INDIVIDUALIZED STUDIES OF TRIGGERS OF PAROXYSMAL ATRIAL FIBRILLATION (I-STOP-AFIB)

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1 I-STOP-AFib Study

This study aims to (1) help patients randomized to N-of-1 trials determine the individual effectiveness of trigger modification in reducing AF severity and frequency, and (2) determine the comparative effectiveness of N-of-1 trial designs vs. symptom surveillance alone in reducing AF severity and frequency.

1.1 Background

1.1.1 Paroxysmal Atrial Fibrillation (AF)

Paroxysmal AF is a common arrhythmia that impairs the lives of otherwise healthy, high-functioning individuals. AF is the most common arrhythmia, has a lifetime risk of 1 in 4, and is expected to affect 16 million Americans in 2050.[1] Each year, AF is responsible for >100,000 strokes, >400,000 hospitalizations, and >$6 billion in direct health care expenditures.[1-5] Paroxysmal AF patients have a similar or worse quality of life than patients with heart failure or myocardial infarctions.[6] To help alleviate the related debilitating symptoms, the American Heart Association (AHA) and other cardiology societies recommend potentially lethal drugs and invasive procedures to reduce AF episodes.[7] Prevention and treatment strategies that are lower risk, lower cost, and more directly under patient-control are needed.

Studies have identified risk factors for new onset AF; however, triggers for discrete episodes have been largely ignored. Behaviors or exposures that may trigger AF episodes have not been studied systematically, but clinical experience, anecdote, and patient reports suggest that personal behaviors (e.g., sleeplessness, stress, caffeine) may trigger AF. Several studies suggest that alcohol may be an acute trigger for AF episodes.[8,9] If triggers could be identified, they might be avoided, providing a strategy to effectively prevent AF. To our knowledge, no previous study has examined if triggers affect AF episodes, demonstrating the profound disconnect between previous research and the interests of the patients suffering from AF. If AF episodes can be manipulated based on personal decisions, a new, inherently patient-centered paradigm in the treatment and prevention of AF may be achieved.

1.1.2 A Critical Research Gap

Identification of AF triggers (the "trigger wars") is a top priority among AF patients. Patients participating in online forums and focus groups frequently discuss what particular factors trigger AF episodes. Mellanie True Hills, CEO of StopAfib.org, refers to these common online discussion as the "trigger wars". It is thus not surprising that identifying factors that trigger AF episodes in particular individuals using single subject study designs emerged as a key research

priority at the 2014 HeH Patient-Powered Research Summit, a research brainstorming session attended by nearly 100 patients, researchers, clinicians and other stakeholders. During this conference, an exercise allowed patients to communicate what they believed to be the most important issue in their disease. Common themes were identified and patients were divided into interest groups – one organically formed around AF. Members of the AF interest group identified individual-level triggers for the AF episodes as their highest research priority, After learning about the concept of mobile technology enabled N-of-1 trials, the AF interest group worked with content and clinical research experts to develop a study idea to test if an N-of-1 approach to identifying and elimination of AF triggers would improve AF outcomes.

1.1.3 Potential for the study to improve health care and outcomes

Using N-of-1 methods to help AF patients identify the best treatment will shift the clinical paradigm towards a more personalized and patient-centric approach to this important disease and provide patients with individualized data about the effectiveness of trigger modification in controlling symptoms. Rigorously applied trials will convince the evidence- focused cardiology community that triggers of AF differ between individuals and carry value. Modern technology and devices that are now so ubiquitous allow implementation of personalized N-of-1 studies in large populations with AF. This extremely common arrhythmia, that has few effective treatment options and yet might be readily manipulated by patients themselves, is ripe for this novel approach.

1.1.4 Study Setting

The study will take place remotely using an internet-based system produced at the University of California, San Francisco within the Health eHeart Alliance Patient Powered Research Network and will leverage the resources available in the Health eHeart Study, a web-based cardiovascular cohort study that enables remote consent, electronic data capture system (Eureka--please see technology platform configuration 1.3.1), and integration with devices and apps. To date, the Health eHeart Study has enrolled > 91,000 individuals from around the world, with >4,700 participants with atrial fibrillation.

1.2 Study Objective

Test the comparative effectiveness of N-of-1 trials versus data tracking alone to identify and eliminate individual- level triggers and reduce AF frequency and severity.

1.3 Technology Platform

1.3.1 Technology Platform Configuration

Eureka: The Eureka Research Platform is a digital research platform developed at the University of California San Francisco as part of a cooperative agreement with the NIH. The purpose of the platform is to facilitate mobile health research for any interested investigator. The Eureka platform includes a participant-facing "front end," an investigator portal, a secure "back end" for data storage and analyses. The platform is designed as an all-inclusive, configurable, easily-scalable research platform, inclusive of all aspects of research—from participant enrollment, onboarding and consent, to multi-modal data collection, study administration/management and data extraction. The platform's front end can be customized by individual investigators to implement their specific research project. Existing functionality includes the ability to obtain remote consent (although in-person consent can also be used), deploy participant surveys, message participants via push notifications, texts, or emails, integrate with external apps, sensors, and Bluetooth enabled devices, and capture data collected from smartphones (such as HealthKit data, geolocation data, accelerometer/ activity data). The investigator portal provides a secure website wherein investigators, coordinators or other individuals with appropriate permissions can visualize relevant participants' data and study status. The back end of the Eureka platform is a multi-tenant system that enables data collection, management and storage derived from multiple sources and from studies of various forms. This architecture rests on a secure and HIPAA-compliant AWS cloud with the capacity to curate dense data from more than 1 million participants. In addition to providing data as needed to investigators, the infrastructure houses a de-identified data repository that is publically available to help fulfill the general mission of advancing science and wellness.

Eureka will configure a study-specific version of the platform to collect data required to execute the research proposed in this study. Study participants will use the Eureka N-of-1 platform (website and mobile app) to collect outcome data, track intervention/exposure status, and review collected data in real time. Upon trial completion, Eureka will present N-of-1 results to patients randomized to N-of-1 trials with easy-to-understand graphics that include probabilistic assessments of the benefits of the intervention.

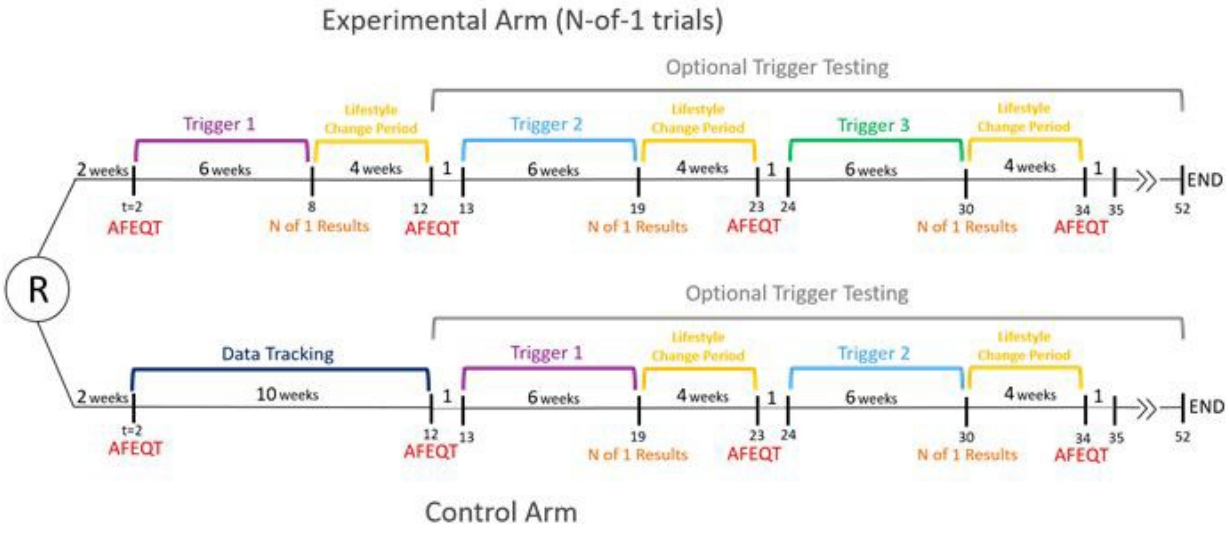
As part of design sessions held prior to enrollment, members of the research team, including patients and clinicians, provided input regarding the study-specific configurations of the Eureka platform. Study specific configurations will include: (1) trial specific onboarding page, (2) study library to generate and perform analyses of trials based on a trial-specific template, (3) server workflow that automates execution of the personal trials, and (4) customization of the user interface for prompts, reminders, forms, surveys, and visualizations. Final configurations will depend on input from key stakeholders. Technology modifications will be done via iterative, rapid development and testing cycles with a firm completion deadline by month 6 of this study, prior to patient enrollment.

AliveCor: AliveCor is a mobile electrocardiogram (ECG) monitoring app that pairs with a smartphone case to enable single lead ECG recordings. To date, >1,000 HeH participants have successfully downloaded this app and fitted the smartphone case, and all have done so remotely using the same work-flows that would be used for the current proposal. The AliveCor device includes an FDA-approved, patient-facing algorithm to detect AF episodes. A connectivity wizard already developed for the Eureka portal will enable linking the AliveCor monitoring to study data.This Eureka integration will allow the study to receive data from the AliveCor device and can be used as validation of atrial fibrillation episodes.

1.4 Study Design

This is a randomized controlled trial that examines the comparative effectiveness of N-of-1 study protocols vs. symptom surveillance (data tracking alone) for reducing AF episode frequency and severity (Figure 1). Throughout the duration of the study, all study participants will use the Eureka mobile app to self-report daily mood and sleep quality, AF episode duration (in minutes) and severity, and will use the AliveCor mobile electrocardiogram (ECG) to record ECG tracings. Participants will be instructed to take ECG tracings at least once per day as well as any time they think they are having an AF episode. Participants will be able to visualize their data in real time and will receive weekly summaries of their AF frequency and severity via Eureka. Due to the rapid growth and availability of mobile apps and devices that can monitor AF episodes, we believe the symptom surveillance condition is a realistic and appropriate comparison group.

Figure 1: Study Design



In addition to tracking mood, sleep and AF data, participants in the N-of-1 trial arm of the study will also test their triggers and track their trigger exposure. N-of-1 trials will be conducted using a

citizen health-scientist approach where patients are empowered and supported in independent experimentation. Together with the HeH Alliance Patient Advisory Board (PAB), the study team designed a menu of triggers that participants will select from to test in their personal AF triggers in a rigorous testing environment. These N-of-1 trials will consist of 6 randomly assigned periods of exposure (trigger exposure/trigger "on") and elimination (avoiding trigger/trigger "off").

