Scripps Translational Science Institute

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mHealth Screening To Prevent Strokes
(mSToPS)

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Study Protocol

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Version 4.0

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Table of Contents

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1. Purpose

This study will investigate whether it is possible to identify a high-risk cohort suitable for screening for asymptomatic atrial fibrillation using claims data, and then engage those individuals in a mobile health technology-enabled home monitoring program in order to document previously undiagnosed atrial fibrillation, and provide clinical evidence of an outcomes benefit associated with this early detection.

2. Background

There are few medical conditions more strongly connected with substantial, yet preventable morbidity and mortality than is atrial fibrillation (AF).   AF is associated with a 5-fold increase in stroke risk,[1] is responsible for at least 15%-25% of all strokes, and is believed to contribute to a significant proportion of the 25% of stroke patients without a clear etiology for their stroke.[2, 3]   The mean direct cost of a stroke is estimated to be ~$20,000, with total annual direct and indirect costs in the US alone of ~$54 billion.[4, 5]

Fortunately very effective therapies are available to prevent strokes in patients with AF. Treatment with oral anticoagulation, either titrated warfarin or one of several novel oral anticoagulants, can reduce stroke risk by nearly 70%.[6] A major challenge to assuring the right individuals are treated with oral anticoagulants is the fact that AF is often intermittent and asymptomatic, and therefore difficult to recognize, although the stroke risk of individuals with asymptomatic or intermittent AF is no different from that of individuals who are symptomatic or have continuous AF.[7, 8]

The overall prevalence of diagnosed AF in the adult US population is roughly 1%.[9] However, the incidence in a population varies greatly with age, with adults over age 60 having a prevalence of 4%, increasing to 9% for those over age 80. In addition the presence of other co-morbidities such as hypertension, diabetes, prior stroke or TIA, and the presence of heart failure are also strongly associated

Figure 2. Prevalence of Diagnosed Atrial Fibrillation Stratified by Age and Sex
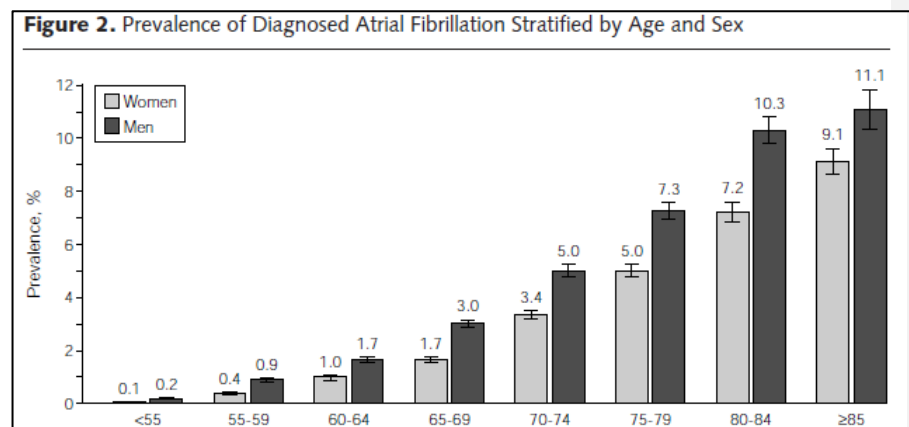
with an increased prevalence of AF. In a small study of adults with an average age of 64 and one or more risk factors the prevalence varied from 3% in those with hypertension alone but up to 9% in those with hypertension, diabetes, and stroke.[10]

The proportion of individuals with AF who are undiagnosed is estimated to be somewhere between 10% and 30% of the total atrial fibrillation population. A study of 1,028 hypertensive patients with a mean age 73 years found 16.0% of patients with AF (16/106) were previously undiagnosed.[11] In another study of individuals with heart failure found almost one-third to have undiagnosed paroxysms of atrial fibrillation.[12] In the largest AF population screening trial reported to date, involving over 6000 individuals ages 75 or 76, 31% of individuals identified as having AF had not been previously diagnosed.[13]

