mHealth Screening to Prevent Strokes
(mSToPS)

NCT02506244

STATISTICAL ANALYSIS PLAN

February 28, 2017

Version 3.0

1. INTRODUCTION AND BACKGROUND

The mHealth Screening to Prevent Strokes (mSToPS) study is designed to determine whether mobile health monitoring can detect previously undiagnosed asymptomatic atrial fibrillation more effectively and lead to a reduction of thromboembolic events compared with usual care in a high-risk cohort identified and tracked using claims data.

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 in the randomized cohort, and at one year in the combined monitored cohorts versus the matched observational control cohort
- As an exploratory analysis, 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 therapeutic interventions (i.e. antiarrhythmic agents excluding beta-blockers and calcium channel blockers, cardioversions, ablation procedures or hospitalizations with a primary diagnosis of AF) 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 embolism, and/or myocardial infarction.

- In the Medicare population only, in who mortality data will be available, the combined endpoint of stroke/TIA, other systemic embolism, myocardial infarction and/or death
- The individual components of the combined endpoint.
- All hospitalizations.
- Hospitalizations for bleeding events.

2. DATA SOURCES

Data for the study will be derived from the following sources:

Aetna

- Aetna Membership – The Membership table captures monthly membership along with current status (e.g., active, terminated, deceased). Several demographic and plan sponsor fields are included.

- Aetna Medical Case Database – Medical Case summarizes clinical events by linking or associating all of the claims submitted for a member during the same treatment event. The logic defines clinical events based on contiguous claims for five places of service (Inpatient Acute, Inpatient Non-Acute, Emergency Room, Facility-based Outpatient Procedure, and Non-Facility Outpatient Procedure). This supports identifying all costs related to one of these events. Important to this study, Medical Case logic assigns all claims linked to a case to one category of service—inpatient, ER, or outpatient facility.

- Aetna Claims Database – Claims data include diagnoses (ICD9-CM v1 and 10-CM); professional encounters (CPT); diagnoses and procedures rendered during inpatient, outpatient and covered skilled facility encounters (ICD9-CMv3 and ICD10-PCS); durable medical equipment (HCPCS); administered (HCPCS) and dispensed (NDC) pharmaceuticals; presence of laboratory, pathology and imaging services; and allowable costs of healthcare services. Hospital claims also include DRGs, which will not be used in this study. Claims for services not covered under a member's healthplan benefits may occasionally appear in the data (i.e. provider or member submitted claim which was subsequently denied), but not reliably, and will bear a cost of zero. Laboratory, pathology and imaging services performed in-hospital or ER may not consistently appear in claims.

- Episode Treatment and Episode Risk Groups – The Aetna data warehouse contains member-level episodes-of-care resource use and cost information (via the Optum Episode Treatment Group® utility) and retrospective risk adjustment and prospective predictive cost modeling (via Optum's Episode Risk Groups®).[1] The ETG software aggregates all medical and pharmacy services related to care for specified acute (distinct beginning and end) and chronic (one year of treatment) conditions.

- Aetna's Care Management (Case and Disease) Programs – Aetna's case management program identifies members with projected limited-term intensive care needs, and helps to coordinate care, referral to specialists and centers of excellence (where

appropriate), and optimize use of insurance benefits. Disease management engages members with longer term (chronic) needs such as education, monitoring adherence, lifestyle/ behavioral aspects of care, and how to work with health care providers. Aetna Total View (ATV) is a web-based clinician application created as part of the Medical Management strategy at Aetna. The Case Management and Disease Management programs are administered in the ATV system. Survey, Assessment, and DGA (deficit goal activity) data are also available.

- Aetna Informatics Health Profile Database (HPD) – HPD identifies members with any of 84+ chronic diseases or medical conditions, the algorithms for which are comprised of medical and pharmacy claims data, and clinical laboratory data from physician claims and encounters, specialist claims, pharmacy, facilities, laboratories and others.

- Aetna Internal/External Pharmacy Data – Pharmacy data are available for all pharmacy retail and mail order claim adjudication.

Scripps Translational Science Institute

- Study Enrollment Database- This database records all interactions with study subjects enrolled in the randomized controlled trial of immediate monitoring vs. delayed monitoring, including enrollment date and randomized group status (performed by Parallel 6 through the study website), activation dates and serial numbers of all Zio patches sent to each individual subject, reasons for and dates of withdrawal from the study (including non-response after 3 attempts to contact), adverse event types and dates, participation in the Amiigo substudy, and notes on all other communications with study subjects.

- Zio Usage and Rhythm Flags-Data provided from iRhythm captured from all study Zio patch devices including patient study number and device serial number, recording start date/time, total wear time, total analyzable time, summary data for heart rate (maximum, minimum, mean), as well as data on specific arrhythmia events flagged for assessment by the study PI, including start date/time, total duration, heart rate during episode (maximum, minimum, mean).