1.4.1 Interventions and Comparators

N-of-1 Trial arm: Participants will use the Eureka mobile application and AliveCor device to execute at least one N-of-1 trial with the goal of identifying and better controlling their AF triggers. Each N-of-1 trial will last a total of 6 weeks and will include up to 3 periods of trigger exposure and 3 periods of trigger elimination with each exposure/elimination period lasting 1 week. Participants will be randomly assigned to start their trial with a period of either trigger exposure or elimination. During each N-of-1 trial, participants will track daily AF duration and severity, daily mood and sleep quality, daily AliveCor tracings and daily trigger exposure. At the end of each trial, participants will be able to review their trial results which will include visualizations of their daily AF symptom and trigger tracking over time. After completing a trial, participants will be instructed to implement any lifestyle changes they deem appropriate based on what they learned from the results of their trial. Participants will implement these changes for a period of 4 weeks during which they will continue to track AF episode duration and severity via the app. At the end of the 4-week lifestyle change period, participants will complete the Atrial Fibrillation Effect on QualiTy of Life survey (AFEQT) (Appendix A) and will then have the option of testing another trigger or ending their study participation.

Symptom Surveillance arm: Participants will use the Eureka app and AliveCor device to record daily AF duration and severity, daily AliveCor readings and daily mood and sleep quality for a period of 10 weeks. Participants will be able to visualize their AF, sleep and mood data in real time and will receive a weekly summary of their data via the Eureka app.At the end of the 10-week data tracking period, participants will complete the AFEQT survey and will then have the option of either ending their study participation or crossing over to the N-of-1 trial arm to test their triggers.

1.5 Study Procedures

Randomization/Baseline evaluation: Potential participants will be identified via the Health eHeart Study and the StopAfib.org patient advocacy organization and reached out to via email campaigns. Of note, invitations will be extended broadly to include friends family and acquaintances of those participants. Patients may also be recruited directly from UCSF clinics or other web-based sources of potentially interested atrial fibrillation patients. The study email campaign will contain an overview of the study. If the patient is interested in participating in the study there will be a link for the participant that will take them to the mobile app store to

download the Eureka app. Potential participants will be prompted to register an account and will complete an inclusion/ exclusion criteria survey within the Eureka app. If eligible, they will continue on to the study consent form (Appendix B). Upon completion of the electronic study consent, Eureka will randomize participants to either the N-of-1 or the symptom surveillance arm of the study with a 1:1 allocation ratio.

Participants will then be asked to complete baseline data collection which will include basic demographics, medical history, and current atrial fibrillation medications. After baseline data collection, the study team will ship AliveCor devices to study participants over a period of two weeks. At the end of this two week period, participant will be prompted to visit the Eureka application to complete a device consent and then will be instructed to download the AliveCor app and link their AliveCor device to their Eureka account. All participants will then complete the Atrial Fibrillation Effect on QualiTy of Life survey (AFEQT) (Appendix A). Once they complete the survey, the app will show participants which study arm they have been randomized to and prompt them to begin the appropriate study activities.

Experimental arm: Participants randomized to the N-of-1 study arm will test AF trigger(s) (ie. diet, exercise, sleep, alcohol, smoking, certain exercises, etc). Using a menu of options in Eureka, participants will select a trigger to test and then will be randomly assigned to start with a period of trigger exposure or elimination. Each exposure/elimination period will last 1 week and each trigger will be tested for a total of 6 periods with 3 weeks of trigger exposure and 3 weeks of trigger elimination. During each testing period, the Eureka app will send participants daily reminders of the behavior that is required, specifying quantity and type of trigger exposure/elimination when appropriate. For example, if the trigger is alcohol consumption, this might include a daily alert that reads:

> Elimination week: *"This week, AVOID your trigger: **ALCOHOL**. Avoid drinking any alcohol. **3** more days left of AVOIDING alcohol this week."*

Or, alternatively:

> Exposure Week: "*This week, TEST your trigger: **ALCOHOL**. Go ahead and consume alcohol this week. **3** more days left to TEST your trigger this week."*

During the testing period, participants will also receive daily reminders prompting them to go to into the Eureka app to complete study activities. Participants will be asked daily about the estimated total duration and severity of their AF episode(s), mood and sleep quality and trigger exposure (e.g. "How many alcoholic drinks did you have yesterday?"). They will also be prompted to take daily AliveCor readings. Participants will be instructed to take ECG tracings at least once per day as well as any time they are experiencing AF symptoms. Following the completion of their N-of-1 trial, participants will be able to view their trial results and interpretations on the Eureka app. Once their N-of-1 trial is complete, participants will stop receiving reminders about trigger exposure/elimination and trigger tracking but will be prompted

to continue to track their AF frequency and severity for 4 more weeks. During this 4 week period, participants will be able to implement any lifestyle changes they deem appropriate based on what they learned from their N of 1 trial. Following the completion of the 4 week “lifestyle change” period, participants will complete the AFEQT survey and will then have the option of either testing another AF trigger or concluding their study participation. Participants that choose to test additional triggers will have up to one week to start their next N-of-1 trial that will follow the same trigger testing protocol as the first. Participants will have the option of testing up to 5 triggers following this protocol.

Symptom Surveillance: Participants randomized to the symptom surveillance arm will engage in data tracking for a period of 10 weeks and receive daily reminders to complete study activities. Participants will be asked daily about the estimated total duration and severity of AF episode(s) and daily mood and sleep quality. They will also be asked to take AliveCor readings at least once per day and anytime they are experiencing AF symptoms. Participants will be able to visualize their AF data in real time and will receive a monthly summary of their AF frequency and severity via the Eureka app. At the end of the 10-week tracking period, participants will complete the AFEQT survey. Then, participants will have the option to cross over to engage in trigger testing. Participants that choose to test their triggers will be able to test up to 4 triggers, one trigger at a time, following the N-of-1 trial protocol described above.

1.5.1 Outcome Measures

The primary study outcome is change in quality of life, measured by the AFEQT, between those randomized to N-of-1 experiments versus those that tracking their data alone. Secondary outcomes will include results of individual-level N-of-1 trials.

1.6 Participant Selection and Withdrawal

At least 478 AF patients will be recruited to participate remotely in the RCT.

1.6.1 Inclusion Criteria

(1) symptomatic paroxysmal AF
(2) a smartphone

1.6.2 Exclusion Criteria

1. Non-English speakers
2. Children (age < 18 years)
3. Patients with plans to substantially change AF management (such as with ablation or change in antiarrhythmic drugs) over the ensuing 6 months
4. Unwillingness to test AF triggers.
5. Patients who have had an AV node or AV Junction ablation

1.6.3 Participant Pre-screening and Recruitment

Participants will be recruited primarily from two sources: (1) the Health eHeart Study, which has >4,000 well-characterized AF participants who have consented to be contacted via the internet about other studies and which recruits >1,500 new participants (58 AF patients) per month; and (2) StopAfib.org, a patient-run website with 765,000 unique visitors, 2.2 million pageviews in 2014 and a mailing list of 13,000 engaged AF patients. Those participants will also be recruited as “ambassadors for the study by inviting others they know that might be interested. Patients may also be recruited directly from UCSF clinics or other web-based sources of potentially interested atrial fibrillation patients. Participants recruited directly from the Health eHeart Study will be emailed by the Health eHeart study team.We will plan to email the Health eHeart Study participants who have indicated they have AF. Participants recruited from StopAfib.org will receive a similar email with a link to the mobile app store. Potential participants will then be prompted to register an account, consent for the study then complete an inclusion/ exclusion criteria survey within the Eureka app.

1.6.4 Early Withdrawal of Participants

Study participants can opt out of testing a trigger or withdraw from the study at any time of their choosing without penalty.

1.7 Statistical Plan

1.7.1 Sample Size Determination

We conservatively estimate that the available pool will include 10,000 engaged individuals meeting the inclusion and exclusion criteria. Given that we estimate that 478 participants will be needed, we need to consent only 5% of eligible patients. Strategies to overcome barriers to enrollment include continuing aggressive efforts to recruit large numbers of HeH participants (in collaboration with the HeH Alliance and partners such as the AHA) and ongoing messaging from the CEO and other leadership encouraging enrollment to StopAfib.org participants and visitors (Std PC-2). In order to achieve at least 478 patients that complete the 6 month study, we will aim to initiate at least 600 patients.

Sample Size & Power Calculations: As those with at least moderate AF severity have an AFEQT score of 58 ± 1958 and the most modest of therapies typically improves this score by a mean of 5-10, we have powered this study conservatively to detect an improvement of 5 points in the AFEQT. We estimate 239 patients in each group would provide 80% power to detect this small, yet still clinically meaningful difference. Given the enthusiasm of >1000 AF patients already engaged by the investigators, we believe enrollment will not pose a challenge.

1.7.2 Statistical Methods

Analysis of Individual N-of-1 Trials: At the end of each person's N-of-1 trial, statistical analysis will be performed to compare results on the two treatments. Each N-of-1 trial requires a separate analysis which is automated to run in the background once each trial is completed. The analysis consists of running Bayesian models that make different assumptions about the nature of the data (e.g., data with and without correlation over time, with and without carryover across interventions). Models will incorporate the appropriate scales for the outcomes (e.g. normal distributions for continuous variables, multinomial distributions for categorical variables) and the appropriate representation of the function linking the expected outcome to the predictors (e.g., cumulative logit link for ordinal outcomes).The results of these models will be automatically compared to determine which best fits the data and the simplest model that accurately fits the data will be chosen using appropriate model selection criteria such as the deviance information criterion. Each patient will be provided with an estimate of the (1) treatment difference, and (2) probability (or likelihood) that each treatment is the best for a particular outcome. Results will be portrayed numerically and graphically. We will develop educational materials to aid patients in interpretation. Posterior probabilities of outcomes will be calculated using an interface that incorporates open-source R software interfacing through Rjags with open-source JAGS software.55 The R code creates the Bayesian model, loads the stored data and chooses intelligent starting values that are then fed into JAGS to return the Markov chain Monte Carlo (MCMC) simulations of the joint posterior distribution. The R package will accept input from Orchestra to construct models. The statistical methods used are being applied currently in another N-of-1 study and will be adapted as necessary to create a connection between the R code and Eureka..

Meta-Analysis of N-of-1 Trials: The collection of individual N-of-1 trials can be thought of as a set of studies whose results can be combined as in a meta-analysis. The data can be considered as a multilevel structure in which a set of patients is studied with each patient having a set of measurements. Standard multilevel mixed model methods will be used to estimate the average effect and variance within and across patients. Across patient values estimate the average effect in the population of patients studied, while the within-patient estimates describe an improved estimate of each patient's true effect assuming exchangeability across patients. We will fit these models using a Bayesian multilevel model with non-informative priors in order to obtain posterior distributions of the within and between effect sizes. We will then compare the multilevel patient estimates with those from the patient's data alone in order to determine how much the effects change and how much additional precision these estimates gain.

Analysis of Comparative Effectiveness: The experimental design is a simple two-arm randomized trial comparing N-of-1 vs. symptom surveillance. The primary outcome is the change in the AFEQT scale from baseline to 12 weeks. The mean change in each treatment group will be compared by a t-test. The average frequency and severity of AF episodes per week during the final month of each participant's enrollment will be the secondary

outcomes.Their group means will also be compared with a t-test. We will check for balance in covariates across the randomized groups and will adjust for any imbalances by including those covariates in regression analyses and reporting the adjusted treatment effect as a secondary analysis.

