensive follow-up of INR (international normalized ratio) blood values at the “Coumadin Clinic,” careful dosage calibration and the intense education of patients regarding dietary restrictions and dangerous drug interactions. The INR monitoring program thus becomes a surrogate marker of medication compliance. Novel oral anticoagulants such as rivaroxaban (Xarelto), apixaban (Eliquis), dabigatran (Pradaxa) and edoxaban (Savaysa) have recently emerged as important therapeutic alternatives. These medications do not have to be followed as carefully as Coumadin and have fewer side effects, drug interactions and no dietary restrictions. The transition from Coumadin to a novel anticoagulant eliminates the need for patients to go to the Coumadin clinic regularly for blood work that confirms compliance (INR test). Thus, the decreased need for close clinical follow-up and education with novel anticoagulants introduces the possibility of further diminished medication adherence. During the preparation of this proposal, Parkview Research conducted a meeting with 10 individuals living with AF and using anticoagulants to obtain their insight and input into the research plan. During this meeting, our patient partners emphasized the importance of getting information at key junctures in treatment, for example when first starting or changing anticoagulant medication.

Figure 1 presents a summary of questions generated by our patient partners. The proposed intervention will attempt to answer these questions and offer support to patients when they need it most, during transitions in therapy. The outcome may be enhanced medication safety/adherence and reduced stroke risk.

Topic	Patient Questions
Staying in therapeutic range	How do I manage INR levels? How do I balance diet and alcohol intake? How often do I need INR blood draws?
Home INR monitoring	What is home INR monitoring? When can I use home monitoring vs. going to clinic for monitoring? Who is best suited for home INR monitoring? Is this a good option for me?
Anticoagulant medication choice	What is the difference between Coumadin (warfarin) and new Novel agents? When will I get to talk about my medication choices with the doctor because my office visit is too short? How can I make an educated decision about switching from Coumadin to a Novel agent when I don't know about lab testing, reversal agents, or how much it will cost me? If I don't go in to the "Coumadin clinic" for testing anymore because I switch to a Novel agent, when will I see my health care team to ask questions between office visits? Why does ATU clinic only test Coumadin patients, can't they provide education on Novel agents in addition?
AF disease process	How does AF affect my other body systems in the long run? What changes can I make in my lifestyle to lessen AF burden on my body, mind and spirit?
Communication with healthcare provider	How can I get more time to talk with my providers about AF? How can I get quick answers to my questions?
Information and data feedback	How do I know my medicine is working? How can I track changes in my heart rhythm? Will I get too much information about how I am doing with my AF and will it make me more stressed?

**Figure 1- Challenges of oral anticoagulant therapy**

Patient engagement is an important goal for this project because it may lead to greater patient satisfaction with their care and better health outcomes in general, not only stroke prevention. Helping patients become aware of their health issues and giving them the knowledge to make the best decisions may lead to better outcomes – key for AF patients is adherence to anticoagulant therapy regimen. Medication adherence is known to be a complex and widespread problem in the US, often called “the other drug problem.” Atreja, et al (2005) grouped adherence-promoting interventions into six categories that form the mnemonic SIMPLE: S-simplify the regimen; I-impart knowledge; M-modify patient beliefs and human behavior; P-provide communication and trust; L-leave the bias; E-evaluate adherence.<sup>13</sup> We are grounding our project on this model and therefore coining the name “Keep it SIMPLE.”



## RESEARCH DESIGN AND METHODS

There will be two phases in this study. In the first phase, we will use a patient-centered approach to design and build a PHR based educational intervention based on patient preferences for content, timing and delivery mechanism. In the second phase, we will test the intervention in a six-month randomized controlled trial.

**Table 1 – High-level timeline for 24-month study**

	Specific Aims	Methods	Timeline*
<i>Phase 1 – Intervention Design and Build</i>	<i>Aim 1:</i> Determine AF patient preference for content, timing, and delivery mode of tailored educational information about AF and anticoagulant therapy	<i>Intervention design:</i> focus groups; wireframe modeling of interaction	~0-6 months
		<i>Intervention build:</i> build trigger from Surescripts data feed and AdhereTech smart pill bottle; implement educational messaging in PHR	~3-10 months
<i>Phase 2 – Intervention Trial</i>	<i>Aim 2:</i> Determine the impact of tailored messaging via personal health record on adherence to anti-thrombotic therapy and health outcomes in people living with AF.	2-arm, 6-month trial of PHR intervention (N= ~160)	~10-22 months
	<i>Aim 3:</i> Determine the feasibility of measuring medication adherence with queries to electronic prescribing software and use of 'smart' pill bottles		
<i>Dissemination</i>	Data analysis and manuscript preparation	Target both cardiology and health informatics venues	~22-24 months

\*Timeline is based on approximate (~) dates

### 1.) PHASE 1: INTERVENTION DESIGN AND BUILD

*Specific Aim 1: Determine AF patient preference for content, timing, and delivery mode of tailored educational information about AF and anticoagulant therapy.*

During the first 10 months of the study, we will recruit a diverse group of AF patients to determine preferences for information about AF and anticoagulant therapy. We will use a user-centered design approach and best practices in human-computer interactions (HCI) to determine the desired content, timing, and delivery of tailored education in the PHR. We will build out wireframe models (low fidelity messaging prototypes) based on focus group findings to perform usability testing and further refine the intervention (PHR tailored messaging) design. The intervention component will assess the impact of pushing tailored health education messages to patients through their PHR. The tailored health education will be specifically aimed at improving patient compliance with

anticoagulant therapy. The tailoring algorithm will be developed through a patient-centered, iterative design process that includes: focus groups, wireframe modeling, prototype development and testing.

### **a.) Focus Groups**

There will be four focus groups (two for patients newly diagnosed for atrial fibrillation and two for patients switching to a novel oral-anticoagulant medication), including separate discussion rooms for partners and caregivers. Each session will last approximately two hours, and each session will have approximately 4-10 patients, along with their partners, caregivers and support persons. Research staff will facilitate discussions.

This data will act to help the research team design the technology intervention best suited for patients' needs who are taking anticoagulant medication for atrial fibrillation. Through a guided presentation and discussion, patients will have the opportunity to share their experiences with atrial fibrillation and anticoagulant use. The focus groups will foster discussion related to patient perceptions of the usability of the PHR as a means to encourage medication adherence.

