Study Protocol

Smartwatch Monitoring for Atrial Fibrillation After Stroke

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PULSEWATCH INVESTIGATOR STUDY PLAN

1) Study Title

Pulsewatch: Smartwatch Monitoring for Atrial Fibrillation After Stroke

2) IRB Review History*

The application has never been submitted for review by an external IRB. NHLBI R01HL13773401A1 from the NIH is funding this project.

3) Principal Investigator

Timothy Fitzgibbons, M.D. PhD.

4) Objectives*

The objectives of this project are to develop a mobile device application with providers and patients that is both usable and accurate. The mobile device application will collect and extract RR interval data and use real-time algorithms for accurate detection of atrial fibrillation (AF) from mobile devices, including a smartwatch. Our central hypothesis is that a wrist-based wearable paired with a smartphone application will detect paroxysmal AF (pAF) with high sensitivity and specificity when compared to conventional cardiac monitors, and will be found acceptable by stroke patients and their providers. To accomplish this goal, our study will have two phases, a developmental phase and a testing phase. The overall objective will be accomplished by testing our central hypothesis after achieving the following specific aims:

Part I (Aim 1):

-To develop a robust and comprehensive mobile device application for analysis of heart rate interval series followed by real-time detection of paroxysmal AF and atrial flutter using our previously developed AF detection algorithm using smartwatch.

-To increase the accuracy and acceptability of our smartwatch-based pAF detection technology by involving older stroke patients and their providers in the design of the application.

Part II (Aims 2-3):

-To evaluate the performance of a smartwatch for pAF detection in stroke patients by examining over 14 days the accuracy of pAF detection from Pulsewatch vs. a state-of-the-art cardiac monitoring device.

-To evaluate rates of adherence and factors associated with successful longer-term smartwatch use among 30 randomly selected stroke patients enrolled in our 14-day validation study. These randomly selected participants will be asked to continue to use the smartwatch/phone dyad for an additional 30 days. We will explore the impact of smartwatch use over 30 days on patientreported quality of life, anxiety, and self-efficacy compared to 30 usual-care stroke patients.

Learnings from these new objectives will support our future goal to extend monitoring periods to many months or years, surpassing the capabilities of event monitors.

5) Background*

Atrial Fibrillation (AF) is the most common sustained dysrhythmia worldwide. Although new AF treatment strategies have emerged over the last decade, a major challenge facing clinicians and

researchers is the paroxysmal, often short-lived, and frequently asymptomatic nature of AF. Given that paroxysmal and asymptomatic AF is a growing clinical and public health problem, better, less expensive, and more readily available AF detection technologies are needed. There is, therefore, a pressing need to develop methods for readily-accessible monitoring devices powered by accurate AF detection algorithm in order to improve patient care and reduce healthcare costs associated with treating these arrhythmias and their complications.

Novel technologies for AF detection have important clinical and research applications for AF screening and monitoring. As was emphasized by a recent National Heart, Lung and Blood Institute (NHLBI) expert panel, there is a pressing need to develop methods for accurate AF detection and easily accessible monitoring devices. To this end, we have previously developed a sensitive, real-time realizable algorithm for accurate AF detection using commercially available, clinically applicable electrocardiographic recordings. Our AF algorithm has been tested using the MIT-BIH AF database and Holter recordings, shown to be accurate, and is now commercially available in a new Holter monitor from Scottcare Corporation. We have also made improvements to the algorithm so that it can detect AF episode that is as short as 12 beats. Further, we have recently developed a software application to measure heart interval series, which can be used to detect AF in real time from pulse plethysmographic (PPG) devices. Given the ever-growing popularity of smartphones and smartwatches, our approach to AF detection using a mobile device will give patients as well as healthcare providers the opportunity to monitor these arrhythmias under a wide variety of conditions outside of the physician's office and outside of the patient's home.

Because our approach uses only standard smart device hardware (e.g., iPhone or Samsung watch), it is cost-effective, thereby leading to better acceptance and use by patients. Our mobile health for AF detection platform has the potential to markedly change the traditional delivery of healthcare, allowing for more frequent, rapid, and patient-directed AF detection. We will test the acceptability and accuracy of our smartwatch-app dyad using smart devices (a smartphone and smartwatch) to be collected from recruited stroke or transient ischemic attack survivors at risk for AF. We believe this research will result in rapid translation into innovative AF detection solutions, leading to more effective monitoring and diagnosis of these common arrhythmias. Finally, the proposed work has the potential to significantly reduce healthcare costs and enhance patient care by accurately and rapidly establishing the diagnosis of AF in at-risk groups, thereby providing clinicians with an opportunity to prevent secondary complications of these life-threatening arrhythmias.

Stroke survivors require cardiac monitoring for AF, the single greatest risk factor for stroke: Current American Stroke Association stroke management guidelines recommend: "For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈7-14 days) for AF is reasonable" and recommended. This is because AF is the primary cause of ~15% of all strokes. Moreover, patients with AF, if not treated with anticoagulation therapies, tend to have larger strokes that lead to significant disability. One in 4 patients leaves the hospital without a cause of their stroke identified (cryptogenic strokes). Of the 200,000 American patients diagnosed with cryptogenic stroke yearly, 1 in 5 has paroxysmal AF identified if long-term post-discharge cardiac monitoring is used. Unfortunately, traditional in–hospital monitoring following stroke identifies AF in only ≈5% of cases and longer-term monitoring, although effective, is rarely used as it presently

necessitates the implantation of an expensive invasive device (e.g., Medtronic LinQ monitor or pacemaker).

Most existing smartphone apps can detect heart rate, but they cannot detect cardiac rhythm. AF detection algorithms used in cardiac devices and monitors are rudimentary and require the use of electrodes or invasive devices implanted underneath a patient's skin. AliveCor - a smartphone-based arrhythmia detection platform - pairs ECG electrodes with a smartphone running a proprietary app, enabling single-lead ECG and intermittent pAF monitoring. No existing algorithm for AF detection uses the combination of passive monitoring, pattern recognition, computational speed, and robust noise cancellation routines our solution employs. Additionally, although there are several smartwatches and wearables, including those from Apple, Philips, and Fitbit, that are capable of heart rate monitoring, the Samsung platform offers 3 unique advantages: 1) provides researchers with access to a secure data management system designed for research (Artikcloud), 2) allows for independent development of opensource applications, 3) has a smartwatch capable of out-of-the-box pulse monitoring.

In our new "Pulsewatch study," we propose to hone our existing smartphone app to work with a smartwatch in concert and in a manner that is accessible and usable by elders with, or at risk for, stroke with input from expert providers and patients. The app will use prompts to promote adherence to daily use of the smartwatch during the monitoring period and will prompt participants to perform a pulse check if they experience a symptom of AF.

6. Inclusion/Exclusion Criteria

Part I: Design/Development of the app-smartwatch dyad

Patient (and Caregiver) Focus Groups and Hack-a-thon (Part 1):
Inclusion: For patients: history of TIA or stroke, presenting at the UMass Memorial Medical Center (UMMMC) inpatient service or ambulatory clinic (neurology clinics and cardiovascular clinics included), age ≥ 50 years. For patient caregivers: history of caring for a family member or loved one with the inclusion criteria listed above in the last five years. For both patients and patient caregivers: able to sign informed consent, and willing to participate in a focus group and/or Hack-a-thon.

Exclusion: For both patients and patient caregivers: serious physical illness (e.g., unable to interact with a smart device, or communicate verbally or via written text) that would interfere with study participation, lacking capacity to sign informed consent, unable to read and write in English, plans to move from the area during the study period, unwilling to complete all study procedures, including attending a focus groups and/or Hack-a-thon.

Provider Focus Groups and Hack-a-thon for Part 1:
Inclusion: medical provider (i.e., cardiology fellow or neurology resident, attending cardiologist, attending neurologist, stroke or cardiology nurse practitioner) at UMMMC, >3 years of experience providing care to stroke or TIA patients, willingness to complete informed consent, and willingness to participate in a focus group and/or Hack-a-thon.

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Part II: Study of the app-smartwatch dyad

Inclusion: History of TIA or stroke, presenting to the inpatient UMMMC neurology service or ambulatory clinic (neurology clinic or cardiovascular medicine clinic/monitoring station), age ≥ 50 years, capable of signing an informed consent, willing and capable of using Pulsewatch (smartwatch and smartphone app) daily for up to 44 days and returning to UMMMC for up to two study visits.

Exclusion: Major contraindication to anticoagulation treatment (i.e., major hemorrhagic stroke). Plans to move out of the area over the 44-day follow-up period. Unable to read or speak English. Unable to sign consent. Unable or unwilling to return for potential study visits (up to two over a 44-day study period).

Major contraindication to anticoagulation treatment is an exclusion due to the goal of this study, which is to help prevent secondary stroke; anticoagulation is a mainstay treatment for these patients. Therefore, if patients are unable to receive anticoagulation treatment, they are not in the ideal target population for this study.

There are no known skin conditions that should exclude an individual from participating.

Special Populations:
- Adults unable to consent - Will not be recruited for this study.
- Individuals who are not yet adults - Will not be recruited for this study.
- Pregnant women - Will not be recruited for this study.
- Prisoners - Will not be recruited for this study

If we struggle to enroll a sufficient number of participants using the campus and clinics outlined above, we will recruit at the stroke treatment centers at UMass Memorial - Health Alliance Hospital in Leominster, MA, and at UMass Memorial - Marlborough Hospital in Marlborough, MA. The inclusion/exclusion criteria will otherwise remain the same.

7. Study-Wide Number of Subjects*

Not a multi-site study.

8. Study-Wide Recruitment Methods*

Not a multi-site study

9. Study Timelines*

The first year to 1.5 years of the study will be focused on achieving Aim I (**Part I – design of the application**). Focus groups will be scheduled on a rolling basis over Year 1 and will be strongly influenced by the coordinator and room availability, as well as participant preference. The Hacka-thon will also be scheduled at or around the end of Year 1 of the study (Spring 2019). Participants will be advised of when the event will be held.

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Enrollment for Aims 2-3 (**Part II**) will begin in Year 2 and will run for 3 years. At enrollment, participants will be asked to use a 14-day cardiac monitor and return for a study visit to evaluate device usability and accuracy. Thereafter, we will ask a randomly selected subsample (N = 30) to continue to use the device for an additional 30 days for a total of 44 days. We will hold additional semi-structured focus groups for participants who used the Pulsewatch device for 14 or 44 days.

The Pulsewatch study will be conducted over a 4-year period; see table below.

Study Year	**1**				**2**				**3**				**4**			
Quarter	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*4*
DEVELOPMENT/ENHANCEMENT (Aim 1)																
Formative patient focus groups & provider interviews	■	■														
Analysis of formative qualitative data		■	■	■												
"Hack-a-thon" Stakeholder-Agile Team Meeting				■												
Refine & Integrate AF, skin contact, & MNA algorithms	■	■	■	■	■											
EVALUATION/DEPLOYMENT (Aims 2 and 3)																
Smartwatch deployed in stroke population						■	■	■	■	■	■	■	■	■	■	■
Follow-up interviews/focus group assessment of app						■	■	■	■	■	■	■	■	■	■	■
Data analysis														■	■	■

10. Study Endpoints*

Not only will we achieve our central hypothesis with our aims, but we will be able to complete the following endpoints as well:

Part I:

- Using focus groups, we will gain feedback on the:
    - App prototype and system as a whole ○ Role of caregivers in technology use ○ Barriers and facilitators of use ○ Preferences and usability of features ○ Enhancements to text and ambient messaging ○ Communication system design
    - Provider preferences regarding notification criteria and format ○ Potential implementation settings
    - Information display, graphical images, and message content

- Hack-a-thon endpoints will ensure developers:

- Hear patient and provider needs
- Obtain feedback on information display, graphical images, and message content

Part II:

- Quantitative Endpoints: We will evaluate the performance of the application for detection of atrial fibrillation compared to a gold-standard ECG monitor. We will also evaluate adherence to the system and factors associated with adherence.
- Qualitative Interview Endpoint: Impact of app use on quality of life, anxiety, and selfactivation (using our questionnaire at baseline and at follow-up). This information will be obtained from study questionnaires administered at enrollment and after study completion, as well as from focus groups convened with participants after they use the system.