Missing Data: A major purpose of this aim is to determine the feasibility and usability of N-of-1 studies for actual application in clinical practice. Therefore, carefully documenting adherence and completion rates and predictors of each will be an important aspect of this study. Within the HeH study, we have found that >90 % of all AF HeH study participants complete all AF-related surveys, including the AFEQT. The primary analysis will be intent-to-treat which uses all participants as randomized. When no endpoint is available, we will assume no change. Further analyses will employ multiple imputation to fill in missing values, particularly in covariate-adjusted models (Std MD-2, MD-3).

Heterogeneity of Treatment Effects (Std HT-1 through 4): HTE between individuals with AF is a major issue that is of particular interest to patients. In secondary analyses, we will test for interactions between treatment and covariates that describe potential pre-specified HTE hypotheses. Predetermined interaction analyses will include testing for effect modification by "lone" AF (age <65 years of age without any cardiovascular risk factor) vs. not, sex, and race (non-Hispanic white race vs. not). Additional post hoc interaction analyses examining currently unrecognized moderators will be planned based on input from patients over the course of the study. These are likely to include testing for effect modification by particular triggers (e.g., setting an early bedtime works well whereas avoiding morning endurance exercise does not). Statistical significance for interaction analyses will use a p-value cut off of ≤0.01.

1.8 Safety and Adverse Events (AE)

1.8.1 Adverse Event Reporting

Participants will receive monthly prompts via the application about the following things: hospitalizations (AF, emergency department, cerebrovascular event, myocardial infarction or heart failure), antiarrhythmic medication changes and ablation plans.

We will share reports with the DSMB outlining the results of the above survey.

1.8.2 Data and Safety Monitoring Board

Although randomization to N-of-1 trials versus symptom surveillance (data tracking) is low risk, we will form a DSMB to ensure the safety of participants. This board will be comprised of a patient, a cardiac electrophysiologist, and a statistician from outside the research groups or institutions of the study personnel otherwise involved in the project. They will meet prior to

implementation of the study to review the safety of a near-final AF-specific N-of-1 platform. They will meet again after 100 patients are enrolled and again after 350 patients are enrolled.

An analyst will prepare summary statistics of results collected prior to the second and third meetings. The DSMB will review study progress and any adverse events that have been reported by patients. The DSMB will also discuss trouble around retention, compliance, protocol violation and recruitment issues. The DSMB will have the authority to stop the study for safety reasons or to alter it if needed. Because the study is expected to be low risk, patients may actually benefit from study participation, and specific subgroups (e.g., those in whom N-of-1 studies identify a trigger), may yield important results, the DSMB will not perform any interim analyses for efficacy or consider stopping the study early for futility. In addition, all potential participant data obtained by the study investigators will be monitored on an ongoing basis to ensure compliance, to provide quality assurance (QA), and to obtain metrics for quality improvement.

See Appendix C for DSMB Charter

1.9 Data Handling and Record Keeping

1.9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

1.10 Technology Platform - Eureka

1.10.1 Short Description of Eureka

The Eureka mHealth Research Platform Resource is a mobilized cohort and infrastructure to carry out clinical research studies using mobile and digital technology. Patients will submit their data via SMS text messages, via mobile applications, via secure websites, or upload their data

from other services they may authorize. Simple, non-PHI carrying messages are sent by the system, and typically unidentifiable numeric responses are returned. The only PHI involved in the transaction is the phone number or unique ID used to identify the patient's phone. This data is then stored on the study platform as previously described.

Eureka Goal: The goal for the Eureka mHealth Research Platform is to provide an infrastructure for efficient data collection, storage, and sharing that can be configured to support Internet- or mobile phone app-based research studies.

1.10.2 Registration, Consents, Eligibility

Eureka will support a registration procedure that will allow registration with identifying information that will generally include name, date of birth, and mobile phone number.

In registering for our study, Eureka will provide a consenting process for participants within the onboarding flow. In this process, the study informed consent as well as the Eureka Privacy Policy and Data Security Measures (Appendix D) will be presented to eligible participants.

1.10.3 Eureka Risks

The risk of loss of privacy in our study hosted by the Eureka Research Platform will be present for all persons participating. Loss of privacy could occur by compromise of the Eureka technical system, or if Eureka is required by law to disclose data to authorities, e.g. to prevent serious harm to the participant or others. This is the primary reason for the Eureka Privacy Policy and Data Security Measures.

1.10.4 Eureka Efforts to Minimize Risk

To minimize risk of loss of privacy, Eureka takes the following steps:

Technical system security: Information will be transmitted and stored using state-of-the-art security systems similar to those that protect websites used by banks and electronic health record systems. Specifically, the Eureka Platform is hosted on Amazon Web Services (AWS), a cloud-based server system and computing services that are HIPAA compliant, and Eureka follows security guidelines of the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). Specifically, all research data are stored behind a secure firewall, guarded by intrusion detection software, and encrypted at rest and in transit in our Amazon Virtual Private Cloud.

Inform patients: As described above, we will include the Eureka Privacy Policy and Data Security Measures that will be referenced in study onboarding and viewable at any time. The statement will inform patients of the risks of loss of privacy, including via technical compromise

or legal requirements. We will also make them aware that they are responsible for keeping their login credentials secure.

1.10.5 Confidentiality Measures

Identifying information (name and email address) will be stored in separate (but linked) data tables so that health-related data can be viewed by approved staff as needed without inadvertent association with identifiers when such linkage is not required.

In the event of a data break, the Eureka Research Platform Team will notify all Study Teams and Study Participants in accordance with UCSF guidelines.

1.10.6 Data Storage

Data is stored on Amazon Web Services (AWS or Amazon Cloud)

1.10.7 Data Security

Data are coded; data key is kept separately and securely. Electronic data are protected with a password. Data are stored on a secure network

1.10.8 Records Retention

The investigator must retain all study records and source documents for the maximum period required by their institution or as required by local and national governing regulations, whichever is longer. Study records include consent forms and source documentation. The investigator must contact the sponsor prior to destroying any records associated with the study.

1.11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 50, part 56 and ICH guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a centralized, properly constituted independent Ethics Committee (EC) or IRB, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The sponsor and investigator will maintain a list of the central EC/IRB members and their affiliates in their files.

All subjects (and/or the subject's legally authorized representative) for this study will be provided a consent form describing this study and providing sufficient information for subjects (and/or their legally authorized representative) to make an informed decision about their participation in this study. The sponsor will provide the investigator with appropriate sample informed consent forms. The formal consent of a subject (and/or the subject's legally authorized representative), using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure.

1.11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned study specific conflict management plan that has been reviewed and approved by the IRB providing oversight for that investigator prior to participation in this study. This information shall also be made available to the study sponsor upon request or as required under any separately executed agreement between the sponsor and study site.

1.12 Stakeholder Involvement

1.12.1 Initial Study Development:

Research Prioritization Process: As a patient-powered research study, patients have been and will continue to be integral in shaping each stage of this study's development. The research question and initial study design emerged out of the 2014 HeH Patient-Powered Research Summit, a research brainstorming session attended by nearly 100 patients, researchers, clinicians and other stakeholders. Members of the Atrial Fibrillation (AF) interest group named identifying individual-level triggers for their AF episodes as their highest research priority. After learning about the concept of mobile technology enabled N-of-1 trials, the AF interest group worked with clinical research experts to develop a study idea that would test if an N-of-1 approach to identifying and eliminating AF triggers would improve AF outcomes (the stimulus for this study).

Designation as an "Alliance Sanctioned" Study: As an "Alliance-sanctioned study," this study was designed to meet the following criteria: there will be (1) at least one HeH Alliance member is participating as a patient-leader in a decision-making role and receiving compensation for that role; (2) accountability reporting on study progress and results back to the HeH Alliance Community and the Steering Committee; (3) co-authorship for at least one Alliance patient-leader on the final results paper; and (4) acknowledgement of the HeH Alliance in the final results paper.

1.12.2 Study Execution:

To maintain the patient-centeredness of the study, patients will be involved throughout the entire process, including in planning, implementation, tracking progress and disseminating results.

The study team will work closely with the Patient PI and Patient Advisory Board: The study's Pt-PI is an AF patient and HeH Alliance Steering Committee member (Kathi Sigona). She will take part in all planning discussions and study design meetings with the study PI (Greg Marcus) and the Alliance Project Director (Madelaine Faulkner) and she will chair quarterly meetings of the Patient Advisory Board (PAB). These meetings will provide an opportunity to discuss progress, milestones, challenges to implementation and modify plans in an iterative fashion with a broader group of patients. Patients will take an active role in identifying potential triggers for testing and in the design and testing of the Eureka N-of-1 and symptom tracking apps. The study team solicited feedback from all HeH Study AF patients and StopAfib.org visitors around atrial fibrillation triggers via a survey delivered via email (Appendix E). We also engaged a group of 4 UCSF AF patients in focus group activities for the initial study design process. In this way, patients were directly involved in the finalizing the study design, including the identifying the potential triggers to be studied, the adaptation of the Eureka platform to accommodate the description of those triggers, and beta-testing of the product before it is finalized.

1.12.3 Disseminating the study results:

Under the leadership of Kathi Sigona (patient PI) and together with the PAB, HeH patients will play an active role in all dissemination activities. In addition to the many existing HeH dissemination channels, we plan on working with the PAB to find the additional methods for dissemination, including atypical arenas to reach a broader population. This may include posting updates via HeH Study communication channels, social media updates, advocacy groups such as Stopafib.org, or other opportunities reported as valuable by our patient population.

1.12.4 Alliance Patient engagement principles:

Reciprocal Relationships: The two study co-PIs for HeH (Marcus & Sigona) along with the leads of the patient engagement and PPRN integration teams, will lead decision making for Aim 2. Our goal is to ensure that patients, clinician, and other stakeholders have a primary voice in key decisions and that the investigator team works in service of implementing their goals while ensuring methodologic rigor. Kathi Sigona (patient co-PI) will lead efforts to more broadly engage patients through both the PAB and study focus group. She will play a critical role in ensuring that the patient voice is represented in investigator team meetings and in HeH specific study meetings.

Co-learning: Within the HeH Alliance, there is an established process for ensuring good communication between researchers and patients. The communication principles developed by the HeH Alliance will be incorporated throughout the study to ensure we are using language that is understandable to patient and researcher stakeholders. Engaging Kathi Sigona (patient co-PI) as a facilitator in meetings where multiple stakeholder groups are represented will also help to alleviate any communication concerns.

Partnership: Patients play a crucial role in studying AF triggers. AF triggers are inherently

patient-centric as they are personalized and patient-defined. We developed the Aim 2 focus group plan and compensation strategy after discussion with AF patients and advocates in order to ensure that participation is worthwhile. We plan to utilize the internet and email as much as possible to facilitate participant convenience and will minimize in-person meetings.