### ***i. Patient Selection***

- a) **Study Population**: The study population for this focus group is comprised of all adult, ambulatory PPG-Cardiology patients with non-valvular atrial fibrillation who are taking an oral anti-coagulant medication. Patients' caregiver, partner, and/or support persons will also be invited to participate in the focus group sessions. When patients are contacted, the following populations will be eligible to enroll:
  1. Both the patient and their caregiver, partner, and/or support persons
  2. The patient only
  3. The patient's caregiver, partner, and/or support persons only
- b) **Sample Size**: Focus Groups: 4 groups;  $20 \leq N \leq 120$
- c) **Inclusion/Exclusion Criteria**:

#### **Inclusion Criteria**

1. Diagnosis of Atrial Fibrillation (Paroxysmal, Persistent, Permanent)
  - focus groups 1 & 2: patients diagnosed  $\leq 6$  months
  - focus groups 3 & 4: patients diagnosed  $\geq 6$  months

2. Receiving Oral Anticoagulation (VKA or NOAC) for non-valvular AF
  - focus groups 1 & 2: on VKA or NOAC
  - focus groups 3 & 4: changed VKA to NOAC within last 6 months
3. \*Physically and Mentally capable of providing Informed Consent
4. \*Age 18 years or older
5. \*Ability to read and understand English
6. Current Patient of PPG-Cardiology

\*3, 4, and 5 must apply to caregivers, partners, and/or support persons

#### Exclusion Criteria

1. Absence of History of Atrial Fibrillation (AF)
2. \*Does not meet Inclusion Criteria
3. Anticoagulation with VKA or NOAC for reasons other than non-valvular AF
4. \*Designated as part of a vulnerable subject population that the investigator or designee identifies to have compromised autonomy related to potential study participation
5. Currently participating in another Parkview study that involves PHR use

\*Only 2 and 4 apply to caregivers, partners, and/or support persons

#### d) Enrollment:

A list of adult patients who meet inclusion criteria will be provided by the Anticoagulation Therapy Unit (ATU) Clinic and Parkview Physicians Group-Cardiology. If needed, an additional list of adult patients who meet inclusion criteria will be obtained from patient records at Parkview Physicians Group-Cardiology using Epic reporting tools. Research staff will review these patient charts to identify if they meet inclusion criteria, or if factors in the exclusion criteria are identified. This study will not affect patient standard of care. Before contacting patients, the principal investigator will leave a series of periodic voicemails for all clinical staff at Parkview Physicians Group-Cardiology to inform them of the study and ask that physicians contact the research team if they do not want any of their patients to be recruited for the study. Research staff will contact patients by telephone. Patients who are interested in participation will be mailed a copy of the informed consent to review prior to their scheduled focus group. Patients, and their participating caregiver, partner, and/or support persons as applicable, will undergo the informed consent process immediately preceding the focus group session.

## **ii. Study Design**

### **a) Quantitative Data Collection and Analysis:**

Besides age, gender, and basic demographics, we will perform detailed testing using five instruments to quantify participant characteristics; 1) the Medication Adherence Survey (MAS)<sup>15</sup>, an eight question survey that is well validated to predict medication compliance, 2) the Patient Activation Measure (PAM), a 13 question survey well-validated to measure patient engagement<sup>16</sup>, 3) the Atrial Fibrillation Knowledge Scale, an 11 item survey designed to assess AF understanding<sup>17</sup>, 4) Newest Vital Sign a six-question health literacy survey<sup>18</sup>, and 5) Altarum Consumer Engagement (ACE) Measure<sup>19</sup>, a 12 question survey validated to measure patient engagement. These five survey instruments will be incorporated into a focus group patient and participant (caregiver/partner/support persons) survey to be built out in Survey Monkey®, an on-line tool to design, collect and analyze surveys and responses. Survey Monkey enables covered entities to collect protected health information (PHI) in online surveys in a way that permits compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). SSL (Secure Sockets Layer), a protocol developed for transmitted private documents or information via the internet, creates a secure connection between a client and a server, encrypting sensitive information being transmitted through the web page. After consenting participants, we will ask them to complete demographic information and survey (Table 2).

All data will be aggregated by Parkview Research Center (PRC) and statistical analysis will be performed by PRC and the Indiana University School of Medicine, Department of Biostatistics. Additional consultants, partners, or business associates will be utilized as necessary.

### **b) Qualitative Data Collection and Analysis:**

Focus groups are used to bring together a collection of individuals and ask them their perceptions, opinions, beliefs, and attitudes towards a product, service, concept, or idea. In this project, researchers will lead group discussion by prompting participants with questions in an interactive group setting where participants are free to engage in conversation. The questions will be focused on understanding the preferred content, timing, and delivery mechanism of tailored health education aimed at understanding AF and related anticoagulant therapy.

All focus group sessions will be video recorded, with participant permission and researchers will take field notes. Investigators will review the transcribed digital recordings and field notes and perform thematic analysis to develop a codebook. All documents will be imported into NVivo, and identified by session date and time. The investigators will independently review each session's recording to identify patterns within the participants' responses, annotating the recording with relevant concepts through NVivo. Using the method of grounded theory and constant comparison<sup>20,21</sup>, the investigators will meet in a series of three or more review sessions to compare concepts, resolve discrepancies in interpretation, explore the various meanings of words, discuss emergent themes, and resolve ambiguities, until consensus is achieved and potential biases in interpretation are reconciled<sup>22</sup>. Important user themes will be built using this iterative process of reviewing and grouping concepts during the review sessions. The relevance and importance of themes will be assessed using a rating schema of frequency, convergence and intensity. Frequency represents the number of times that the topic appears in the users' discussion, and is documented using NVivo's frequency reporting feature. Convergence, the relative occurrence of the topic, will be assessed as high, medium, or low. Intensity is defined as the emotion and importance of the topic to the user, and will be assessed using a scale of high, medium or low based on a subjective analysis of the digital recording for vocal tone, pace and volume. According to grounded theory, we will continue an iterative process of review and data collection until no new concepts are discovered and content saturation is reached<sup>21</sup>. A summary of relevant themes will be compiled and used to develop low fidelity prototypes (wireframes) of the PHR intervention.