- Principal Investigator Diagnosis of Flagged iRhythm Events and Adjudication—This database, maintained by the Principal Investigator of results of flagged rhythms received from iRhythm, records, number of unique episodes of atrial fibrillation lasting >30 seconds, average heart rate during atrial fibrillation episodes, total atrial fibrillation time and percent AF burden, also includes presence of symptoms and symptom type,

whether subject sought medical attention for symptoms, and the adjudication committee decision.

3. ANALYSIS OBJECTIVES

The analysis objectives corresponding to the study objectives listed in 1. INTRODUCTION AND BACKGROUND are the following:

Primary Analysis

1. Compare incidence of newly diagnosed atrial fibrillation (as defined by ≥ 30 seconds of atrial fibrillation or flutter detected by device, or a new clinical diagnosis recorded in claims data) at the end of the 4-month monitoring period in the immediate monitoring cohort (n=1,000) with delayed monitoring cohort (control group) (n=1,000) using ICD-9/ICD-10 codes.

Secondary Analyses

1. Compare time to first event of newly diagnosed atrial fibrillation (as defined by ≥ 30 seconds of atrial fibrillation or flutter detected by device, or a new clinical diagnosis recorded in claims data) at the end of the 4-month monitoring period in the immediate monitoring cohort (n=1,000) with delayed monitoring cohort (control group) (n=1,000) using ICD-9/ICD-10 codes.
2. Compare incidence of newly diagnosed atrial fibrillation (as defined by ≥ 30 seconds of atrial fibrillation or flutter detected by device, or a new clinical diagnosis recorded in claims data) at the end of the 4-month monitoring period in the immediate monitoring cohort (intervention group) (n=1,000) with delayed monitoring cohort (control group) (n=1,000) using HPD definition.
3. Compare prevalence of atrial fibrillation in the actively monitored cohort (n=2,000) with the matched observational control cohort (n=4,000) at 12 months.
4. Compare time to event of newly diagnosed atrial fibrillation in the actively monitored cohort (n=2,000) with the matched observational control cohort (n=4,000) at 12 months.
5. Compare the rate of initiation of anticoagulation therapy in the actively monitored cohort with the matched observational control cohort at 12 months.
6. Compare the rate of initiation of other atrial fibrillation-related therapies (antiarrhythmic agents excluding beta-blockers and calcium channel blockers, cardioversions, ablation procedures or hospitalizations with a primary diagnosis of AF) in the actively monitored cohort with the matched observational control cohort at 12 months.
7. Compare utilization in actively monitored cohort with the matched observational cohort at 12 months.
8. Compare time to first event of the combined endpoint of stroke, systemic embolism, or myocardial infarction in the actively monitored cohort with the matched observational control cohort at 3 years:

a. In the entire cohorts.
b. In the sub-population of individuals newly diagnosed with AF during the 3-year follow-up.

9. Compare time to first event of the combined endpoint of stroke, systemic embolism, myocardial infarction or death among subjects in the Medicare population at baseline in the actively monitored cohort with the matched observational control cohort at 3 years:
    a. In the entire cohorts.
    b. In the sub-population of individuals newly diagnosed with AF during the 3-year follow-up.
10. Compare time to first event of individual components of the combined endpoint (stroke, systemic embolism, myocardial infarction) in the actively monitored cohort with the matched observational control cohort at 3 years:
    a. In the entire cohorts.
    b. In the sub-population of individuals newly diagnosed with AF during the 3-year follow-up.
11. Compare time to first event of all-cause hospitalizations in the actively monitored cohort with the matched observational control cohort at 3 years:
    a. In the entire cohorts.
    b. In the sub-population of individuals newly diagnosed with AF during the 3-year follow-up.
12. Compare total number of all-cause hospitalizations in the actively monitored cohort with the matched observational control cohort at 3 years:
    a. In the entire cohorts.
    b. In the sub-population of individuals newly diagnosed with AF during the 3-year follow-up.

Analysis of Safety Endpoints

1. Compare time to first event of hospitalization for a primary bleeding diagnosis in the actively monitored cohort with the matched observational control cohort at 3 years:
    a. In the entire cohorts.
    b. In the sub-population of individuals newly diagnosed with AF during the 3-year follow-up.
2. Compare incidence of the detection of non-AF, but other actionable heart rhythm issues during monitoring in the actively monitored cohort with the matched observational control cohort in the entire cohorts at 3 years.
3. Describe incidence, timing and etiology of discontinuation of active monitoring in the monitored cohort.

Exploratory Analysis

1. Evaluate the correlation between AF detected by the Amiigo wristband with the incidence of AF detected by the Zio patch in active monitoring cohort during 4 months of active monitoring.