Trust, Transparency, Honesty: The HeH Alliance has rules governing interaction with patients and one of the main principles is radical transparency. HeH believes that involving patients in all processes helps keep the work truly patient- centered. HeH has a system of shared notes and decision tracking so that patient leaders and PRB members have full transparency as to how decisions are made. In addition, all members of the study team will adopt the broader HeH Alliance list of working values (i.e., Trust & Partnership, Respect & Listening, Empowering Solutions) that are meant to encourage meaningful and honest communication with patient partners in research.

1.12.5 Study Participant & Patient Stakeholder Compensation

Patient Advisory Board members will be compensated in a show of appreciation for their time and expertise and will be paid annually at $75/ hour. We plan to hold quarterly meetings with PAB members to track study progress, results dissemination and troubleshoot other potential study concerns. Our PAB members will be involved with the study team for all three years of the grant and will be supported by the Health eHeart Alliance PPRN.

Focus group members who are not on the PAB will be engaged for a total of 8 hours in year one and will be invited to be included on study updates through the life of the study. These members will be compensated at $75/ hour.

Finally a patient will be included on the 3-person, Aim 2 DSMB; for which they will be compensated $500/meeting. We anticipate there will be three meetings during the life of the study.

1.13 References

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1.14 Appendixes

Appendix A: AFEQT

Atrial Fibrillation Effect on Quality of Life
Survey Number: 1-17c

This survey is triggered from 1-06 Medical Conditions,[afib] = '1'.

Everyone who does this survey will also do 1-17a Atrial Fibrillation and 1-17b AF Severity Scale. All 3 are triggered from 1-06 Medical Conditions, [afib] = '1'.

Question? ***Popup Language Title*** ***Popup Language Body*** ***variable name*** ***field type*** ***branching logic*** ***required/not required***	1, Option #1 2, Option #2 **Text Validation** **Triggering Between Survey** ***Note - questions that are triggered have a blue "fill"***
Are you currently in atrial fibrillation? ***Atrial Fibrillation*** ***Atrial Fibrillation (also called AFib or AF) is a quivering or irregular heartbeat (arrhythmia) that can lead to blood clots, stroke, heart failure and other heart-related complications. Some people refer to AF as a quivering heart.*** ***current_af*** ***yesno*** ***none*** ***required***	1, Yes 0, No
When was the last time you were aware of having had an episode of atrial fibrillation? Please check one answer which best describes your situation. ***last_time*** ***radio*** ***[current_af] = '0'*** ***required***	1, Earlier today 2, Within the past week 3, Within the past month 4, 1 month to 1 year ago 5, More than 1 year ago 6, I was never aware of having atrial fibrillation

The following questions refer to how atrial fibrillation affects your quality of life. On a scale of 1 to 7, over the <u>past 4 weeks</u>, as a result of your atrial fibrillation, how much were you bothered by: Please choose <u>one</u> number which best describes your situation. ***section_2*** ***descriptive*** ***none*** ***not applicable***	*Not a question*
Palpitations: Heart fluttering, skipping or racing ***palpitations_heart_flutter*** ***radio*** ***none*** ***required***	1, 1 – Not at all bothered Or I did not have this symptom 2, 2 – Hardly bothered 3, 3 – A little bothered 4, 4 – Moderately bothered 5, 5 – Quite a bit bothered 6, 6 – Very bothered 7, 7 – Extremely bothered
Irregular heart beat ***irregular_heart_beat*** ***radio*** ***none*** ***required***	1, 1 – Not at all bothered Or I did not have this symptom 2, 2 – Hardly bothered 3, 3 – A little bothered 4, 4 – Moderately bothered 5, 5 – Quite a bit bothered 6, 6 – Very bothered 7, 7 – Extremely bothered
A pause in heart activity ***pause*** ***radio*** ***none*** ***required***	1, 1 – Not at all bothered Or I did not have this symptom 2, 2 – Hardly bothered 3, 3 – A little bothered 4, 4 – Moderately bothered 5, 5 – Quite a bit bothered 6, 6 – Very bothered 7, 7 – Extremely bothered
Lightheadedness or dizziness ***lightheadedness*** ***radio*** ***none*** ***required***	1, 1 – Not at all bothered Or I did not have this symptom 2, 2 – Hardly bothered 3, 3 – A little bothered 4, 4 – Moderately bothered 5, 5 – Quite a bit bothered 6, 6 – Very bothered 7, 7 – Extremely bothered

On a scale of 1 to 7, over the past 4 weeks, have you been limited by your atrial fibrillation in your: Please choose one number which best describes your situation. ***limited*** ***descriptive*** ***none*** ***not applicable***	*Not a question*
Ability to have recreational pastimes, sports, and hobbies ***pastimes*** ***radio*** ***none*** ***required***	1, 1 – Not at all limited 2, 2 – Hardly limited 3, 3 – A little limited 4, 4 – Moderately limited 5, 5 – Quite a bit limited 6, 6 – Very limited 7, 7 – Extremely limited
Ability to have a relationship and do things with friends and family ***relationship*** ***radio*** ***none*** ***required***	1, 1 – Not at all limited 2, 2 – Hardly limited 3, 3 – A little limited 4, 4 – Moderately limited 5, 5 – Quite a bit limited 6, 6 – Very limited 7, 7 – Extremely limited
On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much difficulty have you had in: Please choose one number which best describes your situation. ***difficulty*** ***descriptive*** ***none*** ***not applicable***	*Not a question*
Doing any activity because you felt tired, fatigued, or low on energy ***activity*** ***radio*** ***none*** ***required***	1, 1 – No difficulty at all 2, 2 – Hardly any difficulty 3, 3 – A little difficulty 4, 4 – Moderate difficulty 5, 5 – Quite a bit of difficulty 6, 6 – A lot of difficulty

	7, 7 – Extreme difficulty
Doing physical activity because of shortness of breath ***short_breath*** ***radio*** ***none*** ***required***	1, 1 – No difficulty at all 2, 2 – Hardly any difficulty 3, 3 – A little difficulty 4, 4 – Moderate difficulty 5, 5 – Quite a bit of difficulty 6, 6 – A lot of difficulty 7, 7 – Extreme difficulty
Exercising ***exercising*** ***radio*** ***none*** ***required***	1, 1 – No difficulty at all 2, 2 – Hardly any difficulty 3, 3 – A little difficulty 4, 4 – Moderate difficulty 5, 5 – Quite a bit of difficulty 6, 6 – A lot of difficulty 7, 7 – Extreme difficulty
Walking briskly ***walking_briskly*** ***radio*** ***none*** ***required***	1, 1 – No difficulty at all 2, 2 – Hardly any difficulty 3, 3 – A little difficulty 4, 4 – Moderate difficulty 5, 5 – Quite a bit of difficulty 6, 6 – A lot of difficulty 7, 7 – Extreme difficulty
Walking briskly uphill or carrying groceries or other items, up a flight of stairs without stopping ***walking_briskly_uphill*** ***radio*** ***none*** ***required***	1, 1 – No difficulty at all 2, 2 – Hardly any difficulty 3, 3 – A little difficulty 4, 4 – Moderate difficulty 5, 5 – Quite a bit of difficulty 6, 6 – A lot of difficulty 7, 7 – Extreme difficulty
Doing vigorous activities such as lifting or moving heavy furniture, running, or participating in strenuous sports like tennis or racquetball ***vigorous*** ***radio*** ***none*** ***required***	1, 1 – No difficulty at all 2, 2 – Hardly any difficulty 3, 3 – A little difficulty 4, 4 – Moderate difficulty 5, 5 – Quite a bit of difficulty 6, 6 – A lot of difficulty 7, 7 – Extreme difficulty
On a scale of 1 to 7, over the <u>past 4 weeks</u> as a result of your atrial fibrillation, how much did the feelings below bother you? Please choose <u>one</u> number which best describes your situation.	*Not a question*

feelings ***descriptive*** ***none*** ***not applicable***	
Feeling worried or anxious that your atrial fibrillation can start anytime ***worry_af_start*** ***radio*** ***none*** ***required***	1, 1 – Not at all bothered 2, 2 – Hardly bothered 3, 3 – A little bothered 4, 4 – Moderately bothered 5, 5 – Quite a bit bothered 6, 6 – Very bothered 7, 7 – Extremely bothered
Feeling worried that atrial fibrillation may worsen other medical conditions in the long run ***worry_af_worsen*** ***radio*** ***none*** ***required***	1, 1 – Not at all bothered 2, 2 – Hardly bothered 3, 3 – A little bothered 4, 4 – Moderately bothered 5, 5 – Quite a bit bothered 6, 6 – Very bothered 7, 7 – Extremely bothered
On a scale of 1 to 7, over the <u>past 4 weeks</u>, as a result of your atrial fibrillation treatment, how much were you bothered by: Please choose <u>one</u> number which best describes your situation. ***treatment*** ***descriptive*** ***none*** ***not applicable***	*Not a question*
Worrying about the treatment side effects from medications ***side_effects*** ***radio*** ***none*** ***required***	1, 1 – Not at all bothered 2, 2 – Hardly bothered 3, 3 – A little bothered 4, 4 – Moderately bothered 5, 5 – Quite a bit bothered 6, 6 – Very bothered 7, 7 – Extremely bothered
Worrying about complications or side effects from procedures like catheter ablation, surgery, or pacemakers therapy ***complications***	1, 1 – Not at all bothered 2, 2 – Hardly bothered 3, 3 – A little bothered 4, 4 – Moderately bothered 5, 5 – Quite a bit bothered

radio ***none*** ***required***	6, 6 – Very bothered 7, 7 – Extremely bothered
Worrying about side effects of blood thinners such as nosebleeds, bleeding gums when brushing teeth, heavy bleeding from cuts, or bruising. ***blood_thinners*** ***radio*** ***none*** ***required***	1, 1 – Not at all bothered 2, 2 – Hardly bothered 3, 3 – A little bothered 4, 4 – Moderately bothered 5, 5 – Quite a bit bothered 6, 6 – Very bothered 7, 7 – Extremely bothered
Worrying or feeling anxious that your treatment interferes with your daily activities ***daily_activities*** ***radio*** ***none*** ***required***	1, 1 – Not at all bothered 2, 2 – Hardly bothered 3, 3 – A little bothered 4, 4 – Moderately bothered 5, 5 – Quite a bit bothered 6, 6 – Very bothered 7, 7 – Extremely bothered
On a scale of 1 to 7, overall, how satisfied are you at the present time with: Please choose <u>one</u> number which best describes your situation. ***overall_satisfaction*** ***descriptive*** ***none*** ***not applicable***	*Not a question*
How well your current treatment controls your atrial fibrillation? ***treatment_control*** ***radio*** ***none*** ***required***	1, 1 – Extremely satisfied 2, 2 – Very satisfied 3, 3 – Somewhat satisfied 4, 4 – Mixed with satisfied and dissatisfied 5, 5 – Somewhat dissatisfied 6, 6 – Very dissatisfied 7, 7 – Extremely dissatisfied
The extent to which treatment has relieved your symptoms of atrial fibrillation? ***treatment_relieved*** ***radio*** ***none*** ***required***	1, 1 – Extremely satisfied 2, 2 – Very satisfied 3, 3 – Somewhat satisfied 4, 4 – Mixed with satisfied and dissatisfied 5, 5 – Somewhat dissatisfied 6, 6 – Very dissatisfied 7, 7 – Extremely dissatisfied

Appendix B: Consent Form

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

I-STOP-AFib Study

SUMMARY

I-STOP-AFib Study, led by Dr. Greg Marcus from UCSF, is designed to test the comparative effectiveness of studies that allow you to test your personal afib triggers versus daily recording of your AF frequency and severity. This Atrial Fibrillation Study is an internet-based mobile platform-enabled study supported by the Eureka Research Platform.