**Table 2 – Validated Survey Instrument Descriptions\***

Validated Survey Instrument	Description
System Usability Survey (SUS)	SUS is a computer self-efficacy measures questionnaire that has long been used to assess a user’s belief that they have the capability to successfully interact with a computer system. Based on social psychology, self-efficacy has been found to influence the user’s behavior related to use of the system <sup>23</sup> . Within the domain of healthcare, patients must see themselves as capable of successfully using the PHR <sup>24,25</sup> . The ten question survey asks the patient to indicate whether they are able to complete a task under a variety of conditions, such as step by step instructions, on-call user help, or initial training in getting started <sup>26</sup> .
Medication Adherence Survey (MAS)	The MAS is an eight question patient survey that provides reliable predictions of patient medication compliance <sup>15</sup> . The MAS has a strong correlation with clinical outcomes in patients with hypertension and other conditions <sup>27</sup> . Patients with greater knowledge, attitude, satisfaction and coping skills were more likely to have high medication adherence, those stressed or requiring a complex medication scheme were less likely to be adherent <sup>28</sup> .
Patient Activation Measure (PAM)	The patient activation measure (PAM) is a 13 question survey using a 4-point Likert scale. It is a robust and well-validated assessment tool developed by Hibbard and colleagues <sup>16</sup> to measure the level of patient engagement in their health. The PAM is a scale that reflects a developmental model of activation. Activation appears to involve four stages: (1) believing the patient role is important, (2) having the confidence and knowledge necessary to take action, (3) actually taking action to maintain and improve one’s health, and (4) staying the course even under stress. PAM scores are independent of traditional socio-economic and demographic such as race, income or education and instead emphasize what the patient can do to help themselves. Hibbard et al. demonstrated that coaching improves PAM scores, medication adherence and reduces re-hospitalization rates <sup>29,27</sup> .
Atrial Fibrillation Knowledge Scale	The AF Knowledge Scale is a validated tool that consists of 11 items concerning AF in general, symptom recognition. This tool was developed due to a need for a specific instrument to detect gaps in the knowledge of AF patients. The AF Knowledge Scale can be successfully used in an outpatient care setting as an important tool in the tailoring of patient education <sup>17</sup> .
Newest Vital Sign (NVS)	The NVS is a validated instrument that screens for health literacy in approximately three minutes <sup>18</sup> . Participants are given a nutrition label, and then asked six questions about it. A score of 0-1 suggests a high likelihood of limited literacy; a score of 2-3 indicates the possibility of limited literacy; a score of 4-6 indicates adequate literacy <sup>30</sup> . The NVS has been found to provide results comparable to more extensive health literacy tests <sup>31</sup> , but it is considered to be the most practical tool because it also assesses numeracy, an element of health literacy that is often not represented in other tools <sup>32</sup> .

Altarum Consumer Engagement (ACE) Measure	The Altarum Consumer Engagement (ACE) measure is a 12 question survey validated to assess a patient’s level of engagement in their health using the three domains of commitment, informed choice, and navigation. The ACE measure expands upon other validated survey instruments and broadens the measurement of engagement by including questions related to modern sources of information, such as online health resources and provider ratings. The survey serves as a reliable predictor of health status, health behaviors, medication adherence, and health resource utilization <sup>19</sup> .
Ten-Item Personality Inventory (TIPI)	The Ten-Item Personality Inventory (TIPI) measure is a 10-item measure of the Five-Factor Model. The psychometrics for the TIPI are known and reasonable. This measure provides for an assessment to be completed in less than one minute, far less than other personality measures.

\* The items from each of these survey instruments, along with demographics, will be incorporated into participant surveys to be administered during the focus groups and technology trial.

**b.) Design Survey**

The secure online program, Survey Monkey will be used to administer the survey. After prospective participants have been identified, and it is confirmed that they meet the inclusion criteria, the research team will contact individuals to participate in the survey. Potential participants will be contacted through up to three methods as applicable per patient: MyChart message, email, or letter. If individuals wish to participate, they will be instructed through MyChart, email, or letter to access the informed consent and subsequent survey through the provided secure link to Survey Monkey. Individuals who have read and agree to the informed consent online, will then be able to access the online survey. Subjects may opt out of taking the survey at any time. Recruitment and survey materials are additionally being submitted for IRB review.

Survey Monkey enables covered entities to collect protected health information (PHI) in online surveys in a way that permits compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). SSL (Secure Sockets Layer), a protocol developed for transmitted private documents or information via the internet, creates a secure connection between a client and a server, encrypting sensitive information being transmitted through the web page. SSL encryption is automatically turned on for all Survey Monkey surveys in this study. IP (Internet Protocol) address may be tracked to prevent the survey from being taken twice, but this information will not be collected by the research team. However, we will collect participant name and email address in order to send their eGiftcard compensation.

The surveys will be received by research staff and analyzed. The information will be used to develop content for an intervention aimed at enhancing medication adherence.

***i. Patient Selection***

a) Study Population: The study population for the survey is comprised of all adult, ambulatory PPG-Cardiology patients with non-valvular atrial fibrillation who are taking an oral anti-coagulant medication.

b) Sample Size:  $5 \leq N \leq 150$

c) Inclusion/Exclusion Criteria:

Inclusion Criteria

1. Diagnosis of Atrial Fibrillation (Paroxysmal, Persistent, Permanent)
2. Receiving Oral Anticoagulation (VKA or NOAC) for non-valvular AF
3. Physically and Mentally capable of providing Informed Consent
4. Age 18 years or older
5. Ability to read and understand English
6. Current Patient of PPG-Cardiology

Exclusion Criteria

1. Absence of History of Atrial Fibrillation (AF)
2. Does not meet Inclusion Criteria
3. Anticoagulation with VKA or NOAC for reasons other than non-valvular AF

d) Enrollment:

A list of adult patients who meet inclusion criteria will be provided by the Anticoagulation Therapy Unit (ATU) Clinic and Parkview Physicians Group-Cardiology. If needed, an additional list of adult patients who meet inclusion criteria will be obtained from patient records at Parkview Physicians Group-Cardiology using Epic reporting tools. Research staff will review these patient charts to identify if they meet inclusion criteria, or if factors in the exclusion criteria are identified. This study will not affect patient standard of care. Before contacting patients, approval will be obtained in Epic from each patient's primary cardiologist, as well as the principal investigator. Focus Group patients who indicated they would like to be contacted for future phases of the study will also be contacted.



Research staff will contact patients by MyChart message, email, or letter. Patients will be sent up to two reminders to participate in the survey if they wish. Patients who are interested in participation will be able to access the survey through the secure link provided in the MyChart message, email, or letter. Patients will be presented to informed consent in Survey Monkey immediately preceding the survey questions.

## ***ii. Survey Questions***

A copy of the survey questions, as they will appear in Survey Monkey, is included in the submission packet for IRB review.

## **c.) Wireframe Prototyping and Testing (Design Session)**

During the study design sessions, we will use value-based software engineering and agile development methods to link the diverse group of patients with experts in human-computer interaction (HCI) to create models of desired PHR workflow.