Strategies for population screening for AF that have been rigorously evaluated are extremely limited. In fact a 2013 Cochrane Review of the effectiveness of systematic screening for the detection of atrial fibrillation found only one study meeting its review criteria.[14] That study, carried out in the UK between 2001 and 2003, included 50 primary care clinics and just under 15,000 individuals over age 65.[15] Approximately 10,000 individuals were randomized to an intervention arm and ~5000 to a standard-of-care control arm. Half of the individuals in the intervention arm were invited to be systematically screened with a 12-lead ECG in the clinic (Systematic Screening) and the other half had their records flagged to have their pulse checked during routine clinic visits and ECG performed if an irregular pulse was noted (Opportunistic Screening). Both systematic and opportunistic screening strategies were found to similarly effective (OR1.57 and OR 1.58, respectively) in identifying individuals with AF better than routine care at one year. However, this method has multiple limitations to implementation. Notably only half of individuals invited to participate agreed to do so and the cost per additional case of AF identified was £1514 GBP (~$2500 USD) in the systematic screening arm.

The recent availability of mobile health devices can enable simpler and potentially more effective means of screening for AF, with several screening studies utilizing mobile technologies already published or presented. The most ambitious to date is the STROKESTOP study of a planned 25,000 Swedes age 75 or 76 years old with half randomized to the intervention arm that includes intermittent one-lead ECG recording twice a day, 30-seconds each, for 2 weeks.[16] Recently announced preliminary results found 11% of ~6,496 screened individuals to be in AF, with 3% being previously undiagnosed.[13] Another study that randomly screened ~1000 individuals ≥65 years old at ten local pharmacies in Sydney using the AliveCor monitor found an incidence of 1.5%.[17] While these results are encouraging it is clear that intermittent

screening does miss a substantial proportion of AF cases and more targeted screening would improve the effectiveness. For example, in one high-risk cohort with normal sinus rhythm and recently implanted permanent pacemakers newly detected AF or atrial tachycardia were identified in 30% of individuals within one year of monitoring with a median time to detection of 72 days.[18]

As implantable devices solely for the detection of AF is impractical as a means of population screening in an asymptomatic population there is a need to identify the optimal means to non-invasively detect AF in a large, at-risk population. Fortunately several novel mobile health technologies now allow for much more simplified and patient-centric methods of ECG screening. As noted above, the AliveCor monitor or other smartphone-based technologies such as photoplethysmography can be used for intermittent monitoring. [19, 20] But that would require ongoing incentives to assure adequate compliance. Other wearable technologies, such as watch or wristband activity monitoring devices that are also capable of continuously monitoring heart rate and its variability could offer the potential to passively, and non-obtrusively monitor for AF long term with the advantage of helping drive other healthy behaviors. Finally, formal monitoring with wearable, non-obtrusive ECG patches, which are well tolerated, can be worn for up to 2 weeks with continuous single-lead ECG monitoring to screen for AF.[21]

We propose to study two different methods of intermittent rhythm monitoring (see Section 4) in a cohort of individuals without prior history of atrial fibrillation but determined to be at increased risk based on clinical risk factors, and compare the rate of atrial fibrillation detection through monitoring relative to routine care.

3. Objectives

The overarching objective of this study is to demonstrate that screening select individuals in their homes using wearable sensor technology can identify individuals with asymptomatic atrial fibrillation and that doing so will influence treatment and clinical outcomes.

Atrial Fibrillation Detection Objectives

- Identify a high-risk cohort optimized for screening based on claims data information.

- Determine the relative benefit of active screening compared to routine care (i.e., standard of care as defined by the medical care each patient is already receiving) for identifying new cases of atrial fibrillation after 4 months.
- Compare the diagnostic capability of two different methods of rhythm screening – time-limited patch ECG monitoring versus long-term wearable pulse wave monitoring through photoplethysmography – for AF detection and tolerability.

Influence on Clinical Care

- Compare the rate of initiation of anticoagulation and other AF-specific therapies at 12-months in the active monitoring cohort versus the matched observational control cohort.
- Compare the overall incremental costs of active monitoring for AF detection versus standard of care in the 3 years following the onset of monitoring.
- Identify the impact of active AF screening versus routine care on the time to first event of the following endpoints using claims data; A) among individuals diagnosed with new AF at 3 years following the initiation of screening, and B) the entire study cohort: utilizing claims data.
    - The combined endpoint of stroke/TIA, other systemic embolization, and/or myocardial infarction.
    - In the Medicare population only, in who mortality data will be available, the combined endpoint of stroke/TIA, other systemic embolization, myocardial infarction and/or death
    - The individual components of the combined endpoint.
    - All hospitalizations.
    - Hospitalizations for bleeding events.

