DECAF

Does Eliminating Coffee Avoid Fibrillation?

A pilot randomized controlled trial to assess abstinence of coffee compared to continued consumption on recurrent atrial fibrillation following electrical cardioversion

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Protocol name: Does Eliminating Coffee Avoid Fibrillation (DECAF)

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

Gregory M. Marcus, MD, MAS
(Principal Investigator) signature date

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ADMINISTRATIVE INFORMATION SUMMARY

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1.0 INTRODUCTION

1.1. Background and Significance

Atrial fibrillation (AF) is the most common, sustained heart rhythm disorder experienced by humans. It is anticipated that more than 10 million individuals in the United States will have AF by 2050.[1] This is concerning as AF is associated not only with complications including heart failure, stroke, and premature death, but also troubling symptoms such as palpitations, dyspnea, and fatigue.[2] As a result, the burden of AF-related symptoms and complications on affected individuals and society is growing, as represented by increasing hospitalizations and healthcare costs.[3] There is thus a pressing need to characterize modifiable factors that may reduce the incidence, prevalence, and overall impact of AF.

Coffee is one of the most ubiquitously consumed substances worldwide. In addition to caffeine, coffee contains variety of other biologically active compounds.[4] Correspondingly, whether any effect of coffee on health outcomes exist is of considerable interest to physicians, scientists, and individual consumers. While significant data exist on the potential impact of coffee on many cardiometabolic parameters, [4] there is conflicting data on any role of coffee on AF.[5] Given both the increasing population impact of AF and the widespread use of coffee in society, determining even a modest associated benefit or risk would be of great clinical relevance.

1.2. Possible Mechanisms of Coffee and its Constituents

Amongst the constituent compounds in coffee, the majority of prior research has focused on caffeine. While the caffeine content of coffee varies significantly, an average cup is estimated to contain between 95 and 200mg of caffeine.[6] Caffeine is a methylxanthine alkaloid and a potent central nervous system stimulant. It also exerts a range of cardiovascular effects that may facilitate atrial arrhythmogenesis. This includes sympathetic stimulation, enhanced automaticity, and increased after depolarization-induced triggered activity.[5] Conversely, caffeine also has mechanisms that might reduce AF; for example, caffeine inhibits adenosine which can trigger AF, and it additionally has some antioxidant activity. Finally, it has been estimated that coffee contains over 1,000 compounds, including some with described biological effects such as diterpene alcohols and chlorogenic acid.[4] As a result, there are plausible mechanisms for coffee and its constituents to have both beneficial and harmful cardiovascular and arrhythmic effects.

1.3. Prior Observational Studies on Coffee, Caffeine, and AF

A number of prior observational studies have evaluated the role of chronic coffee consumption and incident AF with varied results. In the Multifactor Primary Prevention Study, moderate coffee consumption of 1-4 cups per day was associated with increased risk.[7] Similarly, intermittent coffee consumption of less than 0.5 cups/day appeared to be associated with greater AF risk in the Multi-Ethnic Study of Atherosclerosis.[8] In contrast, several reports have found no clear relationship between coffee or caffeine intake and incident AF. These include reports from the Danish Diet, Cancer, and Health Study,[9] the Framingham heart Study,[10] two Cohort of Swedish Men,[11] and the Swedish Mammography Cohort.[11] Conversely, other studies have described results potentially consistent with a linear benefit of increasing coffee consumption. These include reductions of risk in hospitalized Kaiser Permanente patients,[12] an updated analysis from the Danish Diet, Cancer, and Health Study,[13] an Italian cohort,[14] and the UK Biobank.[15] Finally, a few investigators have demonstrated J- or U-shaped associations with benefit at modest intakes no effect or harm at higher levels, such as that seen in the Women's Health Study,[16] Physicians' Health Study,[17] the Seguimiento Universidad de Navarra (SUN) cohort,[18] and the Prevencion con Dieta Mediterranea (PREDIMED) cohort.[18] Meta-analyses including the aforementioned studies have concluded either no effect or a reduced AF risk with coffee consumption.[11, 19, 20] Furthermore, Mendelian randomization techniques using alleles associated with caffeine metabolism and hence coffee consumption have also not provided supportive evidence for any significant effect on AF.[15, 21]

Comparatively fewer studies exist on the role of acute coffee or caffeine ingestion, or on AF and related outcomes in other settings. One study found that acute intravenous administration of caffeine did not alter invasive measures of cardiac conduction or refractoriness.[22] Two reports suggest that modest coffee consumption may

be associated with a greater likelihood for spontaneous cardioversion compared to higher consumption.[23, 24] Furthermore, no association between caffeine intake and atrial ectopy was found in another analysis from the Cardiovascular Health Study.[25]