11. Procedures Involved*

Focus groups (Parts 1 and 2)

Focus groups will be used to help inform the app development and will include patients, patient caregivers, and provider participants. Focus groups with patients and patient caregivers will occur together, and provider focus groups will be conducted separately. Focus groups will last for approximately 60 minutes. Qualitative data analysis will generate aggregated preferences and recommendations about smartphone application message components, user interface, reporting, alerts, and watch functions. Focus group/interview analyses will inform the Hack-athon and finalize the Pulsewatch design.

All participants (patients, caregivers, and providers) will be told by the study team that their feedback is appreciated and if they feel uncomfortable at any time of the focus group, they have the right to refuse to answer any question(s) and the right to opt-out of the study at any time.

Part I: Semi-structured and open-ended agendas for the focus groups and/or provider interviews have been written and are submitted as part of our application packet. Discussions will be audio-recorded and transcribed, protecting confidentiality by replacing participants' names with study IDs. Focus groups will begin with a broad description of the Pulsewatch system (including smartphone app and watch), its purpose, and general functionality. Each participant will be given a smartwatch and smartphone programmed with the Pulsewatch app and AliveCor ECG app and will be asked to use them during the focus group. In keeping with contemporary user-centric app design processes,[80,81] facilitators will interact with participants as they use the smartwatch and smartphone app. After users have time to wear the watch, perform an ECG, review their data, and use the annotator, we will invite them to ask open-ended questions to explore elements such as the following: the layout of the result and summary screens, including the graphical representation of heart rate and rhythm (e.g., bar graph, slider, stoplight, faces); alert and adherence prompts, including the number of acceptable prompts that Pulsewatch can deliver per day; opinions about personalized intervention messages (e.g., "Mr. Jones, you've not checked your ECG"); and their preferred timing.

Provider interviews will also explore what data outputs the clinicians consider ideal, along with when and how often they would want to receive them. We will conduct up to 6 focus groups with participants and up to 2 focus groups with providers as part of Part I over a 6-month period, then

will pause to review the data. If there is strong consensus or saturation on key areas, we will stop.

Hack-a-thon (Part 1):

The PI (Timothy Fitzgibbons, MD), Co-Is, 4 participants,4 provider champions, and computer programmers and engineers will meet at the University of Massachusetts Medical School (UMMS) in a conference room to create the final Pulsewatch technology to be deployed in Aims 2 and 3. Modeled on "Hack-a-thons" in the software engineering industry, we will drive innovation by creating team synergy and accelerating product development. This meeting will likely occur in the Albert Sherman Center 7th floor conference room. Patient participants will receive parking vouchers and compensation. Providers will not be compensated. Light refreshments will be provided for all. The meeting will take place over a single day (8-hours) to accommodate the busy schedules of providers and participants. After the Hack-a-thon, the study team will meet to review and encode changes to the application.

The purpose of the Hack-a-thon meeting is to optimize the interactivity and usability of Pulsewatch, guided by information gleaned from focus groups. Using this format, end users (providers and patients) can suggest changes, and programmers will make modifications in realtime. Using a combination of focus groups and agile programming is an innovative as well as sound approach to designing apps. This event will be a critical aspect for Aims 2 and 3 to help develop the interface and management of the app for patients to use. At the Hack-a-thon, participants will be asked to use a prototype of the Pulsewatch app and the system, and then provide feedback on what they think of the system. Programmers will make modifications to the application in real time. While programmers are making those modifications, participants may take a break during the Hack-a-thon, and then come back at a later time during the event to see the final product.

The individuals who will be invited to this Hack-a-thon event will be participants and providers from the focus groups. At the focus groups, we will provide a fact sheet about the day-long Hack-a-thon and a contact sheet for people who may be interested in being invited. We will explain that they may accept or decline the invitation. (Please see Fact Sheet: Patient Hack-athon in our eIRB submission). Study staff will follow-up with interested participants and providers by telephone or email. Participants will have the option to opt-out or confirm their attendance at the Hack-a-thon.

Part II, Trial Phase- The trial phase of the study will occur after the design and development of the Pulsewatch system (app and watch algorithms) is complete (Part I). Participants will be randomized into either the intervention or control arm of the study. The control participants will wear a gold standard Holter/patch but will not be offered use of the Pulsewatch system. Please view visual Diagram 1a for an overview of the 14-day participant process.

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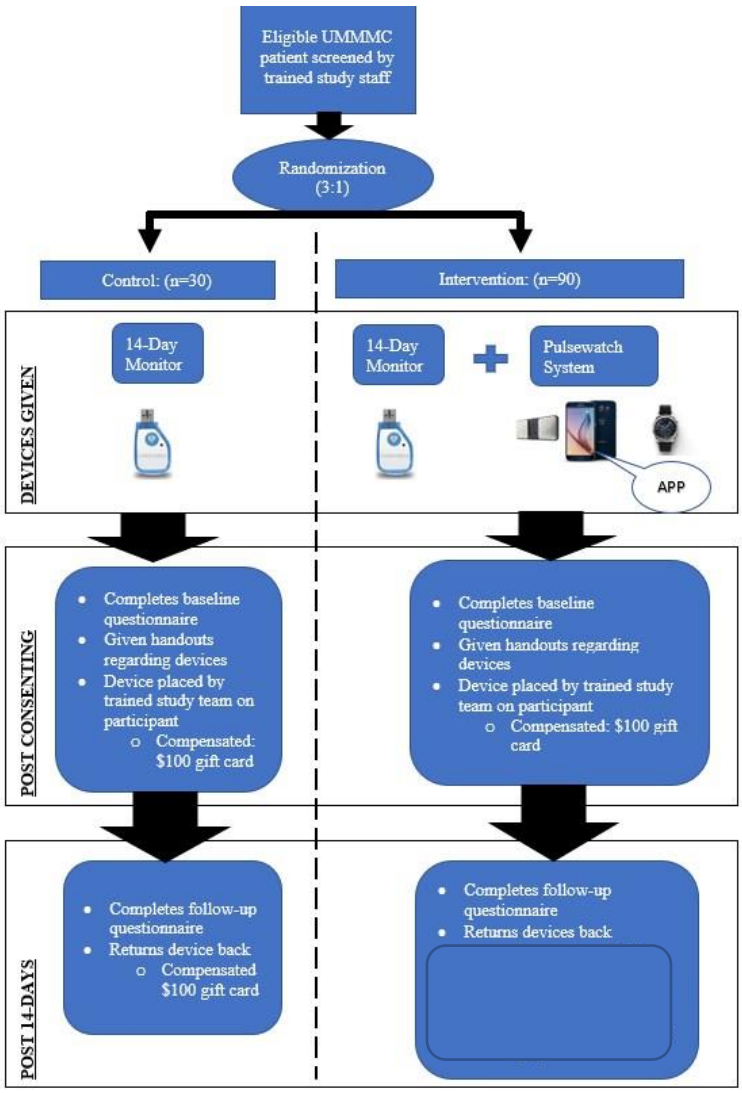

Diagram 1a. Participant process of trial phase.

Part II:

Participants in the control group will be given a gold-standard extended Holter/patch monitor before being discharged from the hospital. A 14-day extended Holter/patch monitor, specifically the CardioKey extended Holter monitor, is a mobile system that automatically captures and transmits irregular heartbeat data. This device goes right over a participant's heart on their skin. Each heartbeat data is transmitted wirelessly to the monitor where it is analyzed and automatically sent for review to a physician. This patch device will allow participants to go home with a continuous AF monitoring method without the hassle of carrying around a bulky Holter device. Our PI has already worked with similar devices in the past and has built a relationship with the study team to ensure proper care and transmission of the data. The device will be placed on the participant at hospital discharge. There is little risk to the participant from this device, which is widely used technology. The major risk with this device is participant discomfort or skin irritation. Participants will be given a number to contact in the event they have discomfort in the 14 days of using the device. Participants will be given a handout with instructions and

care tips for the patch (see CardioKey Patient Guide). Control participants will come back to the clinic for a study visit and to return the monitor after 14 days of continuous use. At their study visit, the participants will be asked to complete an exam and questionnaire that includes standardized scales. Control participants will be compensated for their time and effort, as outlined above. The device will be read by a study physician blinded to intervention/control status. Abnormal findings on the monitor, in either the intervention or control groups, will result in notification to the participant's treating physician. The Holter/patch monitor company, Biotel Lifewatch, may need to contact the participant and/or study team and PI if a participant's monitor is not transmitting data or there is an abnormal arrhythmia that requires medical attention. The PI will be notified by Biotel if there is an abnormal arrhythmia from any of our participants. The PI has provided Biotel with an office fax number, email, day time telephone number, and a 24-hour telephone number to contact if there are abnormal readings from our participants.

All participants will be given a Device Handout regarding instruction for the appropriate devices that they are given. In addition, the study team will review with each participant all instructions regarding how the CardioKey functions and the participant's responsibility. The participant will also go home with a CardioKey Patient Education Guide (included in this submission in eIRB, CardioKey PatientEdGuide). AliveCor instructions will be outlined in the Device Handout - participants will not go home with an AliveCor manual from AliveCor. This manual (submitted with this submission in eIRB) is a document for the IRB Committee to review regarding the device description. The study team, specifically the PI, may need to contact participants directly about their results. This will be disclosed in the informed consent form that participants sign.

The intervention participants (n=90) will be asked to use the same gold-standard extended Holter monitor device for 14 days as the control group described above. Intervention participants will also be given an AliveCor Kardia Mobile ECG unit (FDA approved) and a Samsung smartwatch and a Galaxy smartphone. The Samsung watch and Galaxy smartphone are standard devices that are sold commercially and will be labeled, nonetheless, as research devices. If the participant has a smartphone that is compatible to our Pulsewatch app, then we will download the app onto the participant's smartphone. .

The intervention group (n=90) will be asked to self-monitor using the Pulsewatch system for at least 9 hours daily for 14 days. The intervention system is designed to be minimally intrusive. If the pulse is deemed to represent AF, the participant will be asked by the Pulsewatch app to self-check using the AliveCor ECG (FDA-approved system), which includes the AliveCor app that is downloaded onto the smartphone. Participants will also be asked to check themselves routinely every morning and evening (twice daily) using the AliveCor ECG. Participants will be asked to return all study devices (14-day Holter device, smartwatch, smartphone, and AliveCor ECG) at the end of their 14 days of use at the follow-up study visit. Participants will be asked to complete a questionnaire at this follow-up study visit and will be compensated.

At enrollment in Part II, study participants will be informed of the possibility that they may be randomly selected at the completion of their 14-day monitoring period to use the Pulsewatch system for up to 30 additional days. We chose to assign a larger proportion of participants to the intervention group because the primary analyses for Aims 2 and 3 are focused on Pulsewatch users.