4. ANALYSIS SETS/POPULATIONS/SUBGROUPS

Participants

The study population is derived from the Aetna Commercial Fully Insured and Medicare populations. From this population, specific characteristics associated with an increased proportion of prevalent atrial fibrillation are identified through claims data to identify a population at increased risk for undiagnosed atrial fibrillation based on International Classification of Diseases Ninth (ICD-9) and Tenth (ICD-10) revisions diagnoses in the Aetna Claims Database or Aetna Health Analytics Profile Database (HPD):

Inclusion Criteria:

- Male age > 55 years, or females age > 65 years, 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

Eligible Aetna members will be contacted by letter, electronically or paper, 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 2,000 individuals for randomization and allow for development of a matched observational cohort of 4,000 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 ~2,100 (to account for an assumed 5% drop-out in first year) individuals have agreed to participate and signed the informed consent.

Randomized Controlled Trial Population: Immediate Monitoring (Intervention Group) vs. Delayed Monitoring (Control Group)

Upon signing the informed consent document, subjects will be randomized to either the immediate monitoring group or delayed monitoring group by random number generator. The random number generator uses Ruby's pseudo-random number generator functionality (PRNG) implemented as a modified Mersenne Twister with a period of 2**19937-1. The subject's group assignment will be sent to the STSI coordinating team. Continued eligibility of all randomized subjects for the study will be confirmed upon enrollment using Aetna databases for all inclusion and exclusion criteria.

For subjects randomized to the immediate monitoring group, the first Zio patch will be sent upon confirmation of continued eligibility. The first Zio patch will be worn by subjects in the immediate monitoring group during the first two weeks of the 4-month monitoring period. A second Zio patch will be sent to subjects in the immediate monitoring group for wear during the final two weeks of the 4-month monitoring period.

A subject will be considered withdrawn from the study if they inform the STSI study coordinating center that they wish to withdraw or if they have not initiated use of the first Zio patch after 3 notifications (e-mail/phone/e-mail) from the coordinating center.

Intention-to-treat analysis for the RCT will include all participants who are enrolled in the study according to their randomly assigned group (immediate monitoring or delayed monitoring) with the RCT follow-up time for subjects in the immediate monitoring group beginning at date of enrollment and ending at 4 months following date of enrollment or the time of completion of monitoring with their final patch, whichever is longest, and for subjects in the delayed monitoring group beginning at date of enrollment and ending at 4 months following the date of enrollment.

The per protocol analysis of the RCT will include immediate monitoring participants had analyzable data from the Zio patch for at least 30 continuous minutes any time during their assigned monitoring period and all participants in the delayed monitoring group who did not withdraw from the study prior to 4 months of follow-up.

Delayed Monitoring Group

Subjects randomized to the delayed monitoring cohort for the RCT will be actively monitored following completion of the 4 month RCT follow-up period (for which they serve as unmonitored controls). Subjects in the delayed monitoring group will receive their first Zio patch 4 months following their date of enrollment. The first Zio patch will be worn during the first two weeks of the 4-month monitoring period. A second Zio patch will be sent to subjects in the delayed monitoring group for wear during the final two weeks of the 4-month monitoring period.

Matched Observational Cohort Study: Actively Monitored (Immediate and Delayed) vs. Matched Observational Controls

For the Matched Observational Cohort study, the actively monitored group will include all subjects in the RCT who were randomly assigned to either active monitoring period (immediate or delayed).

Two matched controls will be selected for each of the 2,100 actively monitored subjects in the RCT (1,050 immediate + 1,050 delayed) from 1) the pool of subjects from the original eligible cohort who continue to be eligible based on monthly database updates and did not receive an invitation to enroll. Matching will be performed using the following criteria:

- Sex (exact)
- Age (exact by year of birth)
- CHA_2DS_2 VASc score (exact score)

CHA_2DS_2 VASc scores are re-calculated for monitored subjects at time of enrollment (updating scores calculated for eligibility of original pool). CHA_2DS_2 VASc scores are re-calculated for the pools of potential matched controls following the monthly update of the Aetna claims database and immediately prior to application of the matching protocol. Actively monitored subjects and controls will be matched on these updated CHA_2DS_2 VASc scores. Exact matches are prioritized. Matching of CHA_2DS_2 VASc score ± 1 will be the next option if 2 exact match controls are not found for a monitored subject.

Start date for determination of outcomes from Aetna databases for both monitored subjects and matched controls will be the date of enrollment of the monitored subject. End date for the analysis of prevalence of atrial fibrillation, initiation of anticoagulation and initiation of other AF-specific interventions will be 12 months from the actively monitored subject's date of enrollment (by exact month and day). End date for analysis of outcomes at 3 years will be 3 years from the actively monitored subject's date of enrollment (by exact month and day).