4. Study Design

Participants

The study population will be derived from the Aetna Commercial Fully Insured and Medicare populations. From this population specific characteristics associated with an increased proportion of prevalent atrial fibrillation will be identified through claims data and utilized to identify a population at increased risk for undiagnosed atrial fibrillation.

Inclusion Criteria:

- Male or female age > 75 or
- Male age > 55, or female age > 65, and
- Prior CVA, or
- Heart failure, or
- Diagnosis of both diabetes and hypertension, or
- Mitral valve disease, or
- Left ventricular hypertrophy, or
- COPD requiring home O2, or
- Sleep apnea, or
- History of pulmonary embolism, or
- History of myocardial infarction, or
- Diagnosis of obesity

Exclusion Criteria:

- Current or prior diagnosis of atrial fibrillation, atrial flutter or atrial tachycardia
- Receiving chronic anticoagulation therapy
- Hospice care
- End stage renal disease
- Diagnosis of moderate or greater dementia
- Implantable pacemaker and/or defibrillator
- History of skin allergies to adhesive patches
- Known metastatic cancer
- Aetna Compassionate Care Program (ACCP) participants – individuals with advanced illness and limited life expectancy

Through the use of the above inclusion and exclusion criteria, but not excluding patients with a diagnosis of atrial fibrillation or flutter, we expect to identify a population with an overall prevalence of known AF of 10-15%. Based on prior studies supporting that 30% of the total AF population is undiagnosed, then the total AF population (X) = diagnosed AF population $(0.7X)$ + undiagnosed AF population $(0.3X)$. Therefore with a 12% prevalence of diagnosed AF representing only 70% of the total AF population that would suggest that the true total AF population prevalence is 17%, and therefore the prevalence of undiagnosed AF would be ~5%.
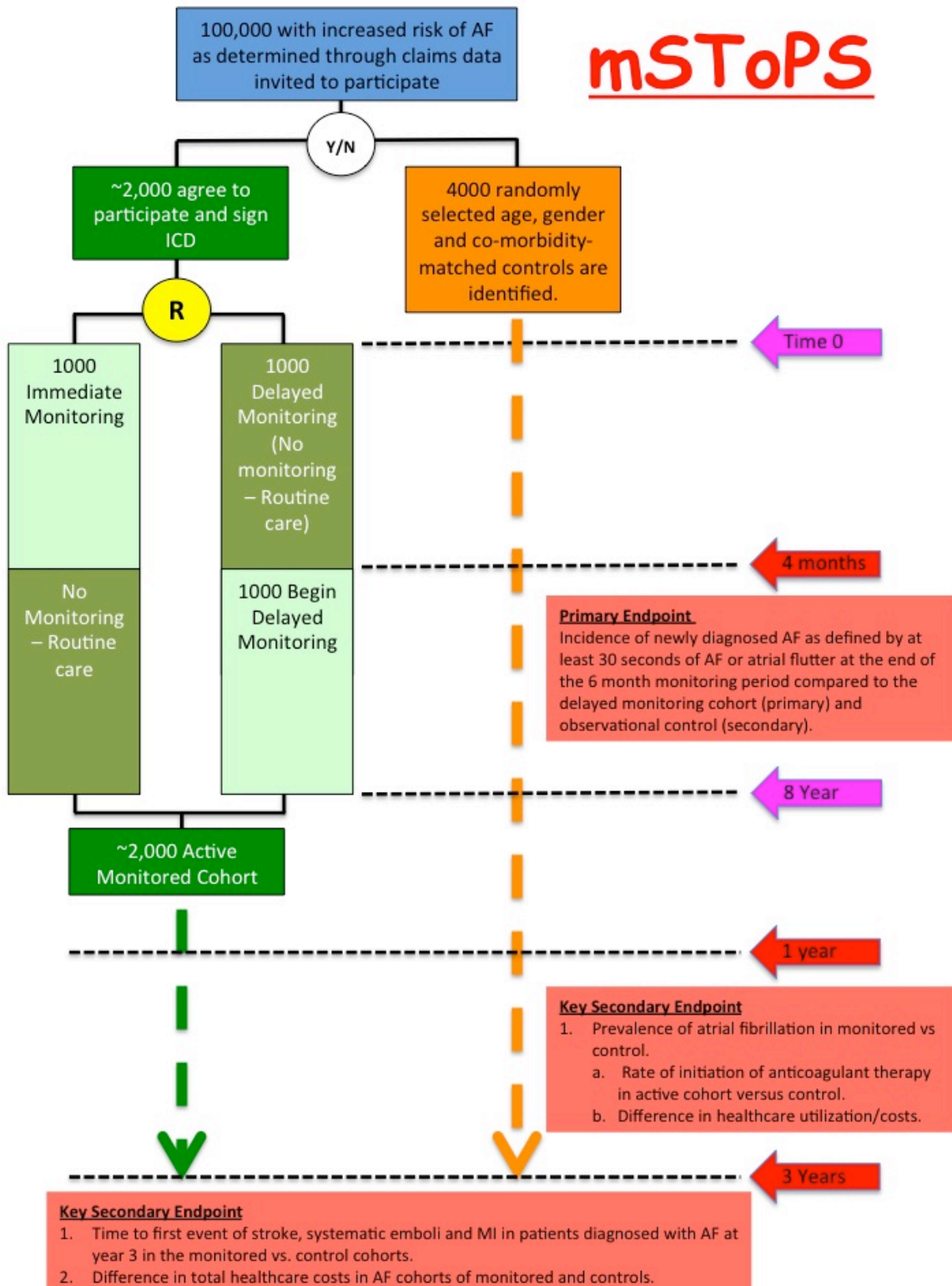
Participant Recruitment