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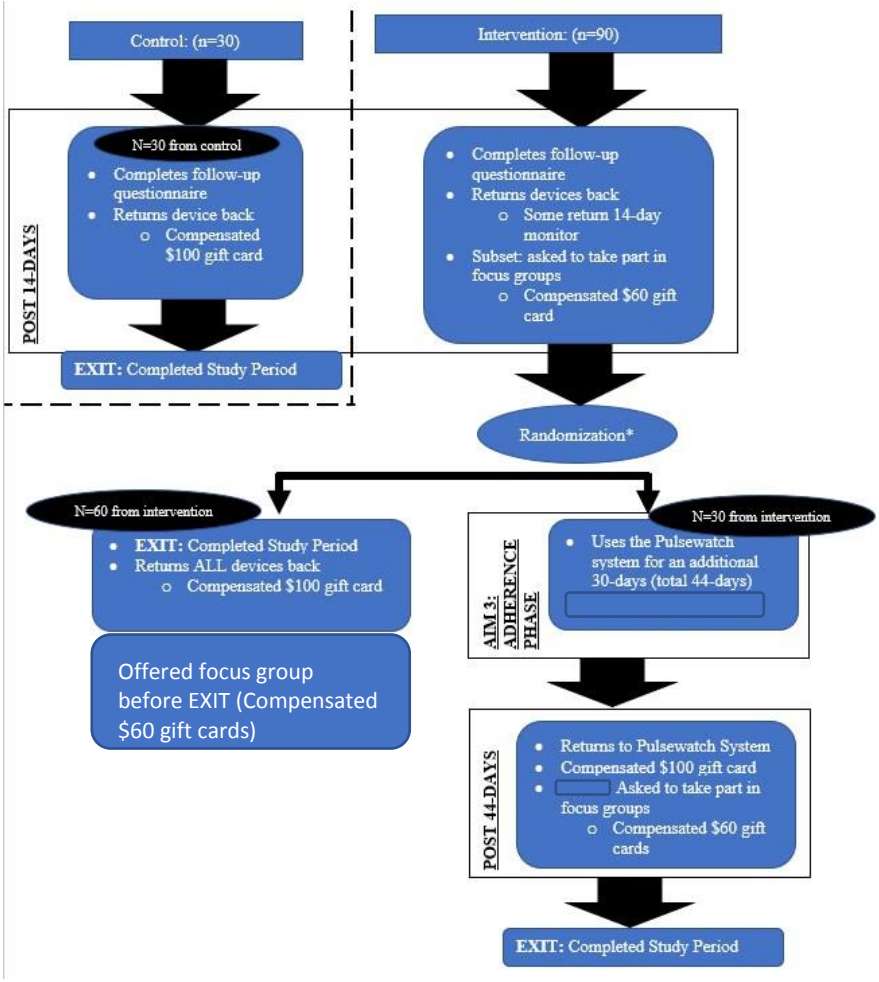

Diagram 1b. Participant process of Part II, trial phase. This diagram outlines what the participant process is after 14 days and after 44 days. Please note: for this "Randomization*" we would like to ask permission from the IRB for an adaptive plan; refer to section 13 Data Analysis and Management for this plan. We have provided further details about this process below.

To accomplish Aim 2, we will examine the performance of Pulsewatch monitoring compared to conventional 14-day cardiac monitoring for pAF detection (accuracy of detection). We will also explore the participant factors (e.g., hearing or cognitive impairment) associated with app performance. If, after enrolling 25 stroke/TIA participants, we have not identified any cases of AF, we will enroll patients at risk for stroke from the UMMMC cardiovascular clinic. At the end at 14 days, if less than 5% of participants have AF based on the gold-standard Holter patch, then we would like to ask participants to extend the use of their monitors for further monitoring.

To accomplish Aim 3, we will randomly select 30 participants from Aim 2 and ask them to continue using the Pulsewatch system to upload their pulse and ECG recordings daily for 1

month. We will also examine factors (e.g., vision) participants report related to their adherence to using the Pulsewatch system.

Part II focus groups: In distinction to Part I focus groups, which center on learning what capabilities users want, Part II focus groups will occur only among Part II trial participants and will center on 'what worked' and 'what didn't' and whether or not long-term use introduces or reduces stress. We will also solicit feedback on the Interactivity Manager and Annotation Panels, features that will be developed too late in Aim 1 to be fully explored by Aim 1 focus groups. Focus groups will happen after either the participant's 14-day study visit or after the participant has used the device for 44 days, depending on whether or not a participant is randomly assigned to be offered and consents to extended watch and app use for 30 days after their study visit. We will conduct up to four Part II focus groups (n=6 participants each); each focus group will last for approximately 60 minutes. Semi-structured and open-ended agendas have been written and submitted to the IRB as part of our packet. Discussions will be audiorecorded and transcribed, protecting confidentiality by replacing participants' names with study IDs. Consent for interviews and taping will be part of the study consent.

Questionnaire- Part II (only):

At enrollment and at their follow-up study visits, all Part 2 participants will complete a questionnaire that includes standardized scales to assess stroke-specific quality of life (QoL), depression, anxiety, and self-activation. Questionnaires will take approximately 45 minutes to complete. If a participant does not return for a follow-up study visit or is unable to complete an in-person questionnaire assessment, then a phone call will be made to the participant to see if they are willing to complete the questionnaire via a phone assessment. These participants will still need to return their devices to receive compensation. We will permit phone calls and assist with return by mail on a case-by-case basis.

We will compare changes from baseline to follow-up in these measures between the intervention (n=90) and control (n=30) groups.

We will create a short-form questionnaire assessment in the event that a participant is unable to complete the full questionnaire. The only difference between the full assessment and short form is that the short form will contain only outcome measurements for the questionnaire.

Here is an overview of the variables our questionnaires will be collecting. We have uploaded all of our questionnaires to eIRB.

Measurement	**Questionnaire Tool**	**Outcome or Stratifier**	**Baseline Assessment (All Part II)**	**14-Days Follow-up Assessment (Control)**	**14-Days Follow-up Assessment (Intervention)**
Physical assessments					
Vision	Questionnaire (4 items)	Stratifier			
Hearing	Questionnaire (3 items)	Stratifier			

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Psychosocial measures					
Cognitive impairment	MoCA (30- items)	Stratifier			
Social support	Social Support Scale (5 items)	Stratifier			
	Lubben Social Network Scale (6 items)	Stratifier			
Depressive symptoms	PHQ-9	Stratifier			
Anxious symptoms	GAD-7	Outcome			
Quality of life measures					
Stroke QoL	Stroke Impact Scale 3.0 (28 items)	Outcome			
Patient activation	PAM (Short Form = 13 items)	Outcome			
Disease management selfefficacy	Stanford Chronic Disease Management Self-Efficacy Scales: Manage Disease in General Scale (5 items)	Outcome			
	Stanford Chronic Disease Management Self-Efficacy Scales: Manage Symptoms Scale (5 items)	Outcome			
Medications					
Medication adherence	Medication Understanding and Use Self Efficacy Scale (MUSE) (8 items)	Outcome			
Health Related Behavior					
Social history	Smoking and alcohol use	Stratifier			
Other					
Interaction with provider	Perceived Efficacy in Patient – Physician interactions (PEPPI)	Stratifier			
Technology use	Device ownership/internet access	Stratifier			
Usability Assessment	System usability scale, Investigator generated questions	Outcome			
Demographics	Social economic status, employment, race and ethnicity questions	Stratifier			

Aims 2-3: Questionnaire will include the following domains-

Anxiety: Anxiety will be assessed using the Generalized Anxiety Disorder-7 scale (GAD-7),[86] a revised version of the anxiety module from the Patient Health Questionnaire, which consists of DSM-IV criteria for generalized anxiety disorder over the past 2 weeks.[87] The GAD-7 score ranges from 0-27 with scores of 5, 10 and 15 representing validated cut-points for mild, moderate and severe levels of anxiety symptoms, with a score ≥10 having high sensitivity (0.89) and specificity (0.82) for psychiatrist diagnosed anxiety disorder and correlates significantly with health-related QoL. [86]

Stroke-Related Quality of Life: Will be assessed using the Stroke Impact Scale 3.0,[88,89] which includes 8 domains (strength, hand function, activities of daily living, mobility, communication, emotion, memory/thinking, participation). Scores range from 0-100 (higher scores=full recovery; 0=no recovery). The Scale scores correlate with stroke outcomes and respond to change.[90]

Patient Activation: Patient activation refers to a patient's ability and willingness to manage their health. Activation will be measured using the Patient Activation Measure (PAM) short-form,[91] a 13-item instrument assessing knowledge, skill, and confidence for self-management. The PAM was designed for patients with chronic diseases (e.g., stroke) and higher scores = better disease self-management.[92] The PAM has been used as a measure of self-management interventions.[93]

Cognitive function: The Montreal Cognitive Assessment Battery (MoCA)[94] is a 10-minute, 30-item screening tool designed to assist physicians in detecting mild cognitive impairment. MoCA correlates well (.89) with the widely used Mini Mental State Exam,[95] but outperforms it in the detection of mild cognitive impairment (CI).[94,96] The MoCA score can be used to examine a magnitude of change over time and offers validated, education-adjusted cut-points for mild CI and dementia..

Social Support: We will use a 5-item modified Social Support Scale and the 6-item Luben Social Network Scale.[99,100] Together these measures assess breadth (e.g., help with activities) and depth (e.g., network size) of the participant's social support.

Depressive Symptoms: We will use the 9-item version of the Patient Health Questionnaire (PHQ-9),[101] the depression module from the Patient Health Questionnaire,[87] which can yield both a provisional diagnosis of depression and a severity score that are associated with functional status, disability days and healthcare utilization.[102] The PHQ-9 consists of the 9 criteria upon which DSM-IV depressive disorders are based. Using a cut-point of ≥10 (range = 0-27), the PHQ-9 has high sensitivity (.88) and specificity (.88) for detecting major depression among patients with CVD.[88,104]Study staff will follow UMass Extreme Emotional Distress protocol approved by the IRB in the event that a patient indicates suicidal thoughts.

Vision: We will test vision using a Snellen eye chart. Participants will also be asked the question, 'How much does your vision interfere with your activities?' based on a 4-point Likert scale from 'not at all' to 'a lot'. **Hearing:** We will use the Whisper test where participants are asked to repeat back numbers whispered into their ear.[105,106] Impairment is defined as hearing ≤6 of 12 numbers. We will complement objective hearing assessments with subjective self-reported responses to the question: 'How much does your hearing interfere with your activities?'

Disease Management Self-Efficacy: Self-efficacy for disease management is associated with engagement in health behaviors and with improved medication adherence[107,108]The General Disease Management scale is a 5-item scale assessing confidence in disease self-management (scores 0-50, higher scores = greater confidence). The Symptom Management scale is a 5-item scale assessing confidence in managing chronic disease symptoms (items tailored to sample).

Medication Adherence: Medication adherence will be measured using the 8-item Morisky Adherence Questionnaire, a well-validated measure of patient-reported adherence.[110] Morisky scores range from 0-8 (higher scores=poorer adherence).

Social history: Social and behavioral factors such as smoking and alcohol use are related to strokes and cardiovascular conditions. Given that the goal of this study is to prevent recurring strokes in this patient population, we believe it is necessary to obtain this information from participants.

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Deployment of devices/app-

Part I: Participants will use the Pulsewatch System prototype version of the app (AFExam), a smartphone, and a smartwatch during focus groups or a Hack-a-thon to provide feedback for further development of the app, and to enhance the deployment of the system in Part II of the study.

Part II: We will provide 90 randomly selected participants with stroke/TIA with an Android smartphone if they do not own a compatible phone. The smartphone will be active – meaning we will pay for a standard cellular data/voice/text plan for the duration of the study period. The smartphone will be preloaded with a Samsung application to enable communication with the smartwatch the study software application, the AliveCor Kardia application, the participant, and the study team. The AliveCor Kardia application, will enable communication between the smartphone and an FDA-approved, commercially available, single-lead ECG. Participants will also be provided with a smartwatch. We will ask participants to wear the smartwatch day and night for 14 days, removing it only to charge each morning or during a shower. The Pulsewatch app interface will allow participants to enter into the app symptoms they may feeling, as well as receive reminder messages on their smartphones to take ECG readings (using the AliveCor ECG system) at least twice daily and more often for symptoms.

We have selected the Android smartphone because it can interface seamlessly with the Samsung watch. If participants have compatible phones they want to use for the study, we will download the Pulsewatch and AliveCor apps onto their phones, and we will pair their phones with the Samsung study watch. To decrease the street value of study phones and minimize the loss of phones, we will program the study phones so they will run only study applications. We will also provide compensation to participants when they return the smartphone and watch to study staff after completing the study Participants will be encouraged to call study staff with any problems encountered when using Pulsewatch during the 14-day monitoring period.

Participants will also have a 14-day ECG cardiac monitor placed on their chest at enrollment. This monitor will serve as a gold-standard comparator in our study and is a diagnostic-grade, FDA-approved, and fully regulated medical device (manufactured by Biotel, the company UMMMC uses for clinical monitoring). We have previously negotiated a research contract with Biotel through the Office of Technology Management. We will engage them again upon IRB approval of the protocol. The gold-standard cardiac 14-day ECG monitor will be placed onto participants by trained study staff at enrollment. Participants will be instructed to call the study team if they have any problems with the monitor. Study staff will be on-call for any detected arrhythmias and will notify the treatment team, including the study cardiologist, the treating cardiologist or neurologist, and, if appropriate, the participant if they detect any arrhythmias during the study period.