Research studies include only people who choose to take part. Please take your time to read this consent form thoroughly to make your decision about being a part of this study.

STUDY PURPOSE and GENERAL INFORMATION

Why is this study being done?

The purpose of this study is to compare the ability to test your individual afib triggers vs tracking your afib severity and duration in order to improve quality of life for afib patients.

Who is paying for the study?

Patient Centered Outcomes Research Institute is paying for the conduct of this study, and AliveCor is providing devices at no cost to the researchers or research participants. The investigators do not have any financial or proprietary interests.

Am I eligible?

You are eligible if you have:

(1) Symptomatic atrial fibrillation that comes and goes with potential triggers for your episodes (e.g. lack of sleep, caffeine or exercise), and
(2) An Android or iOS smartphone with reliable Internet and/or Wi-Fi

How many people will take part in the study?

About 480 people will take part in this study.

Can I decide not to participate?

Taking part in a research study is your choice. You may choose to either take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you.

PROCEDURES

What will happen if I take part in this research study?

- *If you are randomized to test your personal triggers:* The study duration will be at least 3 months but could be up to a year, depending on how many triggers you choose to test. At the start of the study, you will select one trigger to test for a period of 6 weeks using a menu of options in the app. For example, if the trigger is coffee consumption, this might include a daily alert to "avoid coffee today" or "drink coffee today". You will receive daily reminders to record trigger exposure, AF frequency and severity, and to perform a tracing with your AliveCor device. ***It is important to note that you will be identifying your personal triggers and will not be engaging in any activities you would not otherwise, if not enrolled in the study.*** Once your first trigger study is complete, you can view your study results and interpretations in the app. Then you will have 4 weeks to implement any lifestyle changes from what you learned from the 6 weeks of testing your trigger. During this period, you will continue to track AF frequency and severity via the app. At the end of the 4-week lifestyle change period, you will have the option to test another trigger or end your study participation. If you choose to test another trigger, you will follow the same protocol to test up to 5 other AF trigger(s) (i.e. diet, exercise, sleep, alcohol, smoking, certain exercises, etc.) using the app.
- *Afib Tracking Arm*: If you are randomized to this arm you will collect daily AF episode frequency and severity using the app and a daily ECG tracing using your AliveCor device, for 10 weeks. You will be able to visualize your afib data in real time on the app and receive a monthly summary of your AF frequency and severity via the app. At the end of the 10-weeks you will have the option to test your triggers. You will have up to 9 months to test your AF trigger(s) (i.e. diet, exercise, sleep, alcohol, smoking, certain exercises, etc.) using the app and the trigger testing protocol described above.
- *Follow-up Evaluation:* At the end of the 3-month enrollment period, you will complete a follow-up assessment of your AF severity and quality of life via the app.

How long will I be in the study? What if I want to stop participating?

The I-STOP-AFib Study will take 3 months to 1 year to complete (depending on how many triggers you choose to test). You can decide to stop participating at any time. We won't delete the information about you that we've already collected, but the study will stop collecting any new information about you and stop contacting you.

What are the costs of taking part in this study?

There will be no costs to take part in this study. Depending on your situation, there may be some indirect costs to you from participating in this study, including incurring extra mobile data plan charges.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study. By participating, each participant will be able to keep their AliveCor device after they have completed their participation in the study.

BENEFITS/RISKS

What side effects or risks can I expect from being in the study?

Participation in the study should not result in any increased physical risk.

Although we will do our best to protect your study information, there is still a very small risk of loss of privacy.

Taking part in a mobile-based study may also lead to incurring additional data charges due to increased interaction with your smartphone.

If you have additional questions about the risks and side effects of this study, please contact the study researchers (see contact information below).

Are there benefits to taking part in the study?

You may not benefit from participating in this study. Testing triggers may help you identify the role of trigger modification in controlling your AF symptoms. We hope that study participation will lead to a better understanding of the triggers for AF and optimal means to manipulate those triggers to enhance the health of AF patients. We hope that society may benefit from your participation in research.

Will I get advice about my health from the study?

No. While you will have access to the results of your N-of-1 trials and AliveCor readings, we will not provide you with information about your health or clinical interpretations of your data from the study. Participation in this study does not in any way substitute for professional medical advice, diagnosis, or treatment that your doctor or other healthcare provider may give you. Always ask the advice of your healthcare provider if you have any questions about a medical condition. Do not disregard professional medical advice or delay in seeking care because of something you have read as part of this study. If you think you may have a medical emergency, call your doctor or dial 911 immediately.

PRIVACY & SECURITY

You are participating in a research project supported by the Eureka Research Platform, which maintains a Privacy Policy and Data Security Measures. You will be notified of any changes in this policy. Here is the Policy:

<<Clickable link to “Eureka Privacy Policy and Data Security Measures”>>

Who can answer my questions about the study?

Please contact Madelaine Faulkner at madelaine.faulkner@ucsf.edu or 415-476-3393 for questions about this study.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please contact the UCSF Human Research Protection Program at (415) 502-1814 or IRB@ucsf.edu.

CONSENT

You can access and download a copy of this consent form from your N-of-1 Study Settings page.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study network without penalty or loss of benefits to which you are otherwise entitled.

The Experimental Subject's Bill of Rights can be found here:
http://www.research.ucsf.edu/chr/Recruit/English.pdf.

Clicking the button below indicates that you have read and understood the information in this consent form. You freely consent to be in this research study and authorize the use and disclosure of your unnamed and coded data to electronic database(s) to be broadly shared for future research studies.

<<AGREE>> <<NO THANKS>>

Appendix C: DSMB Charter

Data and Safety Monitoring Plan

Although randomization to N-of-1 trials versus symptom surveillance (data tracking) is low risk, we will form a DSMB to ensure the safety of participants. This board will be comprised of a patient, a cardiac electrophysiologist, and a statistician from outside the research groups or institutions of the study personnel otherwise involved in the project. They will meet prior to implementation of the study to review the safety of a near-final AF-specific N-of-1 platform. They will meet again after 100 patients are enrolled and again after 350 patients are enrolled.

An analyst will prepare summary statistics of results collected prior to the second and third meetings. The DSMB will review study progress and any adverse events that have been reported by patients. The DSMB will also discuss trouble around retention, compliance, protocol violation and recruitment issues. The DSMB will have the authority to stop the study for safety reasons or to alter it if needed. Because the study is expected to be low risk, patients may actually benefit from study participation, and specific subgroups (e.g., those in whom N-of-1 studies identify a trigger), may yield important results, the DSMB will not perform any interim analyses for efficacy or consider stopping the study early for futility. In addition, all potential participant data obtained by the study investigators will be monitored on an ongoing basis to ensure compliance, to provide quality assurance (QA), and to obtain metrics for quality improvement.

DATA AND SAFETY MONITORING BOARD (DSMB) CHARTER
PRIVILEGED AND CONFIDENTIAL

I-STOP-AFib

1.0 Overview

This Charter summarizes the roles and responsibilities of the Data and Safety Monitoring Board (DSMB) for the investigator-initiated study protocol titled “I-STOP-AFib”

The DSMB is an autonomous body in charge of reviewing safety data and providing advice to Gregory M. Marcus, MD, Principal Investigator, throughout the conduct of the study. DSMB administration and coordination of all activities during the trial will be conducted by the University of California, San Francisco Coordinating Center (UCSF CC). The Charter is intended to be a living document. The DSMB may review it at regular intervals to determine whether any changes in procedure are needed (see section 8.0).

2.0 Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and validity of study procedures, and for monitoring the overall conduct of the study and outcomes data.

The DSMB members are independent consultants to UCSF and are required to provide recommendations with regard to: starting, continuing, and stopping the study. In addition, the DSMB is asked to make the following recommendations, as appropriate:

- Effectiveness of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol
- Adequacy of and amendments to consent forms
- Performance of individual centers and core labs
- Participant safety

DSMB responsibilities also include:

1. Approval of the initial DSMB Charter and any subsequent revisions, as necessary
2. Reviewing safety and related reports of a pre-specified format and content
3. Based on the review of the reports, making recommendations, as described above
4. Ensure the confidentiality of all reviews and analyses

Although the DSMB may make recommendations to UCSF about changes in the conduct of the study, final decisions will be made by the UCSF Principal Investigator, in consultation with the I-STOP-AF Investigators. In the case of early termination of the trial, consultation with PCORI and the UCSF institutional review board may also be required.

Members of the DSMB will not share any unblinded or partially-blinded information with anyone outside of the DSMB. The study investigators will remain fully blinded* to results related to the overall group randomized to data tracking versus the group randomized to N-of-1 trials throughout the study unless the DSMB recommends changes in the conduct of the study (e.g., early termination due to negative safety findings). Note: the investigators will not be blinded to the results of individual-level N-of-1 trials.

3.0 Membership

The DSMB will be comprised of: an established cardiac electrophysiologist, a patient with atrial, and a statistician from outside the research groups or institutions of the study personnel otherwise involved in the project. The DSMB will be composed of three voting members, who will serve on the Board for the duration of the Afib N-of-1 trial, provided they fulfill the roles and duties in the Charter.

3.1 Membership Selection

The initial Board membership will be chosen by UCSF with a goal of obtaining optimal scientific and clinical expertise.

Additional appointments to the DSMB may be made to replace members of the initial membership (e.g., in cases of member resignation or necessary removal of a member) or if the DSMB believes that additional expertise is required. Any such appointments would be made by UCSF after consultation with the members of the DSMB. Nominations for new members will be accepted from all current Board members.

The DSMB is also empowered to seek additional consultancy with prior agreement from UCS, as to the identity of the consultant. Consultants will not be voting members of the Board and will only be consulted for advice regarding specific issues/situations, as appropriate.

3.2 Conflicts of interest

DSMB members will not be employed by UCSF. None of the DSMB members should have any financial interest that could be substantially affected by the outcome of the study or have any serious conflicts of interests that could affect their objectivity. Should the latter statement no longer hold true for any reason, DSMB members agree to notify the DSMB members and UCSF. Financial support for DSMB members from UCSF beyond the consultation fee specified in their contracts must be disclosed. Any other potential conflicts of interest should be declared to the study investigator.