For the Matched Observational Cohort Study, the ITT population will be all subjects enrolled in the RCT (actively monitored group=immediate monitoring + delayed monitoring) and their matched controls. The per protocol analysis will consist of 1) all subjects in the RCT had analyzable data from Zio patch monitoring of at least 30 continuous minutes during the RCT and who did not request removal from the observational follow-up at time of withdrawal and 2) their matched controls.

Matched Observational Cohort Study: Atrial Fibrillation Sub-population

The sub-population of subjects diagnosed with atrial fibrillation for the analyses of disease endpoints and hospitalization events will consist of subjects in the actively monitored group who received a new diagnosis of atrial fibrillation during active monitoring with the Zio patch or at any time during the 3 year follow-up by claims data and subjects in the matched observational control cohort who received a new diagnosis of atrial fibrillation based on claims data during the 3 year follow-up.

5. ENDPOINTS AND COVARIATES

[Data source in brackets]

Primary Endpoint

1. Atrial Fibrillation/Flutter: new diagnosis of atrial fibrillation or atrial flutter defined as:
    a. ≥ 30 seconds of atrial fibrillation or flutter diagnosed and adjudicated on the iRhythm output (monitored cohort) [PI Diagnosis Database]
        i. Date
        ii. Duration
    b. Claim for atrial fibrillation/atrial flutter with ICD-9 code 427.1 or 427.2 or ICD-10 code I48.91 or I48.9 [Aetna Claims Data; Aetna Medical Case]
        i. Date

Secondary Endpoints

1. Atrial Fibrillation/Flutter: HPD algorithm [Aetna HPD Database]
2. Anticoagulation: Drug NDC codes for new refill for any:
    a. Anticoagulant (dabigatran, rivaroxaban, apixaban) or
        i. Date
    b. P2Y12 Antagonists (clopidogrel, prasugrel or ticagrelor) without a new diagnosis of acute coronary syndrome
        i. Date
4. Other AF-related therapies (i.e. antiarrhythmic agents excluding beta-blockers and calcium channel blockers, cardioversions, ablation procedures or hospitalizations with a primary diagnosis of AF)
5. Utilization
3. Stroke-related visits during follow-up [Aetna Medical Case]
    a. Inpatient
    b. ER
    c. Time to first stroke-related event (Inpatient or ER)
4. Myocardial infarction-related visits during follow-up [Aetna Medical Case]
    a. Inpatient
    b. ER
    c. Time to first myocardial infarction-related event (Inpatient or ER)
5. Systemic thromboembolism-related visits during follow-up [Aetna Medical Case]
    a. Inpatient
    b. ER
    c. Time to first systemic thromboembolism-related event (Inpatient or ER)
6. Death (Medicare population): [Aetna ATV; Aetna Membership Table]
    a. Time to death (within 1 month of date)

Commented [JW1]: Need to further define

b. Cause of death

7. All-Cause Hospital Admissions [Aetna Medical Case]
    a. Total number
    b. Total length of stay
    c. Individual admissions
        i. Primary diagnosis
        ii. Date
        iii. Length of stay

Safety Endpoints

1. Hospital admission for primary bleeding diagnosis: [Aetna]
2. Incidence of non-AF, but other actionable heart rhythms captured by device (and confirmed by PI) [PI Diagnostic Database]
    a. Atrial Tachycardia with variable block of > 30 seconds
    b. Ventricular Tachycardia >5 beats
    c. Pauses ≥ 5 seconds
    d. AV block
3. Early discontinuation of active monitoring in monitored cohort [Scripps Study Database]
    a. Date of discontinuation
    b. Cause of discontinuation

Exploratory Endpoint (Amiigo)

1. Correlation between Amiigo-detected AF and Zio patch detected AF with rate of true and false positives during overlapping monitoring.

Other Endpoints

1. Followup Count of All-Cause ER Visits [Aetna Medical Case]
2. Followup Count of All-Cause IP Visits [Aetna Medical Case]
3. Followup Total Length of Stay for All-Cause IP Visits [Aetna Medical Case]
4. Followup Count of All All-Cause Visits (IP and ER) [Aetna Medical Case]
5. Followup Time to First All-Cause Event (IP or ER) [Aetna Medical Case]
6. Followup Count of Stroke-Related ER Visits [Aetna Medical Case]
7. Followup Count of Stroke-Related IP Visits [Aetna Medical Case]
8. Followup Total Length of Stay for Stroke-Related IP Visits [Aetna Medical Case]
9. Followup Count of All Stroke-Related Visits (IP and ER) [Aetna Medical Case]
10. Followup Time to First Stroke-Related Event (IP or ER) [Aetna Medical Case]
11. Followup Count of Systemic Embolic-Related ER Visits [Aetna Medical Case]
12. Followup Count of Systemic Embolic-Related IP Visits [Aetna Medical Case]
13. Followup Total Length of Stay for Systemic Embolic-Related IP Visits [Aetna Medical Case]