Research staff (RA or study coordinator) will provide enrolled participants with detailed instructions about the operations and proper usage of the Pulsewatch smartwatch, smartphone apps (including the Pulsewatch app and AliveCor app), ECG, and 14-day monitor. A checklist and a YouTube video may be made available to participants to remind them of how to charge, wear, and perform ECG self-checks using the smartwatch and phone app. Participants (including all control and intervention participants) will return smartphones and watches and/or 14-day monitors after their study visit at 14 days. For intervention participants, pulse and ECG

data from the smartwatch and annotations/adherence data from phones will be uploaded by study staff after this visit to the secure cloud server. Control participants will be provided instructions on the gold-standard monitor use. Study staff will be available via telephone to answer any questions participants have with using the watch and smartphone, charging the battery c, and uploading data throughout the 14-day trial period as needed. The 30 randomly selected participants will receive additional training at their 14-day study visit and will be consented to continue to use the Pulsewatch smartwatch and phone for an additional 30 days. Participants in Aim 3 will be asked to upload pulse and ECG data daily. The secure server architecture used by Samsung minimizes the potential for loss of health information and is similar to one used in our prior work.

12. Data and Specimen Banking*

Any data collected by this study may be used for future research. The PI or another approved member of the study team will determine who is allowed to access this data. It may include collaborators or entities external to UMMS.

ECG and pulse data from all smartphones and watches will be sent to a secure server managed by UConn's information technology services. The data will not be transmitted with participant name, DOB, or MRN. The Pulsewatch system will upload data when prompted by participants during Aim 3 or by a trained study staff member during the 14-day study visit. This data management system is encrypted. Data storage capacity on the Pulsewatch is nearly 14 days at the above noted sampling rates for PPG. Thus, pulse data will be safely stored and will be retrieved when the Pulsewatch is returned for Aim 2 after 14 days. All ECG and pulse data will be password protected and encrypted so that only research personnel can access stored data. Once smartwatches are returned, we will have the study coordinator "push" pulse and ECG data from the smartwatch and adherence/annotation data from the smartphone. If the smartphone is lost, however, we will extract the latest adherence and annotation data and then remotely delete the File Store. This protocol protects participants' confidentiality in addition to the data encryption and password protection. We have the programming expertise necessary to carry out these operations.

The AliveCor Kardia platform used to store ECG data from the AliveCor ECG system is a HIPAA-compliant, HL7 compliant service used by the Cleveland Clinic, UMMMC, and other services for clinical grade ECG storage and analysis. This protocol protects participants' confidentiality in addition to the robust means of data encryption and password protection. We will upload only ECG's linked to participant IDs. ECGs will be reviewed within 7 days of uploading by study staff.

The 14-day cardiac monitor data will be transferred to the PI via a summary report for review. This will be reviewed and stored in a locked, secure space (ASC 7th floor cardiology). The Biotel servers, designed for clinical use and used by our UMMMC clinical partners, are encrypted, secure, and HIPAA compliant.

Focus group recordings, Hack-a-thon materials, and questionnaires (baseline and follow-up) will be stored in a digital format (using the nVivo system for audio recordings and the RedCAP system for questionnaire data) as well as on paper. All digital data will be password protected

and encrypted so that only research personnel can access stored data using the RedCAP system. All paper questionnaires, consents, etc., will be stored in a locked, secure UMMS space (ASC 7th floor Cardiology).

Screening documents to identify patients to approach for the study will be stored in the Redcap File Repository and deleted when we have finished enrolling participants. We will destroy the master file of the identifiers of the enrolled participants 5 years after all data analysis is completed. De-identified data coded with the Subject ID of participants will be retained indefinitely to be reviewed for future publication use. Any paper or physical copies will be stored in locked spaces. Audio recordings will be deleted after a research staff member has completed the transcription process and quality check process. Transcription will be de-identified, protecting confidentiality by replacing participants' names with study IDs. The master file that links the participant to the identifiable information will be in a secure database (RedCAP) and only limited research personnel will have access to this information to help protect participants' personal information. Please see our HIPAA Waiver, which is in eIRB.

13. Data analysis and Management*

Overall Data Management:

Each participant enrolled in this study will receive a participant ID to ensure that limited personal information of our participants is not accessed unnecessarily. Our study team, including the study PI, will meet with an independent monitor quarterly to ensure adequacy of human subject's protections, including participant privacy.

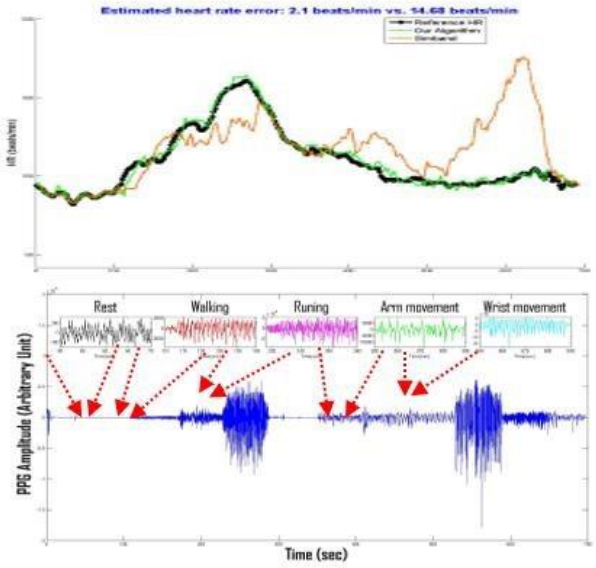
For all patient participants, sociodemographic, clinical, laboratory, and medical care information will be abstracted from records into a web-based centralized data repository, which was developed and is being used in SAGE-AF. As in our prior studies,[73] we will abstract data on history of TIA/stroke, stroke severity, and clinical variables necessary to derive the CHA_2DS_2VASc (stroke) risk scores.[74] We will abstract use of medications (e.g., beta-blockers) known to influence vulnerability to AF.[74] Data from health records will be imported to our data repository as in the SAGE-AF study.[73]

Data streams will be merged into the Pulsewatch master database that will include audio and digital information from focus groups and questionnaires. AF rhythm status will be determined based on ECG data, and summary reports will be stored in the Pulsewatch master database utilizing our data system architecture similar to that used in SAGE-AF. Data acquisition and quality control processes will be the same. Unique, password-protected, registry websites assure consistent staff identification at entry. A data collection manual with coding instructions for each data item in SAGE-AF has been developed and will be updated for Pulsewatch.

Questionnaires will be available in a digital format on password protected iPads (using the REDCap system) as well as on paper copies. All laptops, desktops, and iPads that we use in this study will meet the UMMS encryption policy. All digital data will be password protected and encrypted so that only research personnel can access stored data using the REDCap system. All paper questionnaires, consents, etc., will be stored in a locked, secure UMMS space (ASC

7th floor Cardiology). ECGs will be sent to the AliveCor Kardia Pro platform, a secure provider ECG management system. The AliveCor Kardia Pro platform is a HIPAA-compliant, HL7 compliant service used by the Cleveland Clinic and other services for clinical grade ECG storage and analysis. This protocol protects participants' confidentiality in addition to the robust means of data encryption and password protection.

Smartwatch Data:



We will reduce the potential for false positive AF detection from corrupted (MNA) or low amplitude (poor contact) PPG data using two methods. First, the Pulsewatch app will send a message to participants to remain still and perform a 30-sec ECG self-check (wrist electrode, high accuracy) should they have an AF episode detected. The second approach involves the cancellation of cyclical frequencies, seen in accelerometer data, from the PPG signal. This approach was recently developed in our lab and should allow us to use segments such as shown.[23,24] We demonstrate this MN correction performance via a representative result from offline analysis of raw Samsung watch data.(Looking at the figure above, the top panel of shows the comparison of our MN correction algorithm (green line) on raw data vs. Samsung's own embedded motion artifact correction algorithm (brown line). The black line is the reference heart rate from a 5-lead ECG. The bottom panel shows the raw PPG data recorded from the Samsung watch, and note MN artifacts starting at 100 seconds. The data were recorded during treadmill exercise (first 300 seconds), followed by 30 seconds of cool down, as well as with arm movements (up and down and shaking) on the side of the smartwatch. Despite the severity of the MN artifact, the estimated heart rates calculated by our algorithm closely follow the reference (black line) heart rates. Thus, these 2 approaches can be effectively used to recover some data segments contaminated by MNA or by poor signal quality and correctly identify the presence or absence of AF. Once MN artifacts have been corrected, we will look at patterns to analyze pulse waveforms for AF detection, including discrimination of PVCs and PACs. The MNA and AF algorithms will be embedded using Samsung's Vobio API. Based on our pilot, we estimate 50% usable data during active periods and 90% during rest. The majority of the user's day will be at rest (sitting or sleeping), as older stroke patients typically perform limited exercise.

To fine tune and maximize the accuracy of our MNA algorithm, we will use data collected on AF subjects (Aims 2 and 3) using the Pulsewatch system. We will compare the performance of our MNA algorithm using the Pulsewatch signal to the simultaneous gold-standard Holter ECG, CardioKey. The data analysis and statistical evaluations will be similar to our recently published article on our MNA detection/reconstruction algorithm,[25,77] but will also involve calculation of absolute error of the estimated heart rate via our algorithm to the reference Holter ECG-derived heart rate. Moreover, we will calculate sensitivity, specificity and accuracy of AF detection using our algorithm when compared to Holter, CardioKey reference data.

AF Detection Analysis:

Analysis for the study focus on the performance of daily wear of the Pulsewatch system for 9 hours compared to standard Holter, Cardio Key, monitoring over the course of 14 days. We will examine the system's accuracy for pAF identification as well as estimation of AF burden. A participant will be classified as having pAF or not at the end of the 14-day monitoring period based on the gold standard Holter monitor. Data from the Pulsewatch is divided into 30-second segments for analysis and a positive reading will be defined as AF being detected in at least 7 out of 10 continuous data windows (5 minutes). The total number of positive readings collected over 14 days from Pulsewatch will be used as the independent variable in a logistic regression to predict the binary outcome of pAF (yes vs. no). The area under the receiver operating characteristic (ROC) curve (AUC) will be calculated based on the results from the logistic regression to evaluate Pulsewatch performance for pAF screening. From the ROC curve, we can identify the cutoff point of total number of positive readings that produces the highest sensitivity and specificity combination.

Preliminary data suggest that Pulsewatch will have sensitivity, specificity and AUC of at least .9 to detect pAF. Assuming [115].

Similar analysis will be conducted using the % of positive readings among all readings collected from each participant as the independent variable. The 95% confidence intervals (CI) of the AUC will be calculated using formula given by Hanley and McNeil. We will then conduct exploratory analyses to examine whether characteristics affect watch performance over 14 days. For example, we will compare the area under 2 independent ROC curves of female vs. male participants (or vision impaired vs. not) using a chi-square test. At the end of 14-days we will review the data of 45 participants in Aim 2 intervention and see what % of participants have AF. If we see less than 5% of all participants using the devices have AF, we will have an adaptive protocol for analysis. We would ask participants to extend their use of the devices for an additional 14-days and continue to monitor the participants for potential AF cases. Their follow up assessment for participants in Aim 2 of Part II would be at the end of the 28 days if we take this approach.

Usability Analysis:

We also aim to examine whether participant characteristics (e.g., demographics, level of technology use, cognitive impairment, etc.) affect usability and adherence of the Pulsewatch system. Usability will be examined by semi-structured interviews, investigator generated questions regarding user experience, and the System Usability Scale (SUS), a validated instrument for perceived system usability. Investigator generated questions will have responses in a 5-point Likert-like scale, and ordinal regression will be used to evaluate participant characteristics that may be associated with more favorable responses regarding usability of the Pulsewatch system. The SUS score ranges between 10 and 100, and linear regression will be used to examine the participant level factors that are associated with higher SUS scores. Logistic regression will also be used to examine whether certain participant factors are associated with having a SUS score of over 68, the acceptable cut off being deemed as a highly usable system.