### ***i. Patient Selection***

- a) Study Population: The study population for the individual design sessions is comprised of all adult, ambulatory PPG-Cardiology patients with non-valvular atrial fibrillation who are taking an oral anti-coagulant medication.
- b) Sample Size:  $5 \leq N \leq 20$
- c) Inclusion/Exclusion Criteria:

#### Inclusion Criteria

1. Diagnosis of Atrial Fibrillation (Paroxysmal, Persistent, Permanent)
2. Receiving Oral Anticoagulation (VKA or NOAC) for non-valvular AF
3. Physically and Mentally capable of providing Informed Consent
4. Age 18 years or older
5. Ability to read and understand English
6. Current Patient of PPG-Cardiology

#### Exclusion Criteria

1. Absence of History of Atrial Fibrillation (AF)
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d) Enrollment:

A list of adult patients who meet inclusion criteria will be provided by the Anticoagulation Therapy Unit (ATU) Clinic and Parkview Physicians Group-Cardiology. If needed, an additional list of adult patients who meet inclusion criteria will be obtained from patient records at Parkview Physicians Group-Cardiology using Epic reporting tools. Research staff will review these patient charts to identify if they meet inclusion criteria, or if factors in the exclusion criteria are identified. This study will not affect patient standard of care. Before contacting patients, approval will be obtained in Epic from each patient's primary cardiologist, as well as the principal investigator. Patients who participated in the focus groups and/or the survey who indicated they would like to be contacted for future phases of the study will also be contacted. Research staff will contact patients by telephone. Patients who are interested in participation will be mailed a copy of the informed consent to review prior to their scheduled individual design session. Each patient will undergo the informed consent process immediately preceding their designated design session.

**ii. Study Design**

We will incorporate the use of modeling tools called “wireframes” as part of our user interface design process to generate a prototype. Wireframes are said to be a best practice when designing user interfaces and are especially helpful for interactive projects that are complex and require quick iterative changes. It allows users to see changes instantly. Using the wireframe modeling tool we can start with gray box wireframes and evolve them from low-fidelity to high-fidelity user interface design with ease. Low-fidelity modeling may be as simple as a rough sketch. The creation of PHR models using wireframes will allow us to alter the user interface, often in a matter of minutes so that users can see their suggestions immediately.

Many wireframe tools allow the incorporation of interactivity including flash animation, and front-end web technologies such as, HTML, CSS, and JavaScript. Other features of wireframe tools include: the ability for the

designer to easily drag and drop components, a presentation mode to test wireframe interactions, a revision history for tracking design iterations, access to large libraries of wireframe components, real-time collaboration with all team members through a chat option, and access to a whiteboard for drawing doodles on wireframes.

These “wireframes” help a project team collaborate more effectively since they are more abstract, using rectangles and labeling to represent content. High-fidelity “wireframes” can easily be passed along to developers for implementation because they incorporate a level of detail that matches the design of the fully functional user interface.

The wireframes, after being produced by the research staff, will be evaluated through one-on-one design sessions. This session involves priming a participant with a fictitious scenario and observing their interaction with the system to find relevant content. The objective of this exercise is to identify how successfully the proposed design meets their education and information requirements. In addition, each design session will involve completion of the survey administered in the previous phase (Design Survey) and participation in closing discussion questions. Patients who previously participated in the design survey will not need to retake the survey. The survey, closing discussion questions, and scenarios for patient use are included in the submission packet for IRB review.

Each of these individual sessions will last one to two hours and will be video recorded, with participant permission. Qualitative data from the recorded interviews may be used to iteratively adjust the wireframe models with each design session. The final wireframes will help the project team validate the planned design.

#### **d.) Intervention Build**

We will apply what we learned in the iterative design process described in parts a) and b) above to build a working prototype in a PHR, Epic’s MyChart. One trigger for health education messaging used in the intervention will be failure to take, fill, or refill anticoagulant medication prescription – information obtained from an e-prescribing data feed to the electronic medical record (Surescripts) and use of the AdhereTech smart pill bottle (HIPAA compliant, FDA-registered Class I medical device) that sends notification in real time when participants open or fail to open their pill bottle. Thus, we will build in the necessary elements in the technology to create triggers for push messaging of health information through

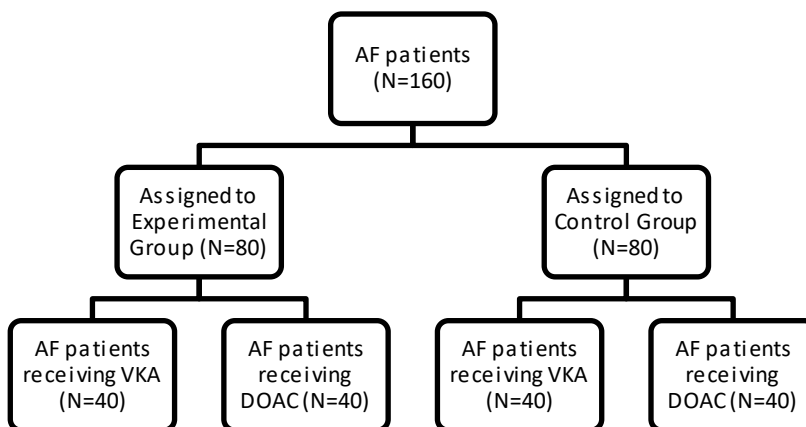
the PHR. We will perform robust testing of the intervention and make adjustments as needed.

## 2.) PHASE 2: INTERVENTION TRIAL

*Aim 2: Determine the impact of tailored messaging via personal health record on adherence to anti-thrombotic therapy and health outcomes in people living with AF.*

*Aim 3: Determine the feasibility of measuring medication adherence with queries to electronic prescribing software and use of ‘smart’ pill bottles.*

During the last 12 months of our study, we will conduct a 6-month trial of the intervention designed and built in Phase 1 of the study to examine the impact on patient engagement and medication adherence. Patients who meet inclusion criteria and agree to participate will be randomly assigned to one of two groups – Experimental or Control. The research team will alternate random assignment to experimental or control group in order to achieve equal numbers of patients receiving VKA and NOAC medication across both groups. Please see Figure 2 below, outlining the study group assignment process.



**Figure 2: Tech Trial Study Group Assignment Process**

### ***i. Patient Selection***

- a) Study Population: The study population is comprised of all adult, ambulatory PPG-Cardiology patients with non-valvular atrial fibrillation who are taking an oral anti-coagulant medication
  
- a. Sample Size: Approximately 160 patients (80 Control/80 Experimental Groups; randomized/un-blinded)

\*Based on prior data, the within-group standard deviation of the medication possession ratio (MPR) is estimated to be 10%.<sup>4,5,6,7,8</sup> MPR is considered a continuous variable and sample size calculations are based on comparing the difference in two mean MPR values. With a final sample size of 64 subjects per group completing the study, the study will have 80% power to detect a 5% difference in MPR between groups, assuming two-sided tests each conducted at a 5% significance level. To account for a 20% dropout rate, 80 subjects will be enrolled per group.

b) Inclusion/Exclusion Criteria:

Inclusion Criteria

1. Diagnosis of Atrial Fibrillation (Paroxysmal, Persistent, Permanent)
2. Receiving Oral Anticoagulation (VKA or NOAC) for non-valvular AF
3. Physically and Mentally capable of providing Informed Consent
4. Age 18 years or older
5. Access to Computer and Internet
6. Ability to read and understand English
7. Current Patient of PPG-Cardiology
8. Willing to have a MyChart account

Exclusion Criteria

1. Absence of History of Atrial Fibrillation (AF)
2. Does not meet Inclusion Criteria
3. Anticoagulation with VKA or NOAC for reasons other than non-valvular AF
4. Prescribed the anticoagulation medication Dabigatran, as this specific NOAC cannot be transferred from its original pill bottle to the study smart pill bottle
5. Unable to physically or cognitively carry out the tasks necessary for utilizing a PHR such as; blindness, loss of function of arms, cognitive impairments (per chart review) that would interfere in learning a new task
6. Designated as part of a vulnerable subject population that the investigator or designee identifies to have compromised autonomy related to potential study participation
7. Currently participating in another Parkview study that involves PHR use
8. Not willing to have a MyChart account

9. Previously participated in the study focus groups
10. Previously participated in the study design sessions

c) Enrollment:

A list of adult patients who meet inclusion criteria will be provided by the Anticoagulation Therapy Unit (ATU) Clinic and Parkview Physicians Group-Cardiology. An additional list of adult patients who meet inclusion criteria will be obtained from patient records at Parkview Physicians Group-Cardiology using Epic reporting tools. Research staff will also recruit participants during education sessions held by the Parkview Heart Institute, which have been funded by Boston Scientific. The research staff will be introduced by the Parkview Heart Institute coordinator, but will not present at any time during the education session. Attendees of the education sessions will be given an information folder already provided by the Parkview Heart Institute. The research team has permission to include a flyer (see attached flyer), that can be included in the folder, which provides a short summary about the study. The research team will also distribute recruitment flyers to individuals who may be interested in participating in the study that are in attendance at the education session. Those attendees who express an interest in participating will have their contact information recorded by the research team or will contact the Informatics Research Nurse coordinator as listed on the flyer. As with all possible participants, research staff will review patient charts to identify if they meet inclusion criteria, or if factors in the exclusion criteria are identified. This study will not affect patient standard of care. Before contacting patients, the study nurse coordinator will contact Parkview Physicians Group-Cardiology physicians to inform them of the study and receive permission to recruit their patients for the study. Eligible patients will be contacted by research staff during scheduled ambulatory care visits or contacted by telephone. Eligible patients may also be notified of the study through MyChart, email, or letter and directed to contact research staff by phone if interested in participating. Patients may decide to proceed with the informed consent process at the time of the office visit or schedule another appointment for the study. If the communication is by telephone, appointments will be made at a time convenient for the patient to undergo the informed consent process and patients will be mailed a copy of the informed consent to review prior to their scheduled appointment. Patients will undergo the informed consent process during their appointment and those who meet

inclusion/exclusion criteria, agree to participate in the study and sign the informed consent will be enrolled in the study.

## ***ii. Study Design***

### **a) Experimental Group:**

Upon enrollment in the study, patients in the experimental group will be requested to do the following for their participation in the study:

- Follow standard of care, which includes access to MyChart

#### **Separate from standard of care:**

- Receive an AdhereTech smart pill bottle to use for dispensing their anticoagulation medication at home.
- Receive training on the use of the AdhereTech smart pill bottle and commit to using in their daily routine for their anticoagulant medication
- Receive one-on-one training aimed at use of the MyChart PHR
- Use the PHR intervention: patients in this group will have the MyChart intervention designed and built in Phase 1 of this study – tailored health messaging delivered via MyChart pertinent to non-valvular atrial fibrillation and oral anticoagulation and stroke.
  - In addition to the tailored health messaging, patients will also receive periodic messages asking them to evaluate the health information they have received.
- Participate in an initial study visit, which includes the enrollment and training process above, as well as one follow up study visit and exit interview at approximately 6 months.
- Complete a patient survey at the initial study visit and follow up visit at approximately 6 months
- Submit information about their prescription history related to their anticoagulant medication for the study period
  - Patients may obtain this information from their pharmacy or print it out from their online pharmacy account. Patients will receive a letter from the Principal Investigators and a Medication dispensing record form to provide to their Pharmacist requesting anticoagulant dispensing information required for the study. The printout will be collected by the patient or a study representative with permission from the patient.

### **b) Control Group:**

Upon enrollment in the study, patients in the control group will be requested to do the following for their participation in the study:

- Receive a smart pill bottle to use for dispensing their anticoagulation medication at home.
- Receive training on the use of the smart pill bottle and commit to using in their daily routine for their anticoagulant medication
- Follow standard of care, which includes access to MyChart
- Receive one-on-one training aimed at use of the MyChart PHR
- Participate in an initial study visit, which includes the enrollment and training process above, as well as one follow up study visit and exit interview at approximately 6 months.
- Complete a patient survey at the initial study visit and follow up visit at approximately 6 months
- Submit information about their prescription history related to their anticoagulant medication for the study period
  - Patients may obtain this information from their pharmacy or print it out from their online pharmacy account. Patients will receive a letter from the Principal Investigators and a Medication dispensing record form to provide to their Pharmacist requesting anticoagulant dispensing information required for the study. The printout will be collected by the patient or a study representative with permission from the patient.
- At the conclusion of the study, participants in the control group will be sent a link to access the tailored health messaging sent to the experimental group, delivered via MyChart.

c) Quantitative Data Collection and Analysis:

Besides age, gender, and basic demographics, we will perform detailed testing using six instruments to quantify patient characteristics; 1) the System Usability Survey (SUS), a commonly used ten question evaluation tool with Likert-scale responses to identify comfort with technology<sup>14</sup>, 2) the Medication Adherence Survey (MAS)<sup>15</sup>, an eight question survey that is well validated to predict medication compliance, 3) the Patient Activation Measure (PAM), a 13 question survey well-validated to measure patient engagement<sup>16</sup>, 4) the Atrial Fibrillation Knowledge Scale, an 11 item survey designed to assess AF understanding<sup>17</sup>, 5) Newest Vital Sign a six-question health literacy survey<sup>18</sup>, 6) Altarum Consumer Engagement



(ACE) Measure<sup>19</sup>, a 12 question survey validated to measure patient engagement, and 7) Ten-Item Personality Inventory (TIPI), a ten question survey used to assess patient personality. The first six survey instruments will be incorporated into a baseline and follow-up patient survey to be built out in Survey Monkey®, an on-line tool to design, collect and analyze surveys and responses. The TIPI survey will be used only at the 6-month study follow-up visit. Survey Monkey enables covered entities to collect protected health information (PHI) in online surveys in a way that permits compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). SSL (Secure Sockets Layer), a protocol developed for transmitted private documents or information via the internet, creates a secure connection between a client and a server, encrypting sensitive information being transmitted through the web page. After consenting participants, we will ask them to complete demographic information and survey (Table 2).