Eligible Aetna members will be contacted by letter, electronically or paper, (Appendix 1) with information about the study and an invitation to learn more via a study-specific web site as well as the option to discuss with a research coordinator. Once an individual agrees to participate they will be directed to an online Informed Consent Document, or if they prefer, one will be mailed to them.

A conservative estimate is that 5% of the approached population will agree to participate in the study. With an estimated >100,000 eligible participants to approach this should allow for the recruitment of a total of 2000 individuals for randomization and allow for development of a matched observational cohort of 4000 individuals.

It is anticipated that 10,000 invitations will be sent out to eligible Aetna members on a rolling basis every one to two weeks with invitations continuing until ~2250 (to account for an assumed 12% drop-out in first year) individuals have agreed to participate and signed the informed consent.

Study Flow

100,000 with increased risk of AF as determined through claims data invited to participate

mSToPS

Y/N

~2,000 agree to participate and sign ICD

4000 randomly selected age, gender and co-morbidity-matched controls are identified.

R

1000 Immediate Monitoring

1000 Delayed Monitoring (No monitoring – Routine care)

Time 0

No Monitoring – Routine care

1000 Begin Delayed Monitoring

4 months

Primary Endpoint
Incidence of newly diagnosed AF as defined by at least 30 seconds of AF or atrial flutter at the end of the 6 month monitoring period compared to the delayed monitoring cohort (primary) and observational control (secondary).

8 Year

~2,000 Active Monitored Cohort

1 year

Key Secondary Endpoint
1. Prevalence of atrial fibrillation in monitored vs control.
    a. Rate of initiation of anticoagulant therapy in active cohort versus control.
    b. Difference in healthcare utilization/costs.

3 Years

Key Secondary Endpoint
1. Time to first event of stroke, systematic emboli and MI in patients diagnosed with AF at year 3 in the monitored vs. control cohorts.
2. Difference in total healthcare costs in AF cohorts of monitored and controls.

Randomized Cohort

Following informed consent individuals will be randomized to either the immediate screening arm or the delayed screening arm. All individuals randomized to immediate screening will be sent their monitoring device(s) immediately after signing their informed consent. Their 4 months of monitoring will begin the first day their monitoring device is activated. Those randomized to delayed monitoring will receive their monitoring device(s) 4 months after the date of their informed consent being signed, with their 4 months of monitoring also starting the first day their monitoring device is activated.

During the 4-month monitoring period all individuals will undergo continuous single-lead ECG monitoring with a wearable patch (iRhythm ZIO® XT Patch) during the first and last 2 weeks of the 4-month study period (total of 4 weeks).