Adherence Analysis:

In Aim 3 of Part II of the study, adherence will be operationalized to determine whether pulse recordings were present on each day over the 30-day period. We will examine whether participant characteristics, e.g., sex, cognitive impairment, or stroke-related quality of life, affect the likelihood of adherence over the 1-month study period. We will use a mixed effects logistic regression model, including the participant as the random effect to capture the correlation among repeated measures from the same participant, using participant characteristics as the fixed effects, and a binary indicator of daily adherence as the dependent variable. We will also examine the adherence time-trend by including time (day) as a fixed effect in the model and participant as a random effect to estimate the slope of adherence over time. To examine whether the time trend varies by participant characteristics, we will include the interaction between characteristics and time in the model so that the slope of adherence over time can be estimated for each category of participant characteristic variables and be compared among the categories (e.g., pAF diagnosed vs. no pAF). Secondary analyses will examine rates of adherence to Pulsewatch ECG prompts and will compare Pulsewatch users to the usual care group with respect to stroke-related quality of life, anxiety, and self-activation. We will calculate the change score between baseline and 1 month as a dependent variable. First, a t-test will be used to compare 2 study groups on the change score. We will use a linear regression model, which will include group indicator (Pulsewatch users vs. usual care) as the independent variable and possible confounders (e.g., medication adherence and participant demographics) as covariates, to estimate adjusted group differences on the change scores.

14. Provisions to Monitor the Data to Ensure the Safety of Subject*

Please review the Data Safety Monitoring Plan (DSMP) in the eIRB for a detailed description regarding human subject's protection.

This plan recognizes the nature of Part II of this study as a clinical trial and this Part involves more intensive data safety monitoring, including involvement of an independent monitor, Dr. Steven Lubitz. The plan has been reviewed and approved by the Director of the Quantitative Methods Core, Dr. Bruce Barton, who has extensive expertise in the design and conduct of clinical trials.

As outlined in the DSMP, we will employ an adverse event reporting system (see DSMP Report template in eIRB) that will be reviewed by the PI and the independent data study monitor to ensure safety of all enrolled participants. However, we have provided an overview of our analysis and management plan herein. For any incidental findings, the PI will review the recording of the pulse/ECG data and make a clinical decision; if necessary, the PI then will contact the participant's treating physician to report the findings and recommend follow-up plans. In the unlikely event of incidental findings during Part I, the PI will be contacted if he is not present.

All recruitment and training will be conducted by trained personnel who are certified according to our study protocols, which include training in procedures for recruitment in the clinical environment. Modeled on the PI's ongoing studies, medical record review protocol uses "gold standard" medical records and requires that each abstractor satisfactorily complete 10 practice cases before certification. We will have ongoing data quality control checks via audited interviews and medical records abstracted in duplicate for 5% random samples. If error rates

are too high, we will retrain staff and increase quality control sampling until the rates decline to acceptable levels. We will continue our ongoing quality control measures with dynamic range and consistency checks, missing data surveillance, and error tracking.

All study participant Pulsewatch ECG recordings (both from the 14-day monitor and individual AliveCor ECGs) will be manually reviewed by trained study staff under the direction of the PI. Two readers, blinded to the determination of the automated rhythm analysis, will review ECG data and code sinus rhythm, AF, or other arrhythmias (e.g., premature atrial beats) using standard criteria.[6] In cases where there is disagreement with respect to rhythm, the PI will review the tracing to obtain consensus. ECG data will be reviewed within 7 days by a study cardiologist. If cases of AF are detected on manual review or if a participant calls the study hotline to report a new health concern, the research coordinator will notify the participant's primary healthcare provider, cardiologist or neurologist and assist in arranging a follow-up. Providers will be given the PI's contact information to arrange care or to speak with a cardiologist familiar with the Pulsewatch protocol.

All 14-day cardiac monitoring data will be de-identified using alpha-numeric study IDs. Biotel will collect the Holter data and transmit it to the PI, Dr. Timothy Fitzgibbons, for review and storage on a secure server. Biotel may need to contact the participant and/or the study team if the transmission signal is poor, technical issues arise, or because of an abnormal cardiac rhythm. The ECG data from the cardiac monitor will be uploaded to a secure server (UMMS),and downloaded for interpretation. Only Dr. Fitzgibbons and the research staff will have access to the code linking the subjects to study IDs. The study cardiologists will review any arrhythmias on the cardiac monitoring device for accuracy. If any arrhythmias are detected, then the Dr. Fitzgibbons will notify the participant's treating clinician.

We will report any issues to the UMMS IRB in accordance with the Investigator Manual and Prompt Reporting Requirements.

We will have independent data safety personnel who will evaluate the process of ECG review and reporting as well as any adverse events related or unrelated to study participation. Please see resource available section.

The PHQ-9 and GAD-7 in the questionnaire are the only instruments that require monitoring and a UMMMC Protocol plan has been submitted with this IRB application. Per our protocol, if study staff detect high PHQ-9 and/or GAD-7 scores, they will suggest that participants discuss their symptoms of depression and/or anxiety with their doctors and/or the trained personnel at the UMMMC Emergency Mental Health hotline (508-334-3562). Study staff will be fully trained to note that the checkbox on the cover page of each questionnaire will remind them to follow the extreme emotional distress protocol when warranted.

15. Withdrawal of Subjects without their consent

Participants, including patients, caregivers and providers, will be able to withdraw from the study at any time. Participants will be withdrawn from the proposed study if they are unable or unwilling to wear the smartwatch and are found to meet exclusion criteria. At that point, they will

be informed of why they are being removed from the study and given an opportunity to ask questions.

16. Risks to Subjects
No more than minimal physical risks will be involved with this study. First, use of a smartphone or smartwatch does not pose any significant health concerns. Use of a single-lead, FDAapproved, commercially available ECG device (AliveCor) does not require placing of electrodes on the human body and does not pose any physical risk. The 14-day cardiac monitor poses no more than minimal risk, but the monitor may cause skin irritation at the site of application. This poses no significant risk to participants since this is the standard device used in clinical practice.

Another potential but minimal risk to participants is feeling psychologically uncomfortable disclosing sensitive information (e.g., depressive symptoms) or performing geriatric assessments (e.g., assessments of cognitive function) while answering questions during the interview process at baseline/follow up visits. Depressive symptoms will be collected as part of the interview and there is the possibility that emotional distress or depression will be identified. There is no risk of extreme stress as a result of participants answering these questions. All study staff interacting with participants will be trained to detect when a participant is feeling uncomfortable and will re-iterate that the participant can stop an interview at any time and can refuse to answer any question for any reason.

Another risk to participants will be the possibility of a breach in confidentiality. However, we will try our best to protect participants' confidentiality to minimize the risk (see data safety plan). All participant data will be held behind secured firewalls at UMMS. As noted in Section 12, ECG and pulse data from all smartphones and watches will be sent to a secure server managed by UConn's information technology services. The data will not be transmitted with participant name, DOB, or MRN.

Access to databases will be restricted to only authorized personnel. We will utilize all electronic data capture procedures and, therefore, no paper records will be kept long-term. Any paper records (such as medical record information) that are needed for the study will be destroyed immediately following entry into electronic databases. All consent and other forms that are required to be kept will be kept in a locked file cabinet in locked study offices.

17. Potential direct benefit to subjects
There are no direct benefits to the subjects.

18. Vulnerable populations
We will not be targeting vulnerable populations; all participant must have capacity to be able to consent. Please see the protocol for determination process of capacity to consent. Providers may be seen as a vulnerable population and we will have a protocol in place for recruiting them to minimize the potential for undue influence. Please, refer to section 24. Local Recruitment Methods to review this protocol.

19. Multi-site research
NA. Not a multi-site study

PULSEWATCH INVESTIGATOR STUDY PLAN

20. COMMUNITY-BASED PARTICIPATORY RESEARCH*

NA. This study is not a community-based research.

21. SHARING OF RESEARCH RESULTS WITH SUBJECTS*

Study results will not be directly shared with participants unless a rhythm abnormality is diagnosed based on their AliveCor ECG or 14-day Holter monitor results. See section 11. Procedures involved (Part II, specifically) for the protocol involving the PI having to contact a participant or participant's clinician about an abnormal rhythm when detected.

22. SETTING

Research assistants will enroll participants with a history of stroke and/or TIA from among those presenting for a clinic visit or to the inpatient service. Embedding this project in the UMMMC neurology and cardiology inpatient and ambulatory clinics will facilitate recruitment.[78] In the stroke clinic alone, four neurologists see over 500 patients with cryptogenic stroke/TIA yearly. Dr. Majaz Moonis (Co-I) has had high success conducting research within this clinic.

We will also enroll up to 10 UMMMC providers (half cardiologists or neurologists, half nurses/nurse practitioners) with experience treating patients with cryptogenic stroke who need AF monitoring.

We will be holding focus groups in a comfortable conference room at UMMS. Any questionnaires, exams, interviews or study appointments will be completed in a private, comfortable room in the UMMS Clinical Trials Center located in the ACC Building. If this center is not available, we will have another private and comfortable area for participants to complete all study protocols here at the UMMS University campus.

23. RESOURCES AVAILABLE

The study will be led by investigators with extensive experience working with stroke and AF patients. All neurologists/cardiologists, and research coordinators/staff will ensure that regulatory paperwork, such as consent forms and patient confidentiality, are used appropriately.

All recruitment and training will be conducted by trained personnel who are certified according to our study protocols, which include procedures for recruiting study participants in the clinical environment. Modeled on the PI's ongoing studies, our medical records review protocol uses "gold standard" medical records review methods, and requires each abstractor to satisfactorily complete 10 practice cases before certification. We will have ongoing data quality control checks via audited interviews and medical records abstracted in duplicate for 5% random samples. If error rates are too high, we will retrain staff and increase quality control sampling until errors decline to an acceptable level. We will continue our ongoing quality control measures with dynamic range and consistency checks, missing data surveillance, and error tracking.

Rhythm diagnoses will be determined based on self-initiated or auto-triggered ECG tracings from the gold-standard 14-day patch monitor. Two readers, blinded to the determination of the automated rhythm analysis, will review all time-stamped monitor recordings and code sinus rhythm, AF, or other arrhythmias using standard criteria. In cases where there is disagreement

between the 2 primary interpreting cardiologists with respect to rhythm, a 3rd physician will review the tracing to obtain consensus.

Personnel Resources are as follows:

- **The PI:** Will be responsible for the direct efforts of the research project and meeting with research coordinators/mangers weekly during the study period. In addition, the PI will adjudicate ECG recordings and, if arrhythmias are detected, will notify the participants' treating clinicians.

- **Co-I's:** Will provide study management, quality assurance, staff oversight, study progress, diagnostic adjudication, data presentation, and preparation of quarterly and annual progress reports. The Co-Is will be available after hours to support research coordinators.

- **Project Manager:** This individual will not be primarily responsible for study enrollment, but will instead take an administrative role and have prior experience managing research staff and overseeing day to day operations and enrollment activities of this research project. She will supervise study progress (enrollment, chart reviews, etc.), maintain records of such progress, and communicate any concerns with the Co-PI's. She will arrange regular meetings with the Co-PI's and the research staff.

- **Research Coordinators:** These individuals will be required to have at least an associate's degree and 6 months of either clinical research or patient care experience as they will be responsible for direct participant enrollment/consent and assisting with chart reviews. They will have completed their CITI certification. They will be trained by the PI's and/or project manager to learn the medical terminology, chart review methodologies, enrollment protocols, and how to interact with clinical staff. In addition, they will also be trained to enter clinical data into a custom REDCap database. The coordinators will be responsible for contacting any potential provider participants and recruiting them.

- **Biostatistician:** There is a budgeted position for a statistician to work on this project. This individual will be responsible for reviewing the study's data calculations and power calculations that are needed to achieve the goal of this study.

- **Research Staff/Research Assistants (RA):** We will develop a manual of operations (MOO) for this study and require that all staff are familiar with this study. We will train all staff on enrollment procedures and will observe 3 enrollments prior to having them work independently to approach patients. The RAs will also be responsible for assuring the proper protocol is followed for the audio recordings obtained in any focus group/interview.

- **Educating Clinical staff:** The study protocol will be vetted with attending neurology/cardiology physicians and staff (residents, nurses, and MD faculty) in several ways. As part of our monthly faculty meetings, the PI will present the study to faculty and provide study updates and opportunities to ask questions.

- **Independent Data Monitor:** This person will be responsible for reviewing smartwatch adherence data. The monitor will be an independent party who is not from UMMS, who is classified as non-investigator personnel, and who is familiar with the data safety monitoring plan.