Patient surveys will be comprised of questions aimed at assessing patient engagement, health literacy, and medication adherence. Patient engagement will be assessed using the validated survey instruments, the Patient Activation Measure (PAM) and the Altarum Consumer Engagement (ACE) Measure, number of logins to MyChart and secure messaging activity with provider/health coach. We will also evaluate health literacy using questions aimed at patient understanding of anticoagulant use in AF. Medication adherence will be measured using the MAS validated survey instrument developed by Morisky and patient pharmacy refill records. In an attempt to make the medication adherence data more robust, we will extract refill record data from electronic prescribing software (Surescripts) on study patients. In addition, all patients will use smart pill bottles to dispense their anticoagulation medication. These bottles will track medication adherence by the opening of the bottle cap, and will record data accordingly. The bottles will not be set up to alert patients or deliver any intervention for medication adherence.

In order to determine the exact tailored health messaging patients will receive, study staff will identify the following information in patients' electronic health records:

1. Duration of time since AF diagnosis (Approximate days, months, and/or years)
2. Current oral anticoagulant prescribed

3. Duration of time since beginning to take the above anticoagulant (Answer in approximate days, months, and/or years)
4. History of switched anticoagulant
5. If yes to above, type of anticoagulant taken before current one

Concurrent with the educational messages sent to patients through MyChart, patients will periodically be sent a short survey asking them to evaluate the health information they just received.

In addition, to measure the impact of the intervention we will collect specific health outcomes related data, PHR login frequency, and frequency of calls to the clinic. Quantitative measures of both study groups, control and experimental will be collected on both study groups, 6 months prior to beginning of study to baseline and baseline to end of 6-month trial.

- 1) Major Adverse Events: Death, Stroke, Any Embolic Event, Major Bleeding (transfusion)
- 2) Health Care Utilization: Hospitalization, ER visits, Office Visits, Calls to Office

See Table 3 for all quantitative measures, purpose and timing of collection.

All data will be aggregated by Parkview Research Center (PRC) and statistical analysis will be performed by PRC and the Indiana University School of Medicine, Department of Biostatistics. Additional consultants, partners, or business associates will be utilized as necessary.

**Table 3 – Quantitative Data Collected and Timing\***

Data Item	Type	Source	Purpose	6-mo prior to trial	Baseline	End of 6 month trial
Age	Numeric	EHR & Survey	Demographic characterization; Risk for Bleeding: HAS-BLED		√	
Gender	Numeric code	EHR & Survey	Demographic characterization		√	
Race/Ethnicity	Numeric code	EHR & Survey	Demographic characterization		√	
Insurance status	Numeric code	EHR	Demographic characterization		√	
Zip Code	Numeric code	Survey	Demographic characterization		√	

Employment status	Numeric code	Survey	Demographic characterization		√	
Yearly income	Numeric code	Survey	Demographic characterization		√	
Education level	Numeric code	Survey	Demographic characterization		√	
Household occupants	Numeric code	Survey	Demographic characterization		√	
Self-reported ability to use a computer	Numeric code	Survey	Demographic characterization		√	√
Self-reported ability to use the internet	Numeric code	Survey	Demographic characterization		√	√
Current proxy MyChart access	Numeric code	Survey	Demographic characterization		√	√
Potential future MyChart proxy access	Numeric code	Survey	Demographic characterization		√	√
Self-reported MyChart usage	Numeric code	Survey	Demographic characterization		√	√
Current anticoagulation medication	Numeric code	EHR & Survey	Demographic characterization		√	√
Marital status	Numeric code	EHR	Demographic characterization		√	
Height	Numeric	EHR	Demographic characterization		√	
Weight	Numeric	EHR	Demographic characterization		√	
BMI	Numeric	EHR	Demographic characterization		√	
Date of AF diagnosis	Numeric	EHR	Demographic characterization		√	
Type of AF	Numeric code	EHR	Demographic characterization		√	
eGFR or Creatinine Clearance	Numeric	EHR	Risk for Bleeding: HAS-BLED		√	
History of Diabetes	Y/N	EHR	Risk of Stroke: CHA <sub>2</sub> DS <sub>2</sub> _VASc		√	
History of Coronary Artery Disease	Y/N	EHR	Risk of Stroke: CHA <sub>2</sub> DS <sub>2</sub> _VASc		√	
History of Congestive Heart Failure	Y/N	EHR	Risk of Stroke: CHA <sub>2</sub> DS <sub>2</sub> _VASc		√	
History of Hypertension	Y/N	EHR	Risk for Bleeding: HAS-BLED Risk of Stroke: CHA <sub>2</sub> DS <sub>2</sub> _VASc		√	
History of stroke/ TIA/thromboembolism	Y/N	EHR	Risk for Bleeding: HAS-BLED Risk of Stroke: CHA <sub>2</sub> DS <sub>2</sub> _VASc		√	
History of MI/ PAD/aortic plaque	Y/N	EHR	Risk of Stroke: CHA <sub>2</sub> DS <sub>2</sub> _VASc		√	
Bleeding History	Y/N	EHR	Risk for Bleeding: HAS-BLED		√	
Specific Medication	Y/N	EHR	Risk for Bleeding: HAS-BLED		√	
Alcohol Use	Y/N	EHR	Risk for Bleeding: HAS-BLED		√	
Arterial embolus	Y/N	EHR	Health outcome	6 mo. – Baseline		Baseline – 6 mo.

Hemorrhage	Y/N	EHR	Health outcome	6 mo. – Baseline		Baseline – 6 mo.
Hospitalizations	Y/N	EHR	Health outcome	6 mo. – Baseline		Baseline – 6 mo.
Stroke	Y/N	EHR	Health outcome	6 mo. – Baseline		Baseline – 6 mo.
Death	Y/N	EHR	Health outcome	n/a		Baseline – 6 mo.
Calls to Anticoagulation Treatment Unit (ATU)	Numeric	ATU	Burden/ Patient Engagement	6 mo. – Baseline		Baseline – 6 mo.
Prescription Refill Frequency	Numeric	EHR	Assess medication adherence	6 mo. – Baseline		Baseline – 6 mo.
Smart Pill Bottle Use	Numeric	Report	Daily report of pill bottle opening, date/time stamped		√	√
MAS	Numeric	Survey	Assess medication adherence		√	√
PAM	Numeric	Survey	Assess patient engagement		√	√
SUS	Numeric	Survey	Computer use self-efficacy		√	√
AF Knowledge Scale	Numeric	Survey	Assesses knowledge of AF disease		√	√
New Vital Sign	Numeric	Survey	Assesses health literacy		√	√
ACE	Numeric	Survey	Assess patient engagement		√	√
TUPI	Numeric	Survey	Assess patient personality			√
PHR Login Frequency	Numeric	EHR	Assess engagement	6 mo. – Baseline		Baseline – 6 mo.
PHR webpage and video view frequency	Numeric	EHR	Assess engagement			Baseline – 6 mo.
PHR messages/phone calls to study staff	Numeric/Qualitative	EHR	Burden/ Patient Engagement			Baseline – 6 mo.
Appointments scheduled	Numeric	EHR	Assess engagement			Baseline – 6 mo.