Consenting participants will also be invited to participate in a ~500 person sub-study to wear an additional monitoring device; a wristband photoplethysmography-based device (Amiigo). Enrollment in this sub-study will be limited to individuals who already own and use a smartphone (iOS or Android). Volunteers will be asked to sign a second informed consent to participate in this sub-study.

Monitoring Devices

All individuals randomized to active screening will receive a ZIO XT Patch (http://www.irhythmtech.com/zio-solution/zio-patch/). The ZIO XT Patch will be mailed to the participant's home with instructions how to place and activate the patch. A link to an instructional video will also be provided as well a call-in number for support.

They will be asked to wear it for the first 2 weeks, and again during the final 2 weeks of the 4-month monitoring period. While wearing the patches a single-lead ECG is recorded

continuously. After the 2-week monitoring period the patch is mailed back to iRhythm in a pre-prepared package where the rhythm is analyzed.

A second exploratory method of rhythm detection in a self-identified subset of the same patients will be carried out using a wristband developed by Amiigo (https://amiigo.com/) that will allow for long term, non-obtrusive monitoring on a daily basis throughout the 4 month period. The Amiigo determines resting pulse rate using photoplethysmography; a technique become more ubiquitous in wearable mHealth devices. Data is analyzed on a near-continuous basis for rhythm abnormalities as well as other physiologic parameters. Individuals agreeing to be monitored with the Amiigo will have one sent to them along with a charging devices and instructions to download the smartphone app. Only routine fitness data, such as activity, calories burned and sleep duration will be available to Amiigo users via the app. Individuals will be encouraged to wear the device as frequently as possible, night and day, throughout the 4-month monitoring period. Rhythm monitoring will occur passively while a subset will also be prompted daily to sit quietly for 60 seconds to allow for active monitoring. As the Amiigo's rhythm detection capability is exploratory anyone identified to potentially have AF during a period when they are not concurrently wearing a ZIO XT Patch, will be sent another ZIO XT Patch to wear for an additional 2 weeks in order to confirm the diagnosis of AF.

Observational Control Group

A risk-matched observational cohort will be developed from among individuals deemed eligible for study participation but not having the opportunity to participate in the randomized study (i.e. randomized cohort filled prior to their being invited). Individuals will be matched 2:1 with the 2,000 actively monitored cohort based on age, gender, CHA_2DS_2-VASc score, and Propensity Score. An individual's CHA_2DS_2-VASc score can range from 0 to 10 and is based on the composite value of points determined by the presence of cardiac failure or dysfunction (1 point), Hypertension (1 point), Age $\geq$ 75 (2 points), Diabetes (1 point), Stroke (2 points)-Vascular disease (1 point), Age 65–74 (1 point) and Sex category (1 point for female).

The observational period of controls will begin the day their matched actively monitored counterpart signed their informed consent.

Atrial Fibrillation Diagnosis

In the actively monitored cohort a diagnosis of atrial fibrillation/flutter will be made based on documented evidence of a minimum of 30 seconds of continuous atrial fibrillation or flutter confirmed by ECG monitoring with the ZIO XT Patch during the active monitoring period, or the new clinical diagnosis of atrial fibrillation or flutter based on claims data. For the control cohort a new diagnosis will be based solely on a new clinical diagnosis documented in claims data.

Individuals who are identified with AF or other actionable rhythm in the monitored cohort will be contacted, as well as their most appropriate provider with the individual's permission) with the diagnosis and necessary documentation.

5. Data Acquisition, Storage and Analysis

Rhythm analysis of ZIO XT Patches will occur as routine through iRhythm.   Amiigo will carry out rhythm detection via the wristband monitor, and if AF suspected at a time when the individual is not also wearing a ZIO XT Patch, the individual will be sent another ZIO XT Patch and concurrent monitoring with a ZIO XT Patch will be repeated. Complete rhythm data for all individuals will be transferred to STSI for over read by the data adjudicating committee.

 Participants and their identified primary provider will be contacted when necessary including all new diagnoses of AF or any other potentially clinically significant rhythms as determined by the adjudication committee. In these instances participants and their provider will be sent copies of full disclosure iRhythm reports.

Results of monitoring will be aggregated at STSI based on study ID number. These data will be periodically securely sent to Aetna for aggregation with all clinical data routinely available to

them. Aetna will generate and securely transfer to STSI the de-identified data sets necessary for endpoint analysis by STSI for all primary and secondary endpoints.