If study staff who have primary affiliations outside of UMMS will interact with subjects or access private identifiable information about them, they will either obtain their own IRB approval or we will work with the UMMS IRB to establish a reliance agreement for UMMS to serve as the Reviewing IRB.

24. Local Recruitment Methods

Part I: Trained research assistants (RAs) will screen the UMMMC neurology and cardiology rosters for patients, then will send introductory letters to eligible patients who meet inclusion criteria and are free of any exclusion criteria. Letters of introduction to the study (Patient FG Invitation in eIRB submission) will be sent to eligible patients 5-7 days before their scheduled clinic visits with an opt-out phone number for patients who do not wish to be approached for study participation. Dr. Keaney, Chief, Cardiovascular Medicine, will sign this letter. RAs will approach patients in the UMMMC out-patient clinics. If patients are interested and deemed capable (using the capacity assessment), then they may be enrolled in the study by signing the IRB-approved informed consent form. Caregivers who accompany a loved one to clinic will also be approached for consent to participate in focus groups. Before approaching patients and their caregivers, RAs and study personnel will be trained on how to explain all of the study's components to potential participants.

We will give the Hack-a-thon Fact Sheet (see Fact Sheet: Patient and Provider Hack-a-thon in eIRB submission) to all focus group participants. We will also ask participants at the focus groups to fill out a form to indicate if they would like to be contacted about participating in the Hack-a-thon (see Hack-a-thon Contact Info sheet in our eIRB submission). A study staff member will call participants who indicate they are interested in participating in the Hack-a-thon, and to disclose that participants have the right to opt-out of this event.

Ten providers will be identified from the UMMMC neurology and cardiology groups for focus group or interview participation. We will approach physicians and advanced care nurses via email or telephone (see Provider email and telephone invitation script with this IRB submission). Providers will be given an IRB-approved Fact Sheet (in eIRB submission). The study coordinator, not the PI or Co-Is, will recruit providers affiliated with UMMMC to minimize the potential for undue influence. The study coordinator will explain to providers that their decision to participate or to not participate in the study will not affect their employment status at UMMMC.

Part II: We will use a rolling enrollment and randomization design with a goal of 90 participants completing the intervention and 30 participants completing the control group procedures (n=120 in the trial). To enroll patients who are admitted to UMMMC, RAs with access to the UMMMC neurology inpatient roster and cardiology/neurology ambulatory clinic schedules will screen the rosters daily to identify potentially eligible patients. We will screen any patient admitted with stroke or TIA to the neurology service (identified from the inpatient neurology roster admitting diagnosis) or presenting with a complaint potentially related to stroke (e.g., facial droop) and evaluated by the stroke service. For potentially eligible participants in whom the diagnosis of

stroke/TIA is suspected (e.g., focal weakness), but not yet listed as a diagnosis, a neurology consultation note or history and physical examination documenting stroke/TIA will be needed to confirm eligibility.

Patients who are admitted to the neurology/cardiology units at UMMMC will be considered eligible to participate if they meet all of our inclusion criteria and are free of exclusion criteria. They will be approached by the study staff before they are discharged from their inpatient stay. The study staff will approach the patient's clinical team prior to entering the patient's hospital room for approval to approach the patient for this study. Study staff will present information to the patient about the study, including the randomization process, and will perform an assessment of the patient's capacity for informed consent. Study staff will demonstrate the features of the cardiac monitor, smartwatch, smartphone/app and the AliveCor ECG unit, and then allow the patient to ask questions about the devices. We will involve family who are present in the patient's room to answer their questions about the study. Patients will be given the opportunity to consider participating in the study until their day of discharge from the hospital. If the patient consents to participate, study staff will administer the baseline questionnaire. Study staff will also place the cardiac monitor on the participant's chest by following the Biotel Patient Guide (submitted in eIRB). We are not altering usual care, and the devices should not be uncomfortable to wear. The participant will be given guidance on how to use the devices and the process for baseline compensation. We anticipate the explanation of the study and consent procedure in the inpatient cohort will take ≤ 30 minutes.

Research assistants will also screen ambulatory patients with a history of stroke or TIA in their problem list or medical history. For ambulatory patients, letters of introduction to the study will be sent to eligible patients 5-7 days before their scheduled clinic visit with an opt-out phone number for patients who do not wish to be approached for study participation. We have successfully used a similar approach in other studies. This invitation letter is enclosed in our application packet.

The consent will include permission for follow-up contacts and medical record review, and will also request access to identified proxies, who would be able to help us contact patients in the event they change practices and do not follow up at UMMMC. We will offer modest incentives for recruitment and retention in Pulsewatch: T-shirts and/or bags and/or pens with Pulsewatch logos offered at recruitment and mailed during follow-up.

All participants will be brought back for a study visit approximately 14 days after enrollment. This visit will take place in a research area that is private and comfortable. There, participants will return their 14-day monitor, smartwatch, and smartphone, and will complete a questionnaire. From the 90 participants in the intervention group, we will randomly select 30 participants to be offered an opportunity to continue self-monitoring at home using the same watch and app for an additional 30 days. At the completion of the 30 days, participants will return for a follow-up visit and to return all equipment. All participants coming back for a focus group/interview in Part II of the study will be sent a Fact Sheet reviewing all the details of the process (Fact Sheet: Part II Focus groups in eIRB submission). Upon receipt of the study equipment, the study team will compensate the participants..

Compensation will be given as an incentive. All patients and caregivers who participate will be compensated for their time and efforts in the study as shown in the table below. Providers will not be compensated for participating.

Participant Sub-groups	Compensation Amount	Time Earned
Part I: Focus Group	$60.00 gift card	After completing the focus group
Care-givers	$60.00 gift card	After completing the focus group
Part I: Hack-a-thon	$15/hour gift card	After completing the Hack-a-thon event
Part II: Control group	$100.00 gift card	After completing the baseline interview
	$100.00 gift card	After completing the follow-up visit
Part II: Intervention group	$100.00 gift card	After completing the baseline interview
	$100.00 gift card	After completing the follow-up visit
	$60.00 gift card	Participants who complete focus groups in Part II

Before the focus groups or the Hack-a-thon are held, w\e will inform all participants that they will receive parking passes if they park in the Visitor Parking Lot to attend these events.. Valet parking uses a different voucher that our study is not purchasing at this time.

To help with participant retention, the study team may contact participants by phone or mail to remind them of upcoming visits or to check in and see how participants are doing, particularly in Part II. The study team may also contact participants by phone or mail if it implements the adaptive design (due to low rates of AF) in which participants are asked to extend wearing the devices for longer than the initial 14-days. Any letters will be submitted to the IRB as a Modification for review and approval prior to use.

25. LOCAL NUMBER OF SUBJECTS

There will be a total of 170 participants in this study.
Part I: Up to 40 out-patient stroke participants or caregivers and 10 providers.
Part II: 120 participants, including 30 in the control group and 90 in the intervention group. Of the 90 participants in the intervention group, 30 will be invited to continue into Aim 3 and use the devices for an additional 30 days.

In order to obtain 170 participants who complete the research, we may over enroll or replace participants who drop out.

Adaptive enrollment design (Part 2): If we struggle to identify sufficient numbers of eligible participants from the inpatient stroke service or clinics over the first 6 months of enrollment (<50% targeted enrollment), we will employ an adaptive design and approach patients presenting to UMMMC out-patient and in-patient cardiology and/or neurology clinics who have high risk for atrial fibrillation and stroke on the basis of a CHADSVASC score >=2. Furthermore, if we struggle to enroll a sufficient number of participants from the UMMS University campus, we will recruit at the stroke treatment centers at UMass Memorial - Health Alliance Hospital in

Leominster, MA, and at UMass Memorial - Marlborough Hospital in Marlborough, MA. The PI has actively sought approval from these sites to approach patients from these locations in order to meet study enrollment goals.

26. CONFIDENTIALITY

Trained RAs will use Subject IDs for all the data collected from participants to limit the use of the participants' personal information. Information will be collected via the UMass EHR system for screening and basic demographic information. The data collected at the focus groups will be recorded but then transcribed later and the recording will be deleted. Please refer to section 13 for more details regarding confidentiality of data and management.
The audio recordings of the focus groups will be deleted after the recording has been transcribed and checked for quality. The transcription will be kept in the secure database of REDCap.

27. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

All PIs and research assistants/coordinators will complete CITI training to understand the necessary measures to protect personal identifiers and reinforce the importance of sound ethics in conducting this research study. The study team will also search for the best and most private setting in the UMMMC environment to help participants feel at ease with the study and explain that their information will be protected. Participants will also be told they have the right to refuse to answer any questions they feel uncomfortable answering or/and the right to refuse to be in this study.

a. PI - Will have ongoing access to REDCap clinical data for data integrity and Q/A checks.
b. RAs/Research coordinators will have access only to EHR data, and study data they are entering into REDCap.
c. We will request a waiver of HIPAA authorization in order to do preliminary EHR and clinical record searches to determine if patients are eligible for study enrollment based on our inclusion and exclusion criteria. A signed HIPAA form will be obtained once a patient is enrolled and able to sign the form.
d. A biostatistician/database manager will be given access to clinical data that does not readily identify subjects by name for data analysis.
e. Independent monitor will review deidentified safety, adverse events, and study reports (see DSMP)

28. COMPENSATION FOR RESEARCH-RELATED INJURY

This study involves research procedures that are considered minimal risk; no funds have been set aside.

29. ECONOMIC BURDEN TO SUBJECTS

There is no economic burden to subjects because of participating in this research. Study funds will be providing all of the devices at no cost to participants.

30. CONSENT PROCESS

Prior to enrolling participants, the study team will have a training session. This training session will focus on all study aspects but particularly to ensure that all study staff are familiar with and will follow HRP-802 INVESTIGATOR GUIDANCE: Informed consent. We will be obtaining IRBapproved informed consent and HIPAA authorizations from all patients who are participants in Part I and Part II of this study. Participants who are caregivers and providers will receive a fact sheet instead of signing an informed consent form - this recommendation for the IRB is because the study team does not need any health record information from these participants to take part in our study procedures.
It is important to obtain HIPAA authorization from the patients who become participants in order for the study team to have access to certain aspects of their EHR. Information such as demographics (age and sex), related medical information like family history, current and past medications or therapies, and information from physical examinations will help the team understand the type of population in this study. For example, medical notes on physical exams can describe how much patients may be able to move their arms; this will help us assess if we should approach patients who have very limited arm movement since our study asks participants to wear a watch. In addition, this information will help us capture the severity of our participants' physical and medical limitations. We will also need this information for patient participants in the focus groups because we would like to be able to compare these participants to the Part II participants who will be using the Pulsewatch System.

After RAs identify a potential participant and explain the study, RAs will ask the potential patient participant to read, sign, and date the consent form. If a caregiver is present, then a fact sheet may be given to them regarding more information about participating in the focus groups. If patients or caregivers want more time to decide whether to participate in the study, RAs will provide them with the study phone number (774-455-3799) on which they can call us. Part I and Part II of the study will have a separate consent form because each part requires different types of participation. In part I, we will have a consent form for eligible patients to participate in the focus groups.

The research coordinator will be responsible for contacting providers who have expressed interest in this study. The coordinator will inform all potential provider participants that this study is completely voluntary and will not affect their status as employees of UMMMC or UMMS. If providers wish to opt-out, they may directly contact that study team and/or coordinator.

In Part II, we will have one consent form that outlines the randomization trial method and what patients will be required to do to participate in the study.
We will only use IRB-approved stamped consent forms.

31. PROCESS TO DOCUMENT CONSENT IN WRITING

Written informed consent will be given to participants who are patients (not caregivers or providers, who will receive a Fact Sheet). All study staff members who a part of this study will be trained properly and have a complete understanding of all study related documentation in order to help answer any questions participants may have. The approaching staff member will assess the capacity of the patients to consent; we have submitted to the IRB a "Capacity for Informed Consent" form that can be used. We anticipate that due to the study selection criteria (older patients), some patients will not be able to provide informed consent. Thus, all patients will be assessed for their understanding of the study, the risks and benefits associated with the study, the voluntary nature of participation, and the confidential nature of all study data. If patients

answer 3 or more questions out of 8 incorrectly, they will be deemed unable to provide informed consent and excluded. Safeguards will be put into place to protect the rights of cognitively impaired participants.
For caregivers and providers, we will obtain informed consent via an unsigned fact sheet given to them prior to study visits.
All participants who sign the consent form will be given a copy to keep for their own records. The study team will keep the original copy of the signed consent forms in a locked cabinet in a locked room. The study team will also make another copy and send it to UMMMC Medical records to be kept on file for each patient who participates in the research.