\*See Appendix for scoring of HAS-BLED risk for bleeding and CHA<sub>2</sub>DS<sub>2</sub>\_VASc risk of stroke

d) Qualitative Data Collection and Analysis:

We will conduct semi-structured interviews at the conclusion of the 6-month study period with all participants in both the control and experimental groups. This data will act to fill the gaps that remain in survey data, as it allows for a deeper examination of particular issues with people living with AF. Participants will be asked questions in order to flesh out more detail around the usage patterns of the tested technologies, patient engagement, technology acceptance and experience with patient-provider communication.

All interviews will be audio recorded, with participant permission and researchers will take field notes. Investigators will review the transcribed digital recordings and field notes and perform thematic analysis to develop

a codebook. All documents will be imported into NVivo, and identified by session date and time. The investigators will independently review each session's recording to identify patterns within the participants' responses, annotating the recording with relevant concepts through NVivo. Using the method of grounded theory and constant comparison<sup>20,21</sup>, the investigators will meet in a series of three or more review sessions to compare concepts, resolve discrepancies in interpretation, explore the various meanings of words, discuss emergent themes, and resolve ambiguities, until consensus is achieved and potential biases in interpretation are reconciled<sup>22</sup>. Important user themes will be built using this iterative process of reviewing and grouping concepts during the review sessions. The relevance and importance of themes will be assessed using a rating schema of frequency, convergence and intensity. Frequency represents the number of times that the topic appears in the users' discussion, and is documented using NVivo's frequency reporting feature. Convergence, the relative occurrence of the topic, will be assessed as high, medium, or low. Intensity is defined as the emotion and importance of the topic to the user, and will be assessed using a scale of high, medium or low based on a subjective analysis of the digital recording for vocal tone, pace and volume. According to grounded theory, we will continue an iterative process of review and data collection until no new concepts are discovered and content saturation is reached<sup>21</sup>. A summary of relevant themes will be compiled and used to further describe the impact of the intervention.

**Table 4 – Qualitative Data Collected and Purpose**

Data Item	Type	Source	Purpose
Lifestyle challenges with AF	Narrative	Patient Interviews	Define needs for intervention Cover gaps in quantitative survey data related to health literacy
Barriers to medication adherence	Narrative	Patient Interviews	Define needs for intervention Cover gaps in quantitative survey data related to medication adherence
Concerns with anticoagulant use	Narrative	Patient Interviews	Define needs for intervention Cover gaps in quantitative survey data related to health literacy
Educational needs for AF	Narrative	Patient Interviews	Define needs for intervention Cover gaps in quantitative survey data related to health literacy
Experience with tested technologies	Narrative	Patient Interviews	Cover gaps in quantitative survey data related to Technology Acceptance

Barriers to use of tested technologies	Narrative	Patient Interviews	Cover gaps in quantitative survey data related to Technology Acceptance
Suggestions for change in tested technologies	Narrative	Patient Interviews	Cover gaps in quantitative survey data related to medication adherence
Usage patterns of patient portal	Narrative	Patient Interviews	Cover gaps in quantitative survey data - patient engagement
Experience with patient-provider communication	Narrative	Patient Interviews	Define needs for intervention Cover gaps in quantitative survey data - patient engagement

e) Intervention:

The study intervention was developed based upon findings from the first phase of the study. The intervention entails sending tailored health educational messaging through MyChart. In order to tailor the health education per patient, an algorithm was developed from the phase 1 findings to determine what messages each patient will receive based on their specific needs. The algorithm was created based on patients' length of AF diagnosis, length of time on current anticoagulant medication, type of anticoagulant medication, and history of past anticoagulant medication.

During enrollment, patients will be instructed to contact study staff if their anticoagulant medication is changed or permanently discontinued at any point during the study. If their anticoagulant medication is permanently discontinued, patients will be instructed to stay in the study even while they are not taking their anticoagulant. Sometimes patients' anticoagulation therapy is temporarily discontinued for surgery or other health reasons. In order to maximize patient safety when these temporary holds on medications occur, tailored messages related to medication administration and compliance will include a disclaimer that if their medication has been stopped then this information is supplementary and they should follow their doctor's instructions first and foremost.

Concurrent with the educational messages sent to patients through MyChart, patients will periodically be sent a short survey asking them to evaluate the health information they just received. These questions will enable patients to evaluate the content, timing and delivery format of the interventional messaging. The survey will be administered through Survey Monkey, and the MyChart message will contain a secure link to access the survey.

**ETHICAL CONCERNS**

## **CONSENT PROCESS AND DOCUMENTATION**

Informed consent will be obtained from patients before any study activities commence.

## **CONFIDENTIALITY PROTECTION**

Data collected through chart review will be coded with the key kept in a separate location. Any data stored electronically will be password protected, encrypted, stored on a secure server and will be kept in an office with limited access. Any paper files will be kept in an office with limited access.

## **SUBJECT WITHDRAWAL**

Patients may withdraw from the study at any time. If funding for this study should be stopped early patients will be notified by telephone. If a patient elects to withdraw, only data collected from enrollment to withdrawal date will be utilized.

## **DATA SAFETY AND MONITORING BOARD**

There will be no Data Safety Monitoring Board (DSMB) for this minimal risk and small sample size study.

## **ALTERNATIVES**

Patients may elect not to participate in the study.

## **RISK ANALYSIS**

Potential risks (adverse effects) to subjects:

- Patients may feel uncomfortable answering questions on the survey(s) or interview(s).
- Possible risk of breach of confidentiality of personal and/or health information.
- Patients may feel anxious or stressed upon receiving push messaging through their PHR if they have difficulty understanding it.

Precautions taken to minimize risk:

Patients will be informed that they can decline to answer any questions at any time. All data will be stored in a password protected electronic format. Collection of Protected Health Information (PHI) will be limited to the amount necessary to achieve study aims. Data will be accessible to the study supporter (Janssen Scientific Affairs), Parkview Research Center study personnel as well as PRC's consultants, partners, and/or business associates who are directly involved in this study. Analog data will be stored in

designated areas with limited access. Computers/electronic files will be password protected. All data will be encrypted during electronic transmission.