<u>Future research</u>

Subject information will be kept for up to 6 years after completion of this study for future research that has not yet been planned. De-identified information will be kept indefinitely for future research studies at Scripps Translational Science Institute.

6. Efficacy and Safety Endpoints

<u>Primary Efficacy Endpoint</u>

Incidence of newly diagnosed atrial fibrillation (as defined by ≥ 30 seconds of atrial fibrillation or flutter, or a new clinical diagnosis) at the end of the 4-month monitoring period, comparing the monitored cohort (n=1000) with the delayed monitoring cohort (n=1000) as the primary analysis, and the observational cohort (n=4000) as a secondary analysis.

<u>Secondary Efficacy Endpoints</u>

1. Incidence of atrial fibrillation in the monitored cohort (n=2000) versus the observation control cohort (n=4000) at 12 months.

   - Rate of initiation of anticoagulation therapy in monitored compared with controls.

   - Differences in healthcare utilization based on claims data in the overall population as well as AF diagnosed individuals only.

2. Time to first event of stroke, systemic emboli, or myocardial infarction in the sub-population of individuals diagnosed with AF in the 2 cohorts, as well as within the entire cohorts during 3 years of follow-up. For the Medicare population in who reliable mortality data are available the time to first event of stroke, systemic emboli, myocardial infarction or death will also be evaluated.

   - Time to first event of individual components of the combined endpoint.

3. Cost effectiveness outcome is a key analysis but because of the many unknowns surrounding event rates, and changes in therapy at the time of diagnosis a Bayesian approach seems most appropriate. The initial determination of cost effectiveness will be limited to those diagnosed with AF by 3 years using available claims data. A secondary analysis can evaluate the entire study population comparing a monitored approach to standard of care.

4. Exploratory analysis of the efficacy of the Amigo wristband in detecting AF relative to ECG confirmation by ZIO XT Patch.

Safety Endpoints

1. Incidence of hospitalization for a primary bleeding diagnosis.

2. Incidence of the detection of non-AF, but other actionable heart rhythm issues during monitoring.

3. Incidence, timing and etiology of early discontinuation of active monitoring.

Endpoint Data Dictionary

1. Atrial Fibrillation/Flutter: Diagnosis of atrial fibrillation or atrial flutter confirmed via the Aetna Informatics Health Profile Database (HPD). The HPD is a foundation database used to identify Aetna members with chronic diseases or medical conditions. The identification algorithms are comprised of medical, pharmacy, and clinical laboratory data from physician claims and encounters, specialist claims, pharmacy, facilities, laboratories and others.

2. Each of the end-points listed below will be identified using ICD9/ICD10 codes within the adjudicated inpatient or ER medical case.

    a. Transient ischemic attack / Stroke

    b. Myocardial infarction

    c. Arterial thromboembolism

3. Hospital admitting, discharge and transfer (ADT) information will be used to identify hospitalizations, and length of stay.

4. Drug NDC codes will be used to identify new refill for any anticoagulant (dabigatran, rivaroxaban, apixaban) or P2Y12 antagonists (clopidogrel, prasugrel or ticagrelor).

5. Mortality will be determined based on the latest Aetna membership tables and hospital discharge status.

7. Statistical Considerations

4 month assumptions: 5% incidence AF in monitored, 0.5% in non-monitored.

|	Sample Size Active Monitoring	Sample Size Delayed Monitoring	Event Rate Active Monitoring	Event Rate Delayed Monitoring	Power
As Designed	1000	1000	5%	0.5%	>0.99
Minimal Size	320	320	5%	0.5%	0.90
Minimal Size, Increased Event Rate	430	430	5%	1.0%	0.90

12 months assumptions: 7% incidence AF in monitored, 2% in the observational control arm.

	Sample Size Active Monitoring	Sample Size Matched Observational Cohort	Event Rate Active Monitoring	Event Rate Delayed Monitoring	Power
As Designed	2000	4000	7%	2%	>0.99
Minimal Size	400	400	7%	2%	0.90
Minimal Size, Increased Event Rate	1278	1278	7%	4%	0.90

3-year assumptions:

- 10% prevalence of AF in both monitored and observational control arms.