14. Followup Count of All Systemic Embolic-Related Visits (IP and ER) [Aetna Medical Case]
15. Followup Time to First Systemic Embolic-Related Event (IP or ER) [Aetna Medical Case]
16. Followup Count of Myocardial Infarction-Related ER Visits [Aetna Medical Case]
17. Followup Count of Myocardial Infarction-Related IP Visits [Aetna Medical Case]
18. Followup Total Length of Stay for Myocardial Infarction-Related IP Visits [Aetna Medical Case]
19. Followup Count of All Myocardial Infarction-Related Visits (IP and ER) [Aetna Medical Case]
20. Followup Time to First Myocardial Infarction-Related Event (IP or ER) [Aetna Medical Case]
21. Followup Diagnosis of Atrial Fibrillation [Aetna Claims Data]; [Aetna HPD]
22. Followup Mortality Aetna ATV; Aetna Membership Table
23. Followup Diagnosis of Alcoholism [Aetna HPD]
24. Followup Diagnosis of Benign Prostatic Hypertrophy [Aetna HPD]
25. Followup Diagnosis of Metastatic Cancer [Aetna Claims Data]
26. Followup Diagnosis of Cardiomyopathy [Aetna Claims Data]
27. Followup Diagnosis of Cataract [Aetna HPD]
28. Followup Diagnosis of Cerebrovascular Disorder [Aetna HPD]
29. Followup Diagnosis of Chronic Liver Disease [Aetna HPD]
30. Followup Diagnosis of COPD [Aetna HPD]
31. Followup Diagnosis of Chronic Renal Failure [Aetna HPD]
32. Followup Diagnosis of Chronic Thyroid Disorder [Aetna HPD]
33. Followup Diagnosis of Congestive Heart Failure [Aetna HPD]
34. Followup Diagnosis of Coronary Artery Disease [Aetna Claims Data]
35. Followup Diagnosis of Dementia[Aetna HPD]
36. Followup Diagnosis of Depression [Aetna HPD]
37. Followup Diagnosis of Diabetes Mellitus [Aetna HPD]
38. Followup Diagnosis of Glaucoma [Aetna HPD]
39. Followup Diagnosis of Hyperlipidemia [Aetna HPD]
40. Followup Diagnosis of Hypertension [Aetna HPD]
41. Followup Diagnosis of Anemia [Aetna Claims Data]
42. Followup Diagnosis of Ischemic Heart Disease [Aetna HPD]
43. Followup Diagnosis of Low Back Pain [Aetna HPD]
44. Followup Diagnosis of Nonspecific Gastritis/Dypsepsia [Aetna HPD]
45. Followup Diagnosis of Obesity [Aetna HPD]
46. Followup Diagnosis of Osteoarthritis [Aetna HPD]
47. Followup Diagnosis of Peripheral Vascular Disease [Aetna Claims Data]
48. Followup Diagnosis of Obstructive Sleep Apnea [Aetna Claims Data]
49. Followup Procedure: Cardioversion [Aetna Claims Data]
50. Followup Procedure: Catheter Ablation [Aetna Claims Data]
51. Followup Procedure: Maze Procedure [Aetna Claims Data]
52. Followup Procedure: Left Atrial Appendage Occlusion Procedure [Aetna Claims Data]
53. Followup Procedure: Coronary Artery Bypass Grafting [Aetna Claims Data]
54. Followup Procedure: Cardiac Stent(s) [Aetna Claims Data]
55. Followup Procedure: Valve Surgery [Aetna Claims Data]