DSMB members will be asked to approve the DSMB Charter, upon their appointment to the DSMB.

4.0 DSMB Meetings

The DSMB meetings will be scheduled as follows, unless more frequent meetings are warranted by issues that arise during the conduct of study or if a meeting is requested by the DSMB Chair:

- Meeting #1: Prior to implementation of the study to review the safety of a near-final AF-specific N-of-1 platform.
- Meeting #2: after n=100 have been randomized
- Meeting #3 after n=300 have been randomized

Individuals from UCSF, and other experts in the field may be invited to attend individual meetings, as needed/appropriate, as non-voting participants.

Each DSMB member will receive an honorarium of $500 per meeting.

They will meet again after 100 patients are enrolled and again after 300 patients are enrolled. An analyst will prepare summary statistics of results collected prior to the second and third meetings. They will review study progress and any adverse events that have been reported by patients. The DSMB will have the authority to stop the study for safety reasons or to alter it if needed. Because the study is expected to be low risk, patients may actually benefit from study participation, and specific subgroups (e.g., those in whom N-of-1 studies identify a trigger), may yield important results, the DSMB will not perform any interim analyses for efficacy or consider stopping the study early for futility. In addition, all potential participant data obtained by the study investigators will be monitored on an ongoing basis to ensure compliance, to provide quality assurance (QA), and to obtain metrics for quality improvement.

4.1 Initial Meeting

At the initial meeting of the DSMB will be held to provide the DSMB with an overview of the study, establish meeting guidelines, as well as review the Charter and safety report format/content which will be used for future DSMB meetings. Additional topics which might be discussed at this meeting include:

- Frequency of meetings and format of future meetings
- Key safety and additional variables to be reviewed for decision making
- Interim analysis planning

4.2 Subsequent Ad hoc Meetings

Meetings will be scheduled according to the timeline noted in Section 6.0. Subsequent ad hoc meetings (by telephone/webinar) may be scheduled at the discretion of the DSMB. UCSF may also request that the DSMB hold additional meetings if warranted by study progress.

4.3 Quorum

DSMB members will make every attempt to attend the meeting by tele/webconference. All three DSMB members will be required to attend each meeting.

4.4 Voting

DSMB members will vote to approve the initial DSMB Charter and amendments, all proposals/recommendations to be submitted to UCSF, and protocol revisions (only those changes to the protocol required by the DSMB need to be reviewed).

To vote, a DSMB member must be a participant in a meeting held by tele/webconference. Each member will have a single vote. Issues will be decided based on a simple majority vote with the following exceptions:

- DSMB member with expertise in statistics must vote on all recommendations regarding protocol changes that impact sample size or planned analysis. Neither proxies nor designees are permitted.
- Approval of the DSMB Charter and any amendments to the Charter require a unanimous vote from all members.

Voting will be conducted verbally at the meetings, but a member may request that a vote be conducted by anonymous written ballot instead. The DSMB will attempt to come to a consensus evaluation by the end of a meeting. When this is not possible, the different opinions (as well as their rationale) will be documented in the meeting minutes and the DSMB will decide how to proceed or follow-up.

5.0 Confidentiality

Any information and materials that a DSMB member may acquire, during the course of his/her membership, with respect to UCSF's business or the I-STOP-AF study will be maintained in secrecy, and each such member will use all reasonable diligence to prevent disclosure of them during the trial.

No obligation of confidentiality shall exist as to information and materials that are in the public domain by public use, publication, general knowledge or the like, or contained in the publication of the HOLIDAY study results.

6.0 Meeting Materials

The UCSF study team will draft the DSMB agenda and will produce/distribute all materials to attendees prior to the meeting.

6.1 Planned Interim Analyses

AS described above, an interim analysis of the primary effectiveness endpoints will not be performed.

6.2 Request for Unscheduled Interim Analyses

It is acknowledged that a significant safety concern entitles the DSMB to request unscheduled formal interim analyses. The DSMB may request unscheduled formal interim analyses of either the primary or secondary endpoints.

Provided that the DSMB unscheduled interim analysis involves the review of safety data and no effectiveness data, no adjustments will be performed to the α level for the primary endpoint evaluation at the end of the study. In the case that a formal unscheduled interim analysis is actually performed involving effectiveness data, the test criteria (i.e. critical boundaries) will be amended according to the appropriate α-spending function and the study sample size may be amended.

6.3 Final DSMB Meeting Minutes/Recommendations Review Process

Meeting minutes, which will include the DSMB recommendations and requests, are to be prepared for all meetings and distributed to the DSMB members after the meeting for review and approval.

A copy of the open session minutes will be available to the Principal Investigators and the UCSF Institutional Review Board (IRB).

6.3.1 DSMB Action Items

Communication of the DSMB recommendations and requests will occur as follows:

- In the event of a safety concern, or other DSMB recommendations/requests should be immediately communicated at the end of the meeting to the UCSF.

All DSMB recommendations and requests will be considered action items, which will require resolution or a response (or update) by the time of the next meeting. Any recommendations of the DSMB involving a possible safety risk to participants will be handled by all parties in as expedited a manner, as possible.

7.0 Approval of and Amendments to the DSMB Charter

DSMB member approval of this version of the Charter represents the entire understanding of the parties with respect to the subject matter hereof and merge and supersede all prior and contemporaneous Charters or understandings, oral or written, with respect thereto. The failure of a member to adhere to any term of this Charter on any occasion may only be excused by waiver. All waivers must be in writing and signed by the party making the waiver (i.e., DSMB chair or UCSF representative).

Amendments to the Charter may be proposed by UCSF or a DSMB member. This Charter shall not be modified except by unanimous vote of all DSMB members.

DSMB Members:

Jonathan C. Hsu, MD, MAS
Assistant Professor of Medicine
Section of Cardiac Electrophysiology, Division of Cardiology
University of California, San Diego

Dr. Jonathan Hsu is an Assistant Clinical Professor of Medicine at UCSD School of Medicine, Division of Cardiology. His primary clinical interest is in cardiac electrophysiology, and he specializes in the medical and procedural care of patients with all types of heart rhythm disturbances.

He is a clinical research investigator with formal advanced training (Master's Degree) in clinical research methods and biostatistics. His research focuses on the epidemiology and clinical outcomes in patients with all types of cardiac arrhythmias and devices, including reducing the risk of stroke in atrial fibrillation patients with oral anticoagulants and reducing complications in implantable-cardioverter defibrillator recipients.

Dr. Hsu has a special clinical interest in quality of cardiovascular care improvement and outcomes research. He has specific expertise in Registry and large database analyses to improve the medical and

procedural care of patients with arrhythmias.

Dr. Hsu completed fellowship training in general cardiology and received additional advanced subspecialty training in cardiac electrophysiology at the University of California, San Francisco (UCSF), where he also completed his Master's Degree in Clinical Research (MAS). He completed both his internship and residency at Massachusetts General Hospital. He earned his undergraduate and medical degree at Northwestern University.

Stephen Belford
Patient DSMB representative

Stephen Belford is a 72 year old male who is retired from a position of technology management. My expertise was program management (including project management) and product usability and the user experience. I am active in retirement. I was diagnosed with paroxysmal AFib in early to mid-2000s but holter monitor and stress cardio test were unable to detect again. I then went to Dr. Jeff Olgin and was diagnosed as having permanent AFib. In fall of 2015, I went for my annual visit with Dr. Olgin, and was found not to have AFib. This resulted, I believe, from reduction in alcohol intake. Using a Kardia monitor regularly, I determined that I would enter AFib, only after drinking in excess of 1 glass of wine daily.

Eric Vittinghoff, Ph.D
Professor at UCSF Department of Epidemiology and Biostatistics

Dr. Vittinghoff is a temporary DSMB member, helping the study team to identify a suitable DSMB statistician for this unique N-of-1 trial. He is an experienced BIostatistician at the University of California San Francisco.

Appendix D: Eureka Privacy Policy

PRIVACY POLICY AND DATA SECURITY MEASURES

You are participating in a research project supported by the Eureka Research Platform, which maintains the following privacy policies and data security measures.

Your information will be used for research
Information about your background, health, behaviors and other factors that might help researchers predict, prevent or treat diseases will be collected for research. This information will be used in research analyses, and results of these analyses will be presented in scientific conferences and published. These presentations and publications will not show information that identifies you or any other individual in the study without your explicit permission.

We will contact you when we need you
We will send you an email, text message (SMS) or app-based notification when we need you, for example when one of your studies needs you to do something. You can set your preferences for how you want to be notified - remember that, depending on your mobile phone plan, you may be charged for text messages you receive from us.

Your identify will not be shared
We will never sell, rent, or lease your identifying information, or voluntarily share it for any reason without your permission.

You decide how to share your data
We'll ask if you want to share the data you donate with other research studies that you're participating in (so you don't have to re-enter data for two different studies), and with other qualified researchers without your name or other identifiers (so your data can used to help people everywhere). You'll also have the option of setting your default data sharing preferences to "Share all data with studies I join", so we don't have to ask you every time.

You are responsible for keeping your login credentials secure
When you registered for Eureka, you provided an email or phone number and a password. You can use this to sign into our system and see some of the health information you've provided to us (your height and weight, medication list, etc). You should be very careful not to provide your login information to anyone else, or they could sign in as you and be able to see that same health information. If you are worried that someone else may be using your login information, please let us know immediately, or change your password yourself through the Participant Homepage .

If required by law, we may need to disclose information about you
In accordance with the law, we may be required to take actions to prevent serious harm to

yourself or others. This may include divulging information about you to authorities. Otherwise, we will do everything we can to keep your study information private, and we will resist any demands for information that would identify you.

We keep our data really secure

While we cannot provide an absolute data security guarantee, your information will be transmitted and stored using state-of-the-art security systems similar to those that protect websites used by banks and electronic health record systems. Specifically, our platform is hosted on Amazon Web Services (AWS), a cloud-based server system and computing services.These systems and services are compliant with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). All research data are stored behind a secure firewall, guarded by intrusion detection software, and encrypted at rest and in transit in our Amazon Virtual Private Cloud.