- A 7.5% event rate in observation cohort (based on ACTIVE A data) and a 50% reduction in the monitored cohort due to earlier diagnosis prior to having an event or symptom.
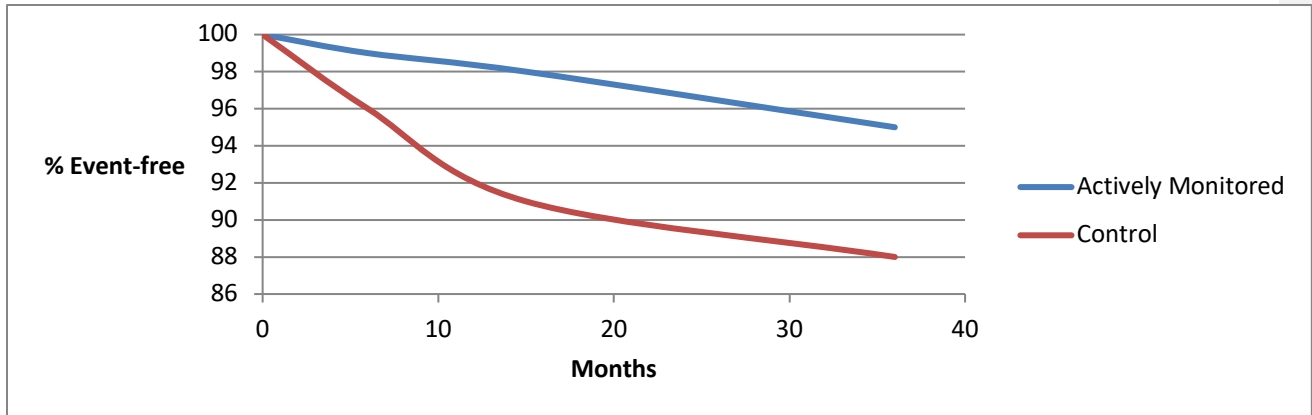
Power = 0.81 for log rank test with assumptions as below (rates are cumulative):

	Actively Monitored		Control	
Sample size with AF (10% prevalence in both groups)	n=200		n=400	
	Diagnosis Rate	Event Rate	Diagnosis Rate	Event Rate
6 months	5%	1%	0.5%	4%
15 months	7%	2%	3%	9%
36 months	10%	5%	10%	12%

A separate, detailed statistical analysis plan will be developed.

8. Possible Benefits

It is possible that participants could benefit by receiving a diagnosis of AF before they would otherwise, which could possibly lead to changes in therapy that might decrease their risk of thromboembolic events.

As determining the optimal method for population screening for AF is recognized as being an important unmet need, the results of this study could benefit a substantial proportion of the population through helping identify and refine screening methods. In addition, participation in this study will provide a greater understanding of the characteristics (e.g. frequency, duration, rate, time of day) of arrhythmias episodes that are or are not associated with symptoms.

9. Possible Risks and Analysis of Risk/Benefit Ratio

There is minimal risk to a patient receiving cardiac rhythm monitoring and, in general, complications are related to the adhesive that affixes the ZIO XT Patch to the subject. The FDA has cleared the ZIO XT Patch for use for patients who do not have known skin allergies or a family history of skin allergies. Company experience for skin allergies in 2011 is 0.02% in over 30,000 patients.

Findings during monitoring may require therapies only a physician can provide to prevent potentially serious complications. Therefore if a participant chooses not to share their physicians contact information with the study team they are potentially placing them at increased risk. All such participants will be informed, verbally and in writing, of their sole responsibility to inform their physician and the potential risk if they don't.

There are no known risks associated with wearing the Amiigo wristband. Because the Amiigo wristband has not yet been validated for heart rhythm detection there is a risk that a real heart rhythm problem may not be detected or that when a heart rhythm problem is thought to be detected it may not be real. Also, all data from the Amiigo device will be analyzed by Amiigo and although all attempts will be made to assure their privacy and security it is not possible to guarantee their security.

Additional risks to the patient include the potential for emotional or mental discomfort of knowingly wearing a cardiac rhythm monitor for an extended period of time. We consider this risk to be quite low.

Study subjects are not expected to receive a direct benefit from participating in this study but they can keep the device, the charger, download the free commercially available Amiigo App, and continue self-monitoring. The study app will be inactivated.

The control arm will receive current standard of care.