1.4. Current Consumer and Physician Beliefs

Despite the varied evidence described above, established notions exist that coffee and caffeine contribute to AF and/or trigger AF episodes. In a large study of symptomatic patients with paroxysmal AF, caffeine was reported as the second most common triggering factor in almost one-third of individuals.[26] Prior surveys of physicians have also suggested reductions in caffeine to assist with arrhythmias.[27] Conversely, professional society guidelines either do not discuss coffee or caffeine [28] or suggest they are unlikely to contribute based on recent studies.[29]

1.4. Rationale for Current Study

A key limitation of existing data on the effects of coffee and caffeine on AF has been their observational nature. Even with careful study design methodology, including prospective data collection, comprehensive characterization of participants, and appropriate analytical techniques, it is challenging if at all feasible to eliminate the possibility of biases in observational studies such as residual confounding and reverse causality.[30] Instead, appropriate randomization of subjects to an exposure of interest is more likely to produce reliable, unbiased results where observational evidence is conflicting or requires confirmation.[31] To the best of our knowledge, no such assessment on the effect of coffee on AF outcomes has been undertaken to date.

While the general effect of coffee or caffeine on incident AF would be of significant interest, undertaking a randomized trial in this setting would be challenging and likely to require an extremely large number of otherwise healthy individuals to agree to consume or abstain. Many individuals may find this objectionable given the widely consumed nature of coffee and caffeine-containing substances.

An alternative and potentially more practical setting would be in patients with existing AF who are not only at higher risk for (recurrent) AF episodes but may be more likely to be interested in such a randomized evaluation given their personal situation.

Thus, this pilot study proposes to evaluate the effect of random allocation to coffee abstinence compared to continued coffee consumption in patients undergoing direct current electrical cardioversion for AF, with patients being followed up for recurrent episodes of AF.

This pilot study will provide the first, randomized evaluation of coffee on AF outcomes. Given the conflicting evidence to date and widespread consumption of coffee, this study will be of significant interest to consumers and physicians alike. It will also provide important information, such as estimates of effect size and acceptability/compliance, which will directly inform the design of a future large, multi-center trial on this topic.

2.0 INVESTIGATIONAL PLAN

2.1 Study Design

This study is a prospective, single-center, pilot randomized (1:1) controlled trial of coffee abstinence compared to coffee continuation on recurrent AF in patients undergoing electrical cardioversion.

This pilot study will be conducted at a single center the United States (the University of California, San Francisco). Two-hundred (200) participants will be enrolled and randomized.

2.1.1 Study Visits and Windows

After screening and eligibility has been determined, participants will be enrolled and randomized at the baseline visit (date of cardioversion).

No in-person follow-up visits will be required. Phone call follow-ups will be conducted at week 1, month 1, month 3, and three-monthly thereafter until first recurrence of AF or study completion (whichever comes first). This will be supplemented with chart review, including scanned medical records if the patient does not return to UCSF for medical care, and analyses of ECG strips obtained from AliveCor (San Francisco, CA) KardiaMobile devices and Apple Watch (Cupertino, CA) devices already owned and in use by patients.

Table 1 outlines the window for each of the study visits. Clinical sites should make every possible effort to ensure that each study visit is conducted within the specified window.

Table 1. Visit Windows

Study Visit	Scheduled Timepoint	Visit Window
V1a-V1b (Screening)		
V1c (Baseline)	Enrollment/Cardioversion	
V2	Day 1*	+/- 0 days
V3	Month 3*	+/- 7 days
V4	Month 6*	+/- 14 days
V5	Month 12*	+/- 14 days

**Follow-up visits will be calculated from the date of cardioversion (i.e., baseline).*

Figure 1. Study Flow Diagram

Pre-Cardioversion Screening

- Initial inclusion/exclusion evaluation
- Screen for coffee consumption habits (≥ 1 cup of coffee per day)
- Screen for significant other caffeinated product consumption
- Informed consent

Baseline Visit (Cardioversion)

- Enrollment
- Pre- and post-cardioversion ECG
- Cardioversion
- Randomization to allocated treatment (coffee abstinence or continuation), provided as an instruction card they receive after cardioversion
- Detailed history of coffee consumption habits
- Detailed history of other caffeinated product consumption