32. DRUGS OR DEVICES

This study will use only commercially available devices (Samsung gear, Android smartphones) or FDA approved devices (AliveCor Kardia Mobile device and app). Part II participants will use the AliveCor Kardia Mobile devices and smartphones that will only run the AliveCor app (FDA approved for single-lead ECG recording) and the Pulsewatch app. A gold-standard, commercially available (Biotel Lifewatch CardioKey) 14-day monitoring technology will be deployed and used by all Part II participants.

The mobile device application (Pulsewatch App) that will be developed in this study at the end of Part I is not commercially available nor FDA approved. This application (Abbreviated IDE) is only to be used with participants of this study. For this reason, we would like to document the following:

i. The device is not a banned device; ii. The device is not intended as an implant that presents a potential for serious risk to the health, safety, or welfare of a subject;

iii. The device is not purported or represented to be for a use in supporting or sustaining human life that presents a potential for serious risk to the health, safety, or welfare of a subject;

iv. The device is not for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health that presents a potential for serious risk to the health, safety, or welfare of a subject; and

v. The device does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject.

vi. The device will be labeled in accordance with 21 CFR 812.5.

vii. The PI as sponsor will

1. Comply with the requirements of 21 CFR 812.46 with respect to monitoring investigations
2. Maintain the records required under 21 CFR 812.140(b) (4) and (5) and make the reports required under 21 CFR 812.150(b) (1) through (3) and (5) through (10)
3. Ensure that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 21 CFR 812.150(a) (1), (2), (5), and (7)
4. Comply with the prohibitions in 21 CFR 812.7 against promotion and other practices

PULSEWATCH INVESTIGATOR STUDY PLAN

References

1. Kishore, A. *et al.* Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke J. Cereb. Circ.* **45,** 520–526 (2014). 2. Furie, K. L. *et al.* Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke J. Cereb. Circ.* **42,** 227–276 (2011).
3. Sanna, T. *et al.* Cryptogenic stroke and underlying atrial fibrillation. *N. Engl. J. Med.* **370,** 2478–2486 (2014).
4. Gladstone, D. J. *et al.* Atrial fibrillation in patients with cryptogenic stroke. *N. Engl. J. Med.* **370,** 2467–2477 (2014).
5. McManus, D. D. *et al.* A novel application for the detection of an irregular pulse using an iPhone 4S in patients with atrial fibrillation. *Heart Rhythm Off. J. Heart Rhythm Soc.* **10,** 315– 319 (2013).
6. McManus, D. *et al.* PULSE-SMART: Pulse-based Arrhythmia Discrimination Using a Novel Smartphone Application. *J. Cardiovasc. Electrophysiol.* In Press
7. European Heart Rhythm Association *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur. Eur. Pacing Arrhythm. Card. Electrophysiol. J. Work. Groups Card. Pacing Arrhythm. Card. Cell. Electrophysiol. Eur. Soc. Cardiol.* **12,** 1360–1420 (2010).
8. Benjamin, E. J. *et al.* Prevention of atrial fibrillation: report from a national heart, lung, and blood institute workshop. *Circulation* **119,** 606–618 (2009).
9. Christensen, L. M. *et al.* Paroxysmal atrial fibrillation occurs often in cryptogenic ischaemic stroke. Final results from the SURPRISE study. *Eur. J. Neurol. Off. J. Eur. Fed. Neurol. Soc.* **21,** 884–889 (2014).
10. Choe, W. C. *et al.* A Comparison of Atrial Fibrillation Monitoring Strategies After Cryptogenic Stroke (from the Cryptogenic Stroke and Underlying AF Trial). *Am. J. Cardiol.* **116,** 889–893 (2015).
11. Tarakji, K. G. *et al.* Using a novel wireless system for monitoring patients after the atrial fibrillation ablation procedure: the iTransmit study. *Heart Rhythm Off. J. Heart Rhythm Soc.* **12,** 554–559 (2015).
12. AliveCor. www.alivecor.com. website last accessed 6/25/17
13. Lee, J. *et al.* Atrial fibrillation detection using an iPhone 4S. *IEEE Trans. Biomed. Eng.* **60,** 203–206 (2013).
14. Lee, J., Reyes, B. A., McManus, D. D., Mathias, O. & Chon, K. H. Atrial fibrillation detection using a smart phone. *Conf. Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Conf.* **2012,** 1177–1180 (2012).
15. Soni, A. *et al.* Using Mobile Technology to Detect Arrhythmias in Rural India." NIH-IEEE 2015 Strategic Conference on Healthcare Innovations and Point-of-Care Technologies for Precision Medicine; Bethesda, MD; November, 2015. (2015).
16. Soni, A., Earon, A., Handorf, A., Chon, K. & McManus, D. High Burden of Unrecognized Atrial Fibrillation in Rural India: results from an innovative community-based cross-sectional screening program. J Med Internet Res Pub Heal and Surv. In-review. doi: 10.2196/publichealth.6517. *J Med Internet Res* in-review

17. Choe, W. C. *et al.* A Comparison of Atrial Fibrillation Monitoring Strategies After Cryptogenic Stroke (from the Cryptogenic Stroke and Underlying AF Trial). *Am. J. Cardiol.* **116,** 889–893 (2015).
18. Gladstone, D. J. *et al.* Atrial fibrillation in patients with cryptogenic stroke. *N. Engl. J. Med.* **370,** 2467–2477 (2014).
19. Flint, A. C., Banki, N. M., Ren, X., Rao, V. A. & Go, A. S. Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. *Stroke J. Cereb. Circ.* **43,** 2788–2790 (2012).
20. Christensen, L. M. *et al.* Paroxysmal atrial fibrillation occurs often in cryptogenic ischaemic stroke. Final results from the SURPRISE study. *Eur. J. Neurol. Off. J. Eur. Fed. Neurol. Soc.* **21,** 884–889 (2014).
21. Samsung. Samsung Simband. *Samsung Simband Documentation* (2016).
22. Chong, J. W., Esa, N., McManus, D. D. & Chon, K. H. Arrhythmia discrimination using a smart phone. *IEEE J. Biomed. Health Inform.* **19,** 815–824 (2015).
23. Salehizadeh, S. M. A. *et al.* Photoplethysmograph signal reconstruction based on a novel motion artifact detection-reduction approach. Part II: Motion and noise artifact removal. *Ann. Biomed. Eng.* **42,** 2251–2263 (2014).
24. Chong, J. W. *et al.* Photoplethysmograph signal reconstruction based on a novel hybrid motion artifact detection-reduction approach. Part I: Motion and noise artifact detection. *Ann. Biomed. Eng.* **42,** 2238–2250 (2014).
25. Dao, D. K., McManus, D. & Chon, K. A Robust Motion Artifact Detection Algorithm for Accurate Detection of Heart Rates from Photoplethysmographic Signals using Time-Frequency Spectral Features. *IEEE Journal of Biomedical and Health Informatics* in press (2016).
26. McManus, D. D. *et al.* A novel application for the detection of an irregular pulse using an iPhone 4S in patients with atrial fibrillation. *Heart Rhythm Off. J. Heart Rhythm Soc.* **10,** 315– 319 (2013).
27. Napolitano, C. *et al.* Pulse-based Arrhythmia Discrimination Using a Novel Smartphone Application.
28. Riley, W. T. *et al.* Health behavior models in the age of mobile interventions: are our theories up to the task? *Transl. Behav. Med.* **1,** 53–71 (2011).
29. January, C. T. *et al.* 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* **130,** e199-267 (2014).
30. Skanes, A. C. *et al.* Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can. J. Cardiol.* **28,** 125–136 (2012).
31. Palmer, A. J. *et al.* Overview of costs of stroke from published, incidence-based studies spanning 16 industrialized countries. *Curr. Med. Res. Opin.* **21,** 19–26 (2005).
32. Kim, M. H., Johnston, S. S., Chu, B.-C., Dalal, M. R. & Schulman, K. L. Estimation of total incremental healthcare costs in patients with atrial fibrillation in the United States. *Circ. Cardiovasc. Qual. Outcomes* **4,** 313–320 (2011).

33. Fak, A. S. *et al.* Expert panel on cost analysis of atrial fibrillation. *Anadolu Kardiyol. Derg. AKD Anatol. J. Cardiol.* **13,** 26–38 (2013).
34. Palmer, A. J. *et al.* Overview of costs of stroke from published, incidence-based studies spanning 16 industrialized countries. *Curr. Med. Res. Opin.* **21,** 19–26 (2005).
35. AliveCor. https://www.alivecor.com/clinicians/. Accessed 6/26/2017.
36. Ricci, R. P. Disease management: atrial fibrillation and home monitoring. *Eur. Eur. Pacing Arrhythm. Card. Electrophysiol. J. Work. Groups Card. Pacing Arrhythm. Card. Cell. Electrophysiol. Eur. Soc. Cardiol.* **15 Suppl 1,** i35–i39 (2013).
37. Dassonville, P. *et al.* Cognitive impairments and impact on activities of daily living after minor stroke. *Ann. Phys. Rehabil. Med.* **59S,** e71 (2016).
38. Carpenter, A. & Frontera, A. Smart-watches: a potential challenger to the implantable loop recorder? *Eur. Eur. Pacing Arrhythm. Card. Electrophysiol. J. Work. Groups Card. Pacing Arrhythm. Card. Cell. Electrophysiol. Eur. Soc. Cardiol.* **18,** 791–793 (2016).
39. Smith, A. Older Adults and Technology Use. *Pew Research Center's Internet & American Life Project*
40. Ho, C.-L. *et al.* Smartphone applications (apps) for heart rate measurement in children: comparison with electrocardiography monitor. *Pediatr. Cardiol.* **35,** 726–731 (2014). 41. Chong, J. W., Esa, N., McManus, D. & Chon, K. Arrhythmia Discrimination using a Smart Phone. *IEEE J. Biomed. Health Inform.* (2015). doi:10.1109/JBHI.2015.2418195
42. Authors/Task Force Members: *et al.* 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). *Eur. J. Cardio-Thorac. Surg. Off. J. Eur. Assoc. Cardio-Thorac. Surg.* (2016). doi:10.1093/ejcts/ezw313
43. *Know Your Pulse*. http://www.heartrhythmalliance.org/aa/uk/about-the-campaign. Accessed 6/25/17.
44. Fak, A. S. *et al.* Expert panel on cost analysis of atrial fibrillation. *Anadolu Kardiyol. Derg. AKD Anatol. J. Cardiol.* **13,** 26–38 (2013).
45. Wolf, P. A., Abbott, R. D. & Kannel, W. B. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke J. Cereb. Circ.* **22,** 983–988 (1991).
46. Lubitz, S. A. *et al.* Atrial fibrillation patterns and risks of subsequent stroke, heart failure, or death in the community. *J. Am. Heart Assoc.* **2,** e000126 (2013).
47. Reiffel, J. A. Atrial fibrillation and stroke: epidemiology. *Am. J. Med.* **127,** e15-16 (2014).
48. Svennberg, E. *et al.* Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. *Circulation* **131,** 2176–2184 (2015).
49. Flint, A. C., Banki, N. M., Ren, X., Rao, V. A. & Go, A. S. Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry. *Stroke J. Cereb. Circ.* **43,** 2788–2790 (2012). 50. Martin, D. T. *et al.* Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. *Eur. Heart J.* **36,** 1660–1668 (2015).
51. Haberman, Z. C. *et al.* Wireless Smartphone ECG Enables Large-Scale Screening in Diverse Populations. *J. Cardiovasc. Electrophysiol.* **26,** 520–526 (2015).