10. Risk Management Procedures

<u>Loss of privacy</u>

Participants will be identified by a 4-digit study ID. Only the investigators and research staff will have access to the patient's fully identified medical information. The information that matches the code to the identifying information will be kept in a safeguarded database that is password protected. Any paper files, such as ECG print outs will be kept in a secure location at STSI without identifying information.

11. Subject Payment/Costs

Subjects will not be directly remunerated for participation in the study. There is no cost to the subject for study participation.

12. Estimated Duration of Study

Participant's active involvement in the study will be 4 months. Clinical endpoints will be collected passively up to 3 years after study initiation. However, the study participants or their physicians may be contacted up to 3.5 years after study initiation to confirm vital status and locate any critical missing data.

13. Consent Procedures

Study purpose, methods, materials, risks, benefits, and alternatives will be provided in a detailed description on line with the ability to discuss with a research coordinator if desired. Informed consent will be obtained online with digital signature or by paper if preferred by the volunteer.

14. Privacy

Monitoring information will be provided to the participants and to their provider if permitted by the patient. If participants wish to review or discuss their results this information will be discussed in private consultation with Scripps study team medical personnel.

15. Data Security

The collection and processing of personal data from subjects enrolled in this study will be limited to the data needed to investigate this study's hypothesis. Access to identifiable data will be limited to Aetna personnel; patient level de-identified data will be available to only Scripps investigators authorized by the Principal Investigator.

Scripps Translational Science Institute affirms the subject's right to protection against invasion of privacy. Data files are stored on a password-protected computer/database and will be accessible only to the above listed investigators and research staff. Only the research staff will have the link that can match the code to traditional identifying information. The data sets used for analysis will be coded and not contain any traditionally used identifying information that could be used to identify the patient.

16. Subject Withdrawal

Subject participation is voluntary and the subject can discontinue participation at any time without loss of benefits or penalty. A subject who wishes to withdraw consent can make a request to the Principal Investigator during the study period. Any data that has been entered in the database will be included in the analysis of the study. No data will be collected until after full consent has been obtained. No personal health information will be retained.

17. Monitoring

STSI will monitor the study. Source documents will be reviewed to ensure all subjects have properly signed and dated the informed consent/HIPAA forms. All information will be reviewed to ensure eligibility criteria as per the protocol, and supporting source data will be verified.

All Adverse Drug Reactions (ADRs) that are attributed to a J&J medicinal product(s) identified during the defined data collection process should be reported to Janssen within 24 hours using the ADR form, as required by legal regulations. The form will be provided to STSI by Janssen.

18. Record Retention

Research records with patient identification will be kept for 6 years after study completion. The collected data and related de-identified health information may be kept indefinitely. Record retention will comply with the specific requirements of the Scripps IRB. (i.e., Scripps- must keep HIPAA form for at least 6 years after study completion) No personal health information will be retained.

19. Publication

The results of this research will be presented at meetings or in publication. However, the subject's identity will not be disclosed in those presentations.

20. Facilities and Personnel

All study activities will occur within the participant's home. All communications with participants will be through either STSI or Aetna.

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Appendix 1: Invitation Letter

You can help with an important heart health study

You're invited to join an important research study on how to better detect irregular heart rhythm. And you can do it from the comfort of your own home.

About the study
Aetna is working with the **Scripps Translational Science Institute** on a research study to try to find new ways to identify people who might be at risk for a heart rhythm called atrial fibrillation. It's an irregular heartbeat and can be associated with a higher risk of stroke. The study uses a new state-of-the-art wearable device that monitors your heart rhythm.

We are reaching out to tens of thousands of Aetna members like you. Please consider being a part of this study. We hope you'll help make a difference to improve health care. Research like this can help enhance the lives of others by improving medical knowledge for future generations.

What's involved in the study
The study is voluntary. You don't have to join. If you do, there won't be any interruption to your daily routine. No doctor visits are needed to participate in this study.

If you take part, Dr. Eric Topol's world-renowned team at Scripps will send you easy-to-wear devices. The devices are simple to use. You'll get a monitoring patch **free of charge** to measure your heart rhythm from your home, workplace, or on the go.

How to join
If you're interested in the study, call **1-855-295-4311**. You can also go to www.mstops.com to get more details. (Visiting this website doesn't automatically enroll you in the study.) Feel free to talk to your doctor about the study.

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