Patients will be advised to contact the study doctor or the study coordinator to have their questions and concerns addressed regarding the condition-specific information provided through their PHR.

#### Management of Safety Data:

This study has been designated as an interventional study. Janssen requirements for Investigator-Initiated Study (IIS) interventional studies are all adverse events regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event will be reported, once the subject's signed and dated Informed Consent Form is obtained until the subject has completed participation in the study and for 30 days after the last dose of study drug. Though this study is not classified as a clinical drug trial, adverse events will be reported to Janssen, the supporter of this study, as some study patients may be taking a medication developed by Janssen Pharmaceuticals, Xarelto (rivaroxaban). Please see appendix for a full description of adverse events and reporting to Janssen Scientific Affairs.

#### **BENEFIT ANALYSIS**

While this project may not be of direct benefit to patients, the information that they provide may improve assistive measures of medication adherence and will contribute to increasing the collective understanding of medication adherence and the use of information technology to improve patient engagement and health literacy.

#### **COST TO PATIENTS**

There will be no cost to patients.

#### **PATIENT COMPENSATION**

To reimburse patients for their time, effort, and travel expenses they will receive \$50 upon completion of the baseline visit and \$50 upon completion of the follow up visit. If patients are requested to and agree to participate in the focus groups, the patient and their partner or caregiver will each receive an additional \$40. If patients are requested to and agree to participate in the design phase session for prototype testing, they will receive an additional \$40. All patients and participants will receive payment on a ClinCard, a secure reloadable debit card specifically used for compensation in research studies. For the design survey only, patients who are requested to and agree to participate in the design survey will receive a \$20 amazon eGiftcard sent to their email.



For the design survey only, patients who are requested to and agree to participate in the design survey will receive a \$20 amazon eGiftcard sent to their email. If patients do not have a valid email address, they will be compensated with a \$20 ClinCard or prepaid credit card.

### **SHARING OF RESULTS**

No individual results will be shared with patients/providers. Results from this study are planned to be submitted to scholarly/scientific journals for publication and shared at scientific conferences. No patients/providers will be identified in these forums.

Results may be shared with consultants, partners, or business associates who are directly involved in this study.

Survey information and patient usage patterns from this study will be aggregated and analyzed and reported in written reports (including publications) and presentations.

### **FINANCIAL SOURCES**

This study is being made possible through a grant from Janssen Scientific Affairs, LLC.

### **CONFLICT OF INTEREST**

There are no known conflicts of interest. All financial and other relationships will be reported to the PH IRB per the IRB policy.

### **SIGNATURE LINE**

My name typed below shall have the same force and effect and is as legally binding as my written signature.

Michael Mirro, MD  
Co-Sponsor-Investigator

11/30/2017  
Date

Tammy Toscos, PhD  
Co-Sponsor-Investigator

11/30/2017  
Date

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## APPENDIX

### i. Quantitative Data—Risk Factor Scoring

**Table 10- CHA<sub>2</sub>DS<sub>2</sub>-VASc Stroke Risk Score**

Risk factor-based approach expressed as a point based scoring system, with the acronym CHA <sub>2</sub> DS <sub>2</sub> -VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/systemic embolism	2
Vascular disease*	1
Age 65-74	1
Sex category (i.e. female sex)	1

<b>Maximum score</b>	<b>9</b>
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\* Myocardial infarction, complex aortic plaque and peripheral artery disease (PAD)

**Table 11- HAS-BLED Score**

Risk Score to Predict Bleeding in Anticoagulated Patients with Atrial Fibrillation	
<b>Risk factor</b>	<b>Score</b>
Hypertension (>160 mmHG systolic)	1
Abnormal renal or hepatic function	1-2
Stroke	1
Bleeding or history of anemia	1
Labile INR (TTR <60%)	1
Elderly (age >75 years)	1
Drugs (antiplatelet, NSAID) or alcohol	1-2
<b>Maximum score</b>	<b>9</b>

\* High risk total score ≥ 4; Moderate risk total score 2-3; Low risk total score 0-1

## ii. Management of Safety Data

For the purposes of this study, the Janssen medicinal product is:

**Xarelto (rivaroxaban)**

### Definitions

#### **Adverse Event (AE)**

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

### **Adverse Events of Special Interest**

Adverse events of special interest are events that Janssen Scientific Affairs is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Suspected severe toxic effect on the bone marrow, such as severe thrombocytopenia (platelet count less than 50,000/ $\mu$ L), severe neutropenia (white blood cell count less than 500/ $\mu$ L), pancytopenia, aplastic anemia
- Suspected severe hypersensitivity reaction (eg, anaphylaxis, angioedema, severe urticaria, bronchospasm, etc.)
- Severe skin reactions such as Stevens-Johnson Syndrome
- Suspected severe liver injury

### **Individual Case Safety Report (ICSR)**

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

### **1.1. Product Quality Complaint (PQC)**

A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules

- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

## 1.2. Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening  
(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important\*

\*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

### **NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.**

#### **Hospitalization**

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study

#### **Life-Threatening Conditions**

The cause of death of a subject in a study within 30 days of the last dose of study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

### **Unlisted (Unexpected) Adverse Event/Reference Safety Information**

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the



expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

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### **Special Reporting Situations**

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs **within 24 hours of becoming aware of the event.**

### **Pregnancy**

All initial reports of pregnancy must be reported to Janssen Scientific Affairs by the Sponsor Investigator **within 24 hours of becoming aware of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the Sponsor Investigator **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required

### **Maintenance of Safety Information:**

All safety data should be maintained in a clinical database in a retrievable format. The Institution and Sponsor Investigator shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs's request.

## **Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to Janssen Scientific Affairs**

All adverse events and special situations whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

### **SAEs and Special Reporting Situations**

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The Sponsor Investigator will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs in accordance with the Transmission Methods noted below, in English **within 24-hours of becoming aware of the event(s).**

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the Sponsor Investigator, **within 24 hours becoming aware,** to Janssen Scientific Affairs using Janssen Scientific Affairs' Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE or special situation is required.

- The Sponsor Investigator is responsible for ensuring that these cases are complete and if not, are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.
- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs using a transmission method noted below **within 24 hours of such report or correspondence being sent to applicable health authorities.**

### **Non-Serious AEs**

All non-serious adverse events should be reported to Janssen Scientific Affairs according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

### **PQC Reporting**

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs by the Sponsor Investigator **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the Sponsor Investigator must report the PQC to Janssen Scientific Affairs according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs.

### **Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products**

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, the Sponsor Investigator should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

### **Transmission Methods:**

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by Janssen Scientific Affairs.

Due to the nature of this study, Janssen Scientific Affairs will not be providing to the Sponsor Investigator IND safety reports for the Study Product.