56. Followup Procedure: Percutaneous Valve Procedures (Transcatheter Aortic Valve Replacement/TAVR, Transcateter Mitral Valve Repair) [Aetna Claims Data]
57. Followup Procedure: Cardiac Transplant [Aetna Claims Data]
58. Followup Device: Cardiac Resynchronizing Therapy Device [Aetna Claims Data]
59. Followup Device: Left Ventricular Assist Device during Followup [Aetna Claims Data]
60. Followup Device: Pacemaker [Aetna Claims Data]
61. Followup Device: Defibrillator [Aetna Claims Data]
62. Followup Rx Fill for Digoxin [Aetna Pharmacy]
63. Followup Rx Fill for Beta Blocker [Aetna Pharmacy]
64. Followup Rx Fill for Calcium Channel Blocker [Aetna Pharmacy]
65. Followup Rx Fill for Antiarrhythmic Drug [Aetna Pharmacy]
66. Followup Rx Fill for ACE Inhibitor or ARB [Aetna Pharmacy]
67. Followup Rx Fill for Loop Diuretic [Aetna Pharmacy]
68. Followup Rx Fill for Spironolactone [Aetna Pharmacy]
69. Followup Rx Fill for Eplerenone [Aetna Pharmacy]
70. Followup Rx Fill for Nitrates/Hydralazine [Aetna Pharmacy]
71. Followup Rx Fill for Entresto [Aetna Pharmacy]
72. Followup Rx Fill for Statin or PCSK9 [Aetna Pharmacy]
73. Followup Rx Fill for P2Y12 Receptor Inhibitor [Aetna Pharmacy]
74. Followup Rx Fill for Diabetes Medication [Aetna Pharmacy]
75. Followup Rx Fill for Novel Anticoagulants [Aetna Pharmacy]
76. Followup Rx Fill for Other Anticoagulants [Aetna Pharmacy]
77. Followup Rx Fill for Warfarin [Aetna Pharmacy]
78. Followup Rx Fill for Heparin [Aetna Pharmacy]

Covariates

1. Sex [Aetna Membership Table]
2. Age [Aetna Membership Table]
3. Race/Ethnicity [Aetna Membership Table]
4. Insurance type (Medicare, Commercial or Both) [Aetna Membership Table]
5. Rural/suburban/urban (based on zip code) [Aetna Membership Table; U.S. Census]
6. Region of residence (based on zip code) [Aetna Membership Table; U.S. Census]
7. Median Household Income (based on zip code) [Aetna Membership Table; U.S. Census]
8. CHA_2DS_2 VASc [Aetna Claims Data; Aetna HPD; Calculation in Appendix]
9. Other co-morbidity scores
    a. Baseline Episode Risk Group (Retrospective) [Aetna Predictive Modeling Table]
    b. Baseline Episode Risk Group (Prospective) [Aetna Predictive Modeling Table]
    c. Baseline Charlson Comorbidity Score [Aetna Claims Data]
    d. Baseline Framingham Score [Aetna Claims Data; Aetna HPD]
10. Baseline months of Aetna Eligibility [Aetna Membership Table]

11. Follow-up months of Aetna Eligibility [Aetna Membership Table]
12. Total device wear time [Zio patch Usage]
13. Analyzable recording time [Zio patch Usage]

Baseline diagnoses:

14. Alcoholism [Aetna HPD]
15. Benign Prostatic Hypertrophy [Aetna HPD]
16. Metastatic Cancer [Aetna Claims Data]
17. Cardiomyopathy [Aetna Claims Data]
18. Cataract [Aetna HPD]
19. Cerebrovascular Disorder [Aetna HPD]
20. Chronic Liver Disease [Aetna HPD]
21. COPD [Aetna HPD]
22. Chronic Renal Failure [Aetna HPD]
23. Chronic Thyroid Disorder [Aetna HPD]
24. Congestive Heart Failure [Aetna HPD]
25. Coronary Artery Disease [Aetna Claims Data]
26. Dementia [Aetna HPD]
27. Depression [Aetna HPD]
28. Diabetes Mellitus [Aetna HPD]
29. Glaucoma [Aetna HPD]
30. Hyperlipidemia [Aetna HPD]
31. Hypertension [Aetna HPD]
32. Anemia [Aetna Claims Data]
33. Ischemic Heart Disease [Aetna HPD]
34. Low Back Pain [Aetna HPD]
35. Nonspecific Gastritis/Dypsepsia [Aetna HPD]
36. Obesity [Aetna HPD]
37. Osteoarthritis [Aetna HPD]
38. Peripheral Vascular Disease [Aetna Claims Data]
39. Obstructive Sleep Apnea [Aetna Claims Data]

Baseline procedures:

40. Cardioversion [Aetna Claims Data]
41. Catheter Ablation [Aetna Claims Data]
42. Maze Procedure [Aetna Claims Data]
43. Left Atrial Appendage Occlusion Procedure [Aetna Claims Data]

44. Coronary Artery Bypass Grafting [Aetna Claims Data]
45. Cardiac Stent(s) [Aetna Claims Data]
46. Valve Surgery [Aetna Claims Data]
47. Percutaneous Valve Procedures (Transcatheter Aortic Valve Replacement/TAVR, Transcateter Mitral Valve Repair) [Aetna Claims Data]
48. Cardiac Transplant [Aetna Claims Data]
49. Cardiac Resynchronizing Therapy Device[Aetna Claims Data]
50. Left Ventricular Assist Device during Baseline [Aetna Claims Data]

Baseline Prescriptions:

51. Digoxin [Aetna Pharmacy]
52. Beta Blocker [Aetna Pharmacy]
53. Calcium Channel Blocker [Aetna Pharmacy]
54. Antiarrhythmic Drug [Aetna Pharmacy]
55. ACE Inhibitor or ARB [Aetna Pharmacy]
56. Loop Diuretic [Aetna Pharmacy]
57. Spironolactone [Aetna Pharmacy]
58. Eplerenone [Aetna Pharmacy]
59. Nitrates/Hydralazine [Aetna Pharmacy]
60. Entresto [Aetna Pharmacy]
61. Statin or PCSK9 [Aetna Pharmacy]
62. P2Y12 Receptor Inhibitor [Aetna Pharmacy]
63. Diabetes Medication [Aetna Pharmacy]

Baseline Utilization

64. Outpatient visit [Aetna Medical Case]

6. HANDLING OF MISSING DATA

Missing data will be quantified for all variables. Given that endpoints are based on claims data, endpoints that do not appear in the claims data are measured as zero or absent and are thus not considered missing during the time that the subject remains enrolled in Aetna. Medical and pharmacy coverage will be assessed to identify truly missing data from zero/absent. For time to event analyses, subjects are censored at time of disenrollment. In addition, age and sex were included in the inclusion criteria for all subjects, and thus are not anticipated to be missing. Patterns of missing-ness of other covariates will be assessed by determining bivariate associations of the missing data (have data/do not have data) with demographic variables and co-morbidity scores. Variables found to be significantly associated with missing data will be used as covariates in the multivariable models used for the primary and secondary endpoints.

7. STATISTICAL METHODOLOGY

Sample Size Determinations

For the 4-month RCT, the sample size of 1,000 subjects for each group (immediate monitoring = active monitoring and delayed monitoring=no active monitoring) achieves >99% power to find a difference between an expected incident atrial fibrillation rate of 5% in the active monitoring group and an expected incident atrial fibrillation rate of 0.5% group without active monitoring with a two-sided alpha of 0.05. This sample size also achieves adequate power for the detection of the difference between the two groups at lower event rates, achieving 98% power for an expected rate of 2% in the active monitoring group and 0.1% in the delayed monitoring group with a two-sided alpha of 0.05.

For the Matched Observational Cohort Study, at 12 months, sample sizes of 2,000 subjects in the active monitoring group (immediate monitoring + delayed monitoring) and 4,000 subjects in the matched control group achieves >99% power to find a difference in the expected atrial fibrillation rate of 7% in the active monitoring group and 2% in the matched control group with a two-sided alpha of 0.05.

For the Matched Observational Cohort Study, based on an expected prevalence of atrial fibrillation of 10% in both the actively monitored (i.e., n=200) and matched control cohorts (i.e, n=400), a 7.5% event rate/year in the matched observational cohort and a 50% reduction in events in the actively monitored cohort due to earlier diagnosis prior to having an event or symptom, the expected combined event rate is 5% in the actively monitored subjects and 12% in the matched observational controls. Given these assumptions, the sample size yields 81% power to detect the expected difference in time to event with a log rank test with a two-sided alpha of 0.05.

Descriptive Statistics

Descriptive statistics (frequency of categorical variables; means (or medians), standard deviations (or interquartile range), and ranges of continuous variables) will be calculated for all variables (endpoints and covariates for both the Randomized Controlled Trial and the Observational Follow-up Study). Distributions of all variables will be examined for outliers and normality (continuous variables) both graphically and by descriptive statistics. Descriptive statistics will also be calculated for the following sub-populations: 1) subjects included in the per-protocol analyses specified below; 2) subjects who receive a diagnosis of atrial fibrillation/atrial flutter by the end of 3 years; and 3) subjects enrolled in Medicare (for analysis

the combined endpoint that includes death). Bivariate analyses will be used to examine differences in subject characteristics at enrollment 1) by randomized group, to assess the effectiveness of randomization, and 2) by actively monitored vs. matched observational control cohort to assess effectiveness of matching. Bivariate associations will be assessed using statistical methods appropriate for the variable types (Fisher's exact for categorical variables; t-test, ANOVA or non-parametric equivalents for continuous variables).

Descriptive statistics for device usage will be calculated separately for immediate monitoring group and the delayed monitoring group for their respective active monitoring periods, starting at date of enrollment and ending with completion of monitoring with final patch.

Analysis of Randomized Controlled Trial

The primary analysis will compare the proportion of subjects newly diagnosed with atrial fibrillation (numerator) per number of total number of subjects in the randomized group (denominator) during the first 4 months of the study between the immediate monitoring (intervention group) and delayed monitoring (control) groups using Fisher's exact test. Multivariable analysis of the primary outcome will also be performed using binomial multivariable logistic regression models to include baseline demographic (age, sex, race/ethnicity, median household income, geography, insurance type), and co-morbidity covariates. The primary analysis will be conducted with the endpoint (AF/atrial flutter) defined by any event in the Aetna databases with the ICD-9/ICD-10 code for AF/atrial flutter. Secondary analysis will be conducted using the same methods with the AF/atrial flutter endpoint defined by the HPD.