Appendix E: Trigger Survey

Atrial Fibrillation Triggers Survey
Survey Number: 3 - 1

Question? ***Popup Language Title*** ***Popup Language Body*** ***variable name*** ***field type*** ***branching logic*** ***required/not required***	1, Option #1 2, Option #2 **Text Validation** **Triggering Between Survey** ***Note - questions that are triggered have a blue "fill"***
The triggers that start an episode of atrial fibrillation are not well understood and appear to be highly variable among patients with AF. Based on a research idea co-developed with atrial fibrillation patients, we have recently received funding from the Patient Centered Outcomes Research Institute to study this exact research question. Specifically, will the identification of triggers objectively demonstrated to influence atrial fibrillation episodes help enhance quality of life among those with the disease. We ill randomly assign approximately 500 individuals who have symptomatic, intermittent atrial fibrillation (at least once a month) to either tract their exposures, behaviors and atrial fibrillation episodes ***or*** follow personalized instructions from a smartphone-based app to determine if certain triggers are indeed significantly associated with atrial fibrillation episodes. Our goal is to help patients identify triggers with the ultimate goal of learning to minimize, eliminate, or at some level control triggers fro purposes of reducing the number of bothersome atrial fibrillation episodes. We are no in the first phase of this novel experiment and need your help. As a patient with atrial fibrillation, we hope you can help us understand what you believe to be important	Not a question. Description before the survey questions.

exposures or behaviors that might trigger atrial fibrillation episodes. To help us with this patient-centered research project on atrial fibrillation, please complete this survey to the best of your ability. If you know others with atrial fibrillation that may wish to participate, please share the link. Ok, let's get started: ***intro*** ***none*** ***[none]*** ***required***	
We want to be sure you have atrial fibrillation episodes that you feel. In other words, some individuals with atrial fibrillation do not feel any differently when they are in atrial fibrillation. Do you have symptomatic atrial fibrillation (i.e., you experience something that tells you when you are in atrial fibrillation) that comes and goes on its own (also known as paroxysmal atrial fibrillation)? ***afib*** ***radio*** ***[none]*** ***required***	1, Yes (include yes even if you feel it sometimes and not other times) 2, No, but I do not feel it or know it when I am in atrial fibrillation 3, No, I am in atrial fibrillation all the time 4, I am not certain

Thank you so much for contributing to our survey. We look forward to engaging you further in patient powered research. If you are interested in helping us combat diseases like atrial fibrillation and have not already done so, please consider joining the Health eHeart Study here {LINK}. OR Sorry, but you are not eligible to participate in this study. Thank you so much for contributing to our survey. We will email you in the future with any future update opportunities! ***ineligible*** ***field type*** ***[afib] = '2, 3'*** ***required***	Not a question. Participant does not take the rest of the survey.
Why are you not certain if you have atrial fibrillation? ***afib_explain*** ***string*** ***[afib] = '4'*** ***required***	Text box
Do you think there are any identifiable things you are exposed to (such as something you eat or drink or in the environment) or things that you do that trigger your atrial fibrillation episodes? ***afib_triggers*** ***radio*** ***branching logic*** ***required***	1, Yes, for all of my atrial fibrillation episodes 2, Yes, but only for some of my atrial fibrillation episodes 3, I'm not sure 4, No

Thank you so much for contributing to our survey. We look forward to engaging you further in-patient powered research. If you are interested in helping us combat diseases like atrial fibrillation and have not already done so, please consider joining the Health eHeart Study here {LINK}. OR Sorry, but you are not eligible to participate in this study. Thank you so much for contributing to our survey. We will email you in the future with any future update opportunities! ***ineligible2*** ***field type*** ***[afib_triggers] = '4'*** ***required***	Not a question. Participant does not take the rest of the survey.
For things that may trigger your atrial fibrillation episodes, can they be modified or influenced by you relatively easily? For example, weather events or pollution levels are not easily modified or influenced by any individual, but intake of alcohol or certain types of exercises are. ***trigger_control*** ***radio*** ***none*** ***required***	1, Yes, at least one of the triggers I think may be important to my atrial fibrillation can be modified or influenced by me 2, No, all of the potential triggers for my atrial fibrillation are completely out of my control 3, I am not sure 4, Other
Please explain below. ***control_explain*** ***string*** ***[trigger_control] = '4'*** ***required***	Text Box

OK, now we're going to ask you about some triggers that some patients have reported. Then, we want to now if you have experience other triggers that we have failed to mention. Importantly, we are going to continue to focus on triggers that can be changed/modified/influenced by you since these are the only types of triggers we can feasibly test in our planned study. ***intro2*** ***none*** ***[none]*** ***required***	Not a question. Description before the survey questions.
Does alcohol trigger your atrial fibrillation? ***alcohol_trigger*** ***radio*** ***none*** ***required***	1, Yes, it is responsible for every one of my atrial fibrillation episodes 2, Yes, it triggers some of my atrial fibrillation episodes 3, It might trigger some of my episodes 4, No, I have not noticed this as a trigger 5, I am not sure
Would you be willing to test the effect of alcohol on your atrial fibrillation episodes? This would mean receiving messages from a mobile app on your phone to go ahead and drink alcohol (to a level you are comfortable with) on some days and then being instructed to avoid all alcohol on other days. ***alctest_willingness*** ***radio*** ***[alcohol_trigger] = '1, 2, 3, 4'*** ***required***	1, Yes – I would not mind and I would be happy to follow those instructions as best I could 2, No – I never drink alcohol 3, No – I do not want to drink alcohol because I already know it will trigger an episode 4, No for some other reason 5, I am not sure
Why are you not sure about testing the effect of alcohol on your atrial fibrillation? ****In Qualtrics, this question does not exist. Instead, the answer choice #4 says, in ( ), "Please explain below" and then a text box that is not required to fill in. Same for all the similar questions below.*** ***alctest_explain***	Text Box

string ***[alctest_willingness] = '4'*** ***not required***	
Do caffeine-containing beverages or foods (such as coffee or chocolate) trigger your atrial fibrillation? ***caffeine_trigger*** ***radio*** ***none*** ***required***	1, Yes, it is responsible for every one of my atrial fibrillation episodes 2, Yes, it triggers some of my atrial fibrillation episodes 3, It might trigger some of my episodes 4, No, I have not noticed this as a trigger 5, I am not sure
Would you be willing to test the effect of caffeine on your atrial fibrillation episodes? This would mean receiving messages from a mobile app on your phone to go ahead and consume caffeine (to a level you are comfortable with) on some days and then being instructed to avoid all caffeine on other days. ***cafftest_willingness*** ***radio*** ***[caffeine_trigger] = '1, 2, 3, 4'*** ***required***	1, Yes – I would not mind and I would be happy to follow those instructions as best I could 2, No – I never consume anything with caffeine in it 3, No – I do not want to consume anything with caffeine because I already know it will trigger an episode 4, No for some other reason 5, I am not sure
Why are you not sure about testing the effect of caffeine on your atrial fibrillation? ***cafftest_explain*** ***string*** ***[cafftest_willingness] = '4'*** ***not required***	Text Box
Does lack of sleep trigger your atrial fibrillation? ***sleep_trigger*** ***radio*** ***none*** ***required***	1, Yes, it is responsible for every one of my atrial fibrillation episodes 2, Yes, it triggers some of my atrial fibrillation episodes 3, It might trigger some of my episodes 4, No, I have not noticed this as a trigger 5, I am not sure

Do you think this is testable? Obviously control over quality of sleep can be difficult. ***sleeptest_willingness*** ***radio*** ***[sleep_trigger] = '1, 2, 3, 4'*** ***required***	1, Yes – I could imagine a strict adherence to a certain routine (such as an earlier bedtime or avoiding some things prior to bedtime) would help my sleep 2, Yes for some reason other than adherence to a certain routine before bed 3, No – while something might help, I would not be able to implement them 4, No – my difficulty with sleeping is not sufficiently under my control 5, No for some other reason 6, I am not sure
Why do you not think lack of sleep is testable on your atrial fibrillation? ***sleeptest_explain*** ***string*** ***[sleeptest_willingness] = '2, 5'*** ***not required***	Text Box
Does vigorous exercise trigger your atrial fibrillation? ***exercise_trigger*** ***radio*** ***none*** ***required***	1, Yes, it is responsible for every one of my atrial fibrillation episodes 2, Yes, it triggers some of my atrial fibrillation episodes 3, It might trigger some of my episodes 4, No, I have not noticed this as a trigger 5, I am not sure
Would you be willing to test the effect of vigorous exercise on your atrial fibrillation episodes? This would mean receiving messages from a mobile app on your phone to go ahead and exercise vigorously (to a level you are comfortable with) on some days and then being instructed to avoid all vigorous exercise on other days.	1, Yes – I would not mind and I would be happy to follow those instructions as best I could 2, No – I never exercise vigorously 3, No – I do not want to exercise vigorously because I already know it will trigger an episode 4, No for some other reason 5, I am not sure

exertest_willingness ***radio*** ***[exercise_trigger] = '1, 2, 3, 4'*** ***required***	
Why are you not sure about testing the effect of vigorous exercise on your atrial fibrillation? ***exertest_explain*** ***string*** ***[exertest_willingness] = '4'*** ***not required***	Text Box
Does lack of exercise trigger your atrial fibrillation? ***noexercise_trigger*** ***radio*** ***none*** ***required***	1, Yes, it is responsible for every one of my atrial fibrillation episodes 2, Yes, it triggers some of my atrial fibrillation episodes 3, It might trigger some of my episodes 4, No, I have not noticed this as a trigger 5, I am not sure
Would you be willing to test the effect of a lack of exercise on your atrial fibrillation episodes? This would mean receiving messages from a mobile app on your phone to limit your exercise (to a level you are comfortable with) on some days and then being instructed to exercise more rigorously on other days. ***noexertest_willingness*** ***radio*** ***[noexercise_trigger] = '1, 2, 3, 4'*** ***required***	1, Yes – I would not mind and I would be happy to follow those instructions as best I could 2, No – I never stop or limit my exercise 3, No – I do not want to stop or limit my exercise because I already know it will trigger an episode 4, No for some other reason 5, I am not sure

Why are you not sure about testing the effect of lack of exercise on your atrial fibrillation? ***noexertest_explain*** ***string*** ***[noexertest_willingness] = '4'*** ***not required***	Text Box
Do cold beverages trigger your atrial fibrillation? ***bev_trigger*** ***radio*** ***none*** ***required***	1, Yes, it is responsible for every one of my atrial fibrillation episodes 2, Yes, it triggers some of my atrial fibrillation episodes 3, It might trigger some of my episodes 4, No, I have not noticed this as a trigger 5, I am not sure
Would you be willing to test the effect of cold beverages on your atrial fibrillation episodes? This would mean receiving messages from a mobile app on your phone to go ahead and consume cold beverages (to a level you are comfortable with) on some days and then being instructed to avoid all cold beverages on other days. ***bevtest_willingness*** ***radio*** ***[bev_trigger] = '1, 2, 3, 4'*** ***required***	1, Yes – I would not mind and I would be happy to follow those instructions as best I could 2, No – I never drink cold beverages 3, No – I do not want to drink cold beverages because I already know it will trigger an episode 4, No for some other reason 5, I am not sure
Why are you not sure about testing the effect of cold beverages on your atrial fibrillation? ***bevtest_explain*** ***string*** ***[bevtest_willingness] = '4'*** ***not required***	Text Box