52. Tarakji, K. G. *et al.* Using a novel wireless system for monitoring patients after the atrial fibrillation ablation procedure: the iTransmit study. *Heart Rhythm Off. J. Heart Rhythm Soc.* **12,** 554–559 (2015).
53. Street, 1615 L., NW, Washington, S. 700 & Inquiries, D. 20036 202 419 4300 | M. 202 419 4349 | F. 202 419 4372 | M. Mobile Technology Fact Sheet. *Pew Research Center's Internet & American Life Project*
54. Barret, L. Health and Caregiving among the 50+: Ownership, Use and Interest in Mobile Technology. (2011).
55. Fitzner, K. & Moss, G. Telehealth--an effective delivery method for diabetes selfmanagement education? *Popul. Health Manag.* **16,** 169–177 (2013).
56. Arora, S., Peters, A. L., Burner, E., Lam, C. N. & Menchine, M. Trial to examine text message-based mHealth in emergency department patients with diabetes (TExT-MED): a randomized controlled trial. *Ann. Emerg. Med.* **63,** 745–754.e6 (2014).
57. McManus, D. D. *et al.* Plasma microRNAs are associated with atrial fibrillation and change after catheter ablation (the miRhythm study). *Heart Rhythm Off. J. Heart Rhythm Soc.* **12,** 3–10 (2015).
58. Chong, J. W. *et al.* Photoplethysmograph signal reconstruction based on a novel hybrid motion artifact detection-reduction approach. Part I: Motion and noise artifact detection. *Ann. Biomed. Eng.* **42,** 2238–2250 (2014).
59. Chong, J. W., Esa, N., McManus, D. D. & Chon, K. H. Arrhythmia discrimination using a smart phone. *IEEE J. Biomed. Health Inform.* **19,** 815–824 (2015).
60. Dash, S., Chon, K. H., Lu, S. & Raeder, E. A. Automatic real time detection of atrial fibrillation. *Ann. Biomed. Eng.* **37,** 1701–1709 (2009).
61. Lee, J. *et al.* Atrial fibrillation detection using an iPhone 4S. *IEEE Trans. Biomed. Eng.* **60,** 203–206 (2013).
62. McManus, D. D. *et al.* A novel application for the detection of an irregular pulse using an iPhone 4S in patients with atrial fibrillation. *Heart Rhythm Off. J. Heart Rhythm Soc.* **10,** 315– 319 (2013).
63. Lee, J., McManus, D. D., Bourrell, P., Sörnmo, L. & Chon, K. H. Atrial flutter and atrial tachycardia detection using Bayesian approach with high resolution time–frequency spectrum from ECG recordings. *Biomed. Signal Process. Control* **8,** 992–999 (2013).
64. Gold, M. R. *et al.* Head-to-head comparison of arrhythmia discrimination performance of subcutaneous and transvenous ICD arrhythmia detection algorithms: the START study. *J. Cardiovasc. Electrophysiol.* **23,** 359–366 (2012).
65. Sarkar, S., Ritscher, D. & Mehra, R. A detector for a chronic implantable atrial tachyarrhythmia monitor. *IEEE Trans. Biomed. Eng.* **55,** 1219–1224 (2008).
66. Petterson, M. T., Begnoche, V. L. & Graybeal, J. M. The effect of motion on pulse oximetry and its clinical significance. *Anesth. Analg.* **105,** S78-84 (2007).
67. Lee, J., McManus, D. D., Merchant, S. & Chon, K. H. Automatic motion and noise artifact detection in Holter ECG data using empirical mode decomposition and statistical approaches. *IEEE Trans. Biomed. Eng.* **59,** 1499–1506 (2012).
68. O'Day, K. *et al.* Abstract 129: Severity of Symptoms from Atrial Fibrillation is Associated with Depression and Anxiety: Preliminary Data from the InRhythm Study. *Circ. Cardiovasc.*

Qual. Outcomes **7,** A129–A129 (2014).
69. Suter, D. *et al.* Quality of Life in Symptomatic Patients with Atrial Fibrillation: Preliminary Data from the InRhythm Study. (2014).
70. Boriani, G. *et al.* Device-detected atrial fibrillation and risk for stroke: an analysis of >10,000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). *Eur. Heart J.* **35,** 508–516 (2014).
71. Boriani, G. & Pettorelli, D. Atrial fibrillation burden and atrial fibrillation type: Clinical significance and impact on the risk of stroke and decision making for long-term anticoagulation.

Vascul. Pharmacol. **83,** 26–35 (2016).
72. Boyle, M. A Shared Vocabulary for Privacy. in *5th International Conference on Ubiquitous Computing* (2003).
73. O'Day, K. *et al.* Abstract 129: Severity of Symptoms from Atrial Fibrillation is Associated with Depression and Anxiety: Preliminary Data from the InRhythm Study. *Circ. Cardiovasc.*

Qual. Outcomes **7,** A129–A129 (2014).
74. Lip, G. Y. H., Lane, D. A., Buller, H. & Apostolakis, S. Development of a novel composite stroke and bleeding risk score in patients with atrial fibrillation: the AMADEUS Study. *Chest* **144,** 1839–1847 (2013).
75. Cristianini, N. & Shawe-Taylor, J. *An introduction to support vector machines : and other kernel-based learning methods*. (Cambridge University Press, 2000).
76. Kecman, V. *Learning and soft computing: Support vector machines, Neural networks, and Fuzzy logic models*. (The MIT Press, 2001).
77. Salehizadeh, S. M. A. *et al.* A Novel Time-Varying Spectral Filtering Algorithm for Reconstruction of Motion Artifact Corrupted Heart Rate Signals During Intense Physical Activities Using a Wearable Photoplethysmogram Sensor. *Sensors* **16,** (2015).
78. Schmitt, E. M. *et al.* Novel risk markers and long-term outcomes of delirium: the successful aging after elective surgery (SAGES) study design and methods. *J. Am. Med. Dir.*

Assoc. **13,** 818.e1-10 (2012).
79. Morgan, D. L. & Krueger, R. A. *Planning Focus Groups*. (SAGE, 1998).
80. Davis, F. D. Perceived Usefulness, Perceived Ease of Use, and User Acceptance of Information Technology. *MIS Q.* **13,** 319–340 (1989).
81. De Vito Dabbs, A. *et al.* User-centered design and interactive health technologies for patients. *Comput. Inform. Nurs. CIN* **27,** 175–183 (2009).
82. Agile Science. Available at: http://www.agilescience.org/. (Accessed: 31st August 2015)
83. Bastian, Z. The Power of Hackathons: A Roadmap for Sustainable Open Innovation. *Wilson Center* (2013).
84. Leckart, S. The Hackathon Is On: Pitching and Programming the Next Killer App. *WIRED* (2012). Available at: http://www.wired.com/2012/02/ff_hackathons/all/. (Accessed: 31st August 2015)
85. Suter, D. *et al.* Quality of Life in Symptomatic Patients with Atrial Fibrillation: Preliminary Data from the InRhythm Study. (2014).
86. Spitzer, R. L., Kroenke, K., Williams, J. B. W. & Löwe, B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch. Intern. Med.* **166,** 1092–1097 (2006).
87. Spitzer, R. L., Kroenke, K. & Williams, J. B. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders.

Patient Health Questionnaire. *JAMA* **282,** 1737–1744 (1999).
88. Duncan, P. W. *et al.* Development of a comprehensive assessment toolbox for stroke. *Clin. Geriatr. Med.* **15,** 885–915 (1999).
89. Duncan, P. W. *et al.* The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. *Stroke J. Cereb. Circ.* **30,** 2131–2140 (1999).
90. Lai, S.-M., Studenski, S., Duncan, P. W. & Perera, S. Persisting consequences of stroke measured by the Stroke Impact Scale. *Stroke J. Cereb. Circ.* **33,** 1840–1844 (2002).
91. Hibbard, J. H., Mahoney, E. R., Stockard, J. & Tusler, M. Development and testing of a short form of the patient activation measure. *Health Serv. Res.* **40,** 1918–1930 (2005).
92. Hibbard, J. H., Mahoney, E. R., Stock, R. & Tusler, M. Do increases in patient activation result in improved self-management behaviors? *Health Serv. Res.* **42,** 1443–1463 (2007).
93. Dixon, A., Hibbard, J. & Tusler, M. How do People with Different Levels of Activation Self-Manage their Chronic Conditions? *The Patient* **2,** 257–268 (2009).
94. Nasreddine, Z. S. *et al.* The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* **53,** 695–699 (2005).
95. Folstein, M. F., Folstein, S. E. & McHugh, P. R. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatr. Res.* **12,** 189–198 (1975).
96. McLennan, S. N., Mathias, J. L., Brennan, L. C. & Stewart, S. Validity of the montreal cognitive assessment (MoCA) as a screening test for mild cognitive impairment (MCI) in a cardiovascular population. *J. Geriatr. Psychiatry Neurol.* **24,** 33–38 (2011).
97. Hachinski, V. *et al.* National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. *Stroke J. Cereb. Circ.*
37, 2220–2241 (2006).
98. Pendlebury, S. T. *et al.* Telephone assessment of cognition after transient ischemic attack and stroke: modified telephone interview of cognitive status and telephone Montreal Cognitive Assessment versus face-to-face Montreal Cognitive Assessment and neuropsychological battery. *Stroke J. Cereb. Circ.* **44,** 227–229 (2013).
99. Lubben, J. *et al.* Performance of an abbreviated version of the Lubben Social Network Scale among three European community-dwelling older adult populations. *The Gerontologist* **46,** 503–513 (2006).
100. Sherbourne, C. D. & Stewart, A. L. The MOS social support survey. *Soc. Sci. Med. 1982* **32,** 705–714 (1991).
101. Kroenke, K., Spitzer, R. L. & Williams, J. B. The PHQ-9: validity of a brief depression severity measure. *J. Gen. Intern. Med.* **16,** 606–613 (2001).
102. Katon, W., Lin, E. H. B. & Kroenke, K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen. Hosp. Psychiatry* **29,** 147–155 (2007).
103. Gilbody, S., Richards, D., Brealey, S. & Hewitt, C. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. *J. Gen.*
Intern. Med. **22,** 1596–1602 (2007).
104. Stafford, L., Berk, M. & Jackson, H. J. Validity of the Hospital Anxiety and Depression Scale and Patient Health Questionnaire-9 to screen for depression in patients with coronary artery disease. *Gen. Hosp. Psychiatry* **29,** 417–424 (2007).

105. Macphee, G. J., Crowther, J. A. & McAlpine, C. H. Screening for impaired hearing in the elderly. *JAMA* **260,** 3589–3590 (1988).
106. Macphee, G. J., Crowther, J. A. & McAlpine, C. H. A simple screening test for hearing impairment in elderly patients. *Age Ageing* **17,** 347–351 (1988).
107. Sarkar, U., Fisher, L. & Schillinger, D. Is self-efficacy associated with diabetes selfmanagement across race/ethnicity and health literacy? *Diabetes Care* **29,** 823–829 (2006). 108. Scherer, Y. K. & Bruce, S. Knowledge, attitudes, and self-efficacy and compliance with medical regimen, number of emergency department visits, and hospitalizations in adults with asthma. *Heart Lung J. Crit. Care* **30,** 250–257 (2001).
109. Lorig, K. *Outcome Measures for Health Education and Other Health Care Interventions*. (SAGE, 1996).
110. Morisky, D. E., Ang, A., Krousel-Wood, M. & Ward, H. J. Predictive validity of a medication adherence measure in an outpatient setting. *J. Clin. Hypertens. Greenwich Conn* **10,** 348–354 (2008).
111. Granger, C. V., Dewis, L. S., Peters, N. C., Sherwood, C. C. & Barrett, J. E. Stroke rehabilitation: analysis of repeated Barthel index measures. *Arch. Phys. Med. Rehabil.* **60,** 14– 17 (1979).
112. Guest, G., MacQueen, K. M. & Namey, E. E. *Applied Thematic Analysis*. (SAGE, 2011).
113. Gale, N. K., Heath, G., Cameron, E., Rashid, S. & Redwood, S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med. Res. Methodol.* **13,** 117 (2013).
114. Lee, J. *et al.* Atrial fibrillation detection using an iPhone 4S. *IEEE Trans. Biomed. Eng.* **60,** 203–206 (2013).
115. Wittes J and Brittain E. The Role of Internal Pilot Studies in Increasing the Efficiency of Clinical Trials. Stat in Med 1990: 9: 65-72