Intention-to-treat analysis will include all subjects who were randomized to the immediate monitoring or delayed monitoring groups and follow-up for outcomes from the device and the Aetna databases will be from date of enrollment to time of completion of monitoring with final patch or 4 months following enrollment, whichever is longest.

A per-protocol analysis will also be performed which will be limited to subjects in the immediate monitoring group who has a Zio patch reading of a total of at least 30 minutes and all subjects randomized to the delayed monitoring group.

Analysis of Matched Observational Cohort Study—12 month Follow-up

Analyses for the Matched Observational Cohort Study will involve comparison of outcomes in the actively monitored group from the randomized controlled trial (intervention = exposure to Zio patch monitoring) and the matched controls. Analysis at 12-month follow-up will include

the outcomes of new atrial fibrillation diagnosis and new prescriptions for 1) anticoagulants and 2) other AF-related medications.

The analysis will compare the proportion of subjects with newly diagnosed atrial fibrillation (numerator) per number of total number of subjects in group (denominator) during the first 12 months from the date of enrollment of the actively monitored subject between the actively monitored cohort and matched observational cohort using Fisher's exact test. Multivariable analysis of the AF/atrial flutter outcome will also be performed using binomial multivariable logistic regression models to include baseline demographic (age, sex, race/ethnicity, median household income, geography, insurance type), co-morbidity covariates. The same analysis will be performed for the other 12-month follow-up outcomes of new prescription for anticoagulation medication and new prescription of other AF-related medications. All analyses will be conducted first as intention-to-treat and second among the per-protocol population.

Matched Observational Cohort Study – 3 year Follow-up

Analyses at 3 years of follow up will focus on time to event for disease outcomes (stroke, myocardial infarction, and systemic thromboembolism) and hospitalizations (all-cause and for bleeding) compared between the actively monitored cohort and the matched observational control cohort after 3 years of follow-up. Bivariate time-to-event analysis will be conducted using Kaplan-Meier analysis with the time to event calculated from the date of the enrollment of the actively monitored subject and the date of the first event of the specific disease outcome (separate analysis for each outcome). Subjects not having an endpoint event during the observation period will be censored at the end of the 3-year follow-up or date of discontinued enrollment from Aetna. Multivariable analyses will be conducted using Cox proportional hazard models and will include potential confounders including age, sex, race/ethnicity, insurance type, variables related to geography and co-morbidity scores. For the Cox models, if assumptions of proportionality are not met (as assessed by Kaplan-Meier and plots of Schoenfeld residuals), models accounting for non-proportionality (using time*covariate interaction terms) will be run.

We will use the same time to event analyses with 3 year follow-up to evaluate the same disease and hospitalization endpoints among the subset of subjects included in the matched observational cohort study who receive a diagnosis of atrial fibrillation during the study. All analyses will be performed as intention-to-treat with parallel exploratory analyses performed on per-protocol basis restricted to subjects enrolled in the monitoring group who underwent Zio patch monitoring.

Analysis of Safety Endpoints

For analysis of safety endpoints at 3 year follow-up, we will compare incidence of hospitalization for bleeding per person-years of follow-up between the actively monitored group and the matched observational control group. Hospitalizations for bleeding will also be characterized by length of stay. Other safety outcomes will be characterized for the period of active monitoring in the active monitoring group only. These include Incidence of non-AF, but other actionable heart rhythms captured by the Zio patch device, specifically: 1) Atrial Tachycardia with variable block of > 30 seconds; 2) Ventricular Tachycardia >5 beats; 3) Pauses ≥ 5 seconds; and 4) AV block. We will also characterize early discontinuation of active monitoring in monitored cohort by cause and time to event.

8. SENSITIVITY ANALYSES

Time to event analyses for the Matched Observational Cohort Study at 3-year follow-up will be conducted using Cox proportional hazards analysis without adjustment for matching, as has been suggested in the literature.[2] We will also run conditional Cox proportional hazard models to account for matching and compared to the regular Cox models conducted for these outcomes using the same covariates.

9. PROGRAMMING PLANS

Databases maintained by Aetna and Scripps as Excel flat files. Files will be merged in SAS to create a SAS Masterfile for analysis using SAS 9.4 and SAS Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC).

10. REFERENCES

1 Optum (https://www.optum.com/providers/analytics/health-plan analytics/symmetry/symmetry-episode-risk-groups.html)
2. Stuart EA. Matching methods for causal inference: A review and a look forward. Stat Sci 2010; 25:1-21.

11. APPENDICES