Do cold foods (such as ice cream) trigger your atrial fibrillation? ***food_trigger*** ***radio*** ***none*** ***required***	1, Yes, it is responsible for every one of my atrial fibrillation episodes 2, Yes, it triggers some of my atrial fibrillation episodes 3, It might trigger some of my episodes 4, No, I have not noticed this as a trigger 5, I am not sure
Would you be willing to test the effect of cold foods on your atrial fibrillation episodes? This would mean receiving messages from a mobile app on your phone to go ahead and consume cold foods (to a level you are comfortable with) on some days and then being instructed to avoid all cold foods on other days. ***foodtest_willingness*** ***radio*** ***[food_trigger] = '1, 2, 3, 4'*** ***required***	1, Yes – I would not mind and I would be happy to follow those instructions as best I could 2, No – I never consume cold foods 3, No – I do not want to consume cold foods because I already know it will trigger an episode 4, No for some other reason 5, I am not sure
Why are you not sure about testing the effect of cold foods on your atrial fibrillation? ***foodtest_explain*** ***string*** ***[foodtest_willingness] = '4'*** ***not required***	Text Box
Does a high salt diet trigger your atrial fibrillation? ***salt_trigger*** ***radio*** ***none*** ***required***	1, Yes, it is responsible for every one of my atrial fibrillation episodes 2, Yes, it triggers some of my atrial fibrillation episodes 3, It might trigger some of my episodes 4, No, I have not noticed this as a trigger 5, I am not sure

Would you be willing to test the effect of a high salt diet on your atrial fibrillation episodes? This would mean receiving messages from a mobile app on your phone to go ahead and consume high salt levels (to a level you are comfortable with) on some days and then being instructed to avoid all salt on other days. ***salttest_willingness*** ***radio*** ***[salt_trigger] = '1, 2, 3, 4'*** ***required***	1, Yes – I would not mind and I would be happy to follow those instructions as best I could 2, No – I never consume a high salt diet 3, No – I do not want to consume a high salt diet because I already know it will trigger an episode 4, No for some other reason 5, I am not sure
Why are you not sure about testing the effect of a high salt diet on your atrial fibrillation? ***salttest_explain*** ***string*** ***[salttest_willingness] = '4'*** ***not required***	Text Box
Do large meals or over-eating trigger your atrial fibrillation? ***meals_trigger*** ***radio*** ***none*** ***required***	1, Yes, it is responsible for every one of my atrial fibrillation episodes 2, Yes, it triggers some of my atrial fibrillation episodes 3, It might trigger some of my episodes 4, No, I have not noticed this as a trigger 5, I am not sure

Would you be willing to test the effect of large meals or over-eating on your atrial fibrillation episodes? This would mean receiving messages from a mobile app on your phone to go ahead and consume large meals or over-eat (to a level you are comfortable with) on some days and then being instructed to avoid all over-eating and large meals on other days. ***mealstest_willingness*** ***radio*** ***[meals_trigger] = '1, 2, 3, 4'*** ***required***	1, Yes – I would not mind and I would be happy to follow those instructions as best I could 2, No – I never consume large meals or over-eat 3, No – I do not want to consume large meals or over-eat because I already know it will trigger an episode 4, No for some other reason 5, I am not sure
Why are you not sure about testing the effect of consuming large meals or over-eating on your atrial fibrillation? ***mealstest_explain*** ***string*** ***[mealstest_willingness] = '4'*** ***not required***	Text Box
Does dehydration (not drinking 6-8 glasses of water per day) trigger your atrial fibrillation? ***dehyd_trigger*** ***radio*** ***none*** ***required***	1, Yes, it is responsible for every one of my atrial fibrillation episodes 2, Yes, it triggers some of my atrial fibrillation episodes 3, It might trigger some of my episodes 4, No, I have not noticed this as a trigger 5, I am not sure

Would you be willing to test the effect of dehydration on your atrial fibrillation episodes? This would mean receiving messages from a mobile app on your phone to limit your liquid consumption (to a level you are comfortable with) on some days and then being instructed to fully hydrate on other days. ***dehydtest_willingness*** ***radio*** ***[dehydrate_trigger] = '1, 2, 3, 4'*** ***required***	1, Yes – I would not mind and I would be happy to follow those instructions as best I could 2, No – I never drink 6-8 glasses of water per day 3, No – I do not want to drink less that 6-8 glasses of water per day because I already know it will trigger an episode 4, No for some other reason 5, I am not sure
Why are you not sure about testing the effect of dehydration on your atrial fibrillation? ***dehydtest_explain*** ***string*** ***[dehydtest_willingness] = '4'*** ***not required***	Text Box
Does laying on your left side trigger your atrial fibrillation? ***lay_trigger*** ***radio*** ***none*** ***required***	1, Yes, it is responsible for every one of my atrial fibrillation episodes 2, Yes, it triggers some of my atrial fibrillation episodes 3, It might trigger some of my episodes 4, No, I have not noticed this as a trigger 5, I am not sure

Would you be willing to test the effect of laying on your left side on your atrial fibrillation episodes? This would mean receiving messages from a mobile app on your phone to go ahead and lay on your left side (to a level you are comfortable with) on some days and then being instructed to avoid laying on your left side on other days. ***laytest_willingness*** ***radio*** ***[lay_trigger] = '1, 2, 3, 4'*** ***required***	1, Yes – I would not mind and I would be happy to follow those instructions as best I could 2, No – I never lay on my left side 3, No – I do not want to lay on my left side because I already know it will trigger an episode 4, No for some other reason 5, I am not sure
Why are you not sure about testing the effect of laying on your left side on your atrial fibrillation? ***laytest_explain*** ***string*** ***[laytest_willingness] = '4'*** ***not required***	Text Box
Now we would like to know what other triggers might be important to you. ***other_trig*** ***none*** ***none*** ***required***	Not a question. Description before the survey questions.
Please tell us what trigger you think might be important for your atrial fibrillation (you will have an opportunity to list more than one, so let's just start with one here): ***describe_othertrig*** ***none*** ***none*** ***required***	Not a question. Description before the survey questions.

What is it? ***trigger_idea*** ***string*** ***none*** ***required***	Text box
After exposure to this trigger begins, how long until atrial fibrillation occurs? ***trigger_exposure*** ***string*** ***none*** ***required***	Text box (hours and minutes)
How would you propose to test this? On days you might want to TEST the trigger, what message would you like us to send you?; (i.e., if alcohol were the trigger, this might say something like "go ahead and drink alcohol to your comfort level today"): ***lang_trigtest*** ***string*** ***none*** ***required***	Text box
On days when you might want to AVOID the trigger (i.e., if alcohol was the trigger to be tested, this might be something like "avoid all alcohol today"): ***lang_trigavoid*** ***string*** ***none*** ***required***	Text box
Do you have another trigger you can tell us about? ***otheridea_trig*** ***radio*** ***none*** ***required***	1, Yes 2, No
Continue for **3** total trigger ideas. ***otheridea_trig***	

string ***[other_trigidea] = '1'*** ***required***	
Great – thanks for sharing your thoughts about potential triggers. ***great*** ***none*** ***none*** ***required***	Not a question. Description before the survey questions.
We're almost done. Now to make the best use of these data as we can and make sure it's applied effectively to our study design, it will be important to know a few things about you. ***demo_intro*** ***none*** ***none*** ***required***	Not a question. Description before the survey questions.
How old are you? ***age*** ***string*** ***none*** ***required***	Text box
What is your biological sex? ***sex*** ***radio*** ***none*** ***required***	1, Male 2, Female 3, Prefer not answer
Are <u>*you*</u> of Hispanic, Latino or Spanish origin or ancestry? ***Ethnicity*** ***This is a question about ethnicity, rather than race, as used in the US Census. For example, someone may be of white race and Hispanic ethnicity or black race and Hispanic ethnicity.*** ***hispanic*** ***radio***	1, No 2, Yes, Mexican, Mexican American or Chicano 3, Yes, Puerto Rican 4, Yes, Cuban 5, Yes, Other or Mixed Hispanic, Latino or Spanish origin 6, Don't know

none ***required***	
What is *your* racial background? Check all that apply. ***race*** ***checkbox*** ***none*** ***required***	1, Black or African American 2, White 3, Asian (including South Asian and Asian Indian) 4, Native Hawaiian or Pacific Islander 5, American Indian or Alaska Native 6, Some other race 7, Don't know
What is *your* Asian background? ***asian*** ***radio*** ***none*** ***required***	1, Chinese 2, Filipino 3, Asian Indian 4, Japanese 5, Korean 6, Vietnamese 7, Other Asian or Mix 8, No Asian background
What is *your* Pacific Island background? ***pacisland*** ***radio*** ***none*** ***required***	1, Native Hawaiian 2, Samoan 3, Guamanian or Chamorro 4, Other Pacific Islander or Mix 5, No Pacific Islander background
Do you have or have you ever been treated for high blood pressure? ***hbp*** ***radio*** ***none*** ***required***	1, Yes 2, No 3, I don't know
Do you have or have you ever been treated for diabetes or high blood sugar? ***diabetes*** ***radio*** ***none*** ***required***	1, Yes 2, No 3, I don't know
Do you have or have you ever been treated for heart failure or too much fluid in the lungs? ***heartfailure***	1, Yes 2, No 3, I don't know

radio ***none*** ***required***	
Do you have or have you ever been treated for coronary artery disease or blockages in the arteries? ***cad*** ***radio*** ***none*** ***required***	1, Yes 2, No 3, I don't know
Do you have or have you ever been treated for sleep apnea? ***sleepapnea*** ***radio*** ***none*** ***required***	1, Yes 2, No 3, I don't know
How tall are you? ***height*** ***radio*** ***none*** ***required***	Text box (**feet and inches**)
What is your current weight? ***weight*** ***radio*** ***none*** ***required***	Text box (**lbs**)
Does anyone in your immediate family also have atrial fibrillation (including biologically related parents, brothers, sisters, or children)? Note – if ONLY more distant relatives had atrial fibrillation (such as cousins or grandparents) this should be answered no. ***afib_family*** ***radio*** ***none*** ***required***	1, Yes 2, No 3, I don't know

Do you drink alcohol? If yes, how many drinks, on average, do you have a week? ***alcohol*** ***radio*** ***none*** ***required***	1, Yes, <1 2, Yes, 1-3 3, Yes, 4-7 4, Yes, 8-11 5, Yes, 12-14 6, Yes, 15-18 7, Yes, 19-21 8, Yes, >21 9, No 10, I don't know
Have you smoked at least one cigarette in the last month? ***cigarettes*** ***radio*** ***none*** ***required***	1, Yes 2, No – I used to smoke cigarettes, but I quit 3, No – I have never smoked
Have you used any electronic cigarettes or "vaped" at least once in the last month? ***ecigs*** ***radio*** ***none*** ***required***	1, Yes 2, No, but I do use them occasionally 3, No, but I have used them in the past and quit 4, No, I have never used them

Thank you for your participation in this survey. Your answers are extremely valuable in helping us to design this study and ultimately to understand more about atrial fibrillation. If you are interested in helping us combat diseases like atrial fibrillation and have not already done so, please consider joining the Health eHeart Study here {LINK}. Also, please keep a look out for the study invitation when it launches in a few months. Thank you! Kathi Sigona Atrial Fibrillation Patient Patient Co-Principal Investigator Gregory M Marcus, MD, MAS Endowed Professor of Atrial Fibrillation Research University of California, San Francisco Co-Principal Investigator ***thanks*** ***none*** ***none*** ***required***	