Follow-Up Phone Call on Day 1

- Reinforce randomization allocation and answer any questions

Follow-Up Phone Calls at Month 3, and 6, and 12

- Compliance with allocated treatment
- Consumption of coffee or other caffeinated products, if applicable
- AE/SAE evaluation
- Symptomatic and/or known diagnosis of recurrent AF
- Any ECG strips from patient owned AliveCor KardiaMobile or Apple Watch

Recurrent AF Documentation from Physician/Healthcare Provider

- Documentation of ECG or any ambulatory ECG monitoring to confirm recurrent AF obtained from physician/healthcare provider if:
    - If patient reports diagnosis of recurrent AF
    - Patient not sure if has been diagnosed with recurrent AF
    - Patient declines further phone follow-up but still consents to access to physician/healthcare provider documentation
    - Patient unable to be contacted via phone

2.2 Study Objectives

The objectives of this pilot clinical trial are to assess the effect and acceptability of abstaining from coffee compared to continuation of coffee on the first recurrence of AF following direct current electrical cardioversion.

Primary objectives:

- to assess the time to first confirmed AF recurrence following direct current electrical cardioversion

Secondary exploratory objectives include assessment of the following:

- change in symptoms specific to AF or premature atrial contractions
- symptoms or adverse events secondary to coffee abstention
- rate of recurrent other arrhythmias determined as part of routine clinical care

2.3 Inclusion/Exclusion Criteria

2.3.1 Inclusion Criteria

Patients must meet **all** of the following to be eligible:

1. Men and women ≥ 21 years of age
2. Sustained AF
3. Planned/scheduled direct current electrical cardioversion
4. Consumption greater than or equal to one cup of coffee per day in the past 5 years
5. Willing and able to comply with coffee abstinence or continuation
6. Life expectancy of at least 1 year
7. Willing and able to return and comply with scheduled phone follow up visits
8. Willing and able to provide written informed consent

2.3.2 Exclusion Criteria

Patients will be excluded if they meet **any** of the following:

1. Established allergy or adverse reaction to coffee
2. Stated inability to comply with coffee abstinence or continuation
3. AF ablation in preceding 6 months or planned in next 12 months
4. Recent cardiothoracic surgery in preceding 3 months
5. Cardioversion for atrial flutter rather than AF
6. Pregnancy or desire to get pregnant within next 6 months.
7. Current enrollment in an investigation or study of a cardiovascular device or investigational drug that would interfere with this study
8. Any other criteria, which would make the patient unsuitable to participate in this study as determined by the Principal Investigator (e.g., an uncontrolled drug and/or alcohol addiction)

3.0 STUDY TREATMENT

After eligibility for the study has been confirmed, participants will be randomized to abstinence from coffee or continued consumption of caffeinated coffee.

3.1 Coffee Abstinence

If allocated to coffee abstinence, patients will be encouraged to completely abstain from coffee and other caffeine-containing products as much as feasibly possible. As some decaffeinated coffee can also contain caffeine, patients will be encouraged to abstain from decaffeinated coffee as well. Other non-coffee caffeine-containing products will include, but not be limited to, tea, cola, energy drinks, chocolate, chewing gum, and chocolate- or coffee-flavoured foods (e.g. ice cream).

3.2 Continued Coffee Consumption

If allocated to continued coffee consumption, patients will be encouraged to drink at least one cup of caffeinated coffee or one espresso shot) daily and other caffeine-containing products as per their usual lifestyle. It will be recommended that patients do not intentionally increase or decrease consumption of these products.

4.0 EARLY TERMINATION

If a randomized participant terminates participation in the study early (i.e., prior to completion of all follow-up), the Principal Investigator will determine the primary reason for early termination and report this. Participants who early terminate from the study will not be replaced with newly enrolled participants.

4.1 Randomized Participants – with exclusion found on day of cardioversion

A proportion of patients scheduled for cardioversion spontaneously convert to sinus rhythm. Thus, randomization will be undertaken after successful cardioversion from AF to sinus rhythm in order to minimize exclusion of randomized patients for this reason.

In the event that another exclusion criterion is identified on the day of cardioversion after randomization has occurred, the participant may or may not continue to be treated as allocated as deemed appropriate by the Principal Investigator. All randomized patients will be included in the ITT analyses.

4.2 Unsuccessful cardioversion

Patients will be interviewed and consented prior to cardioversion occurring. However, a small proportion of patients do not have successful cardioversion. As a result, randomization will occur after successful cardioversion from AF to sinus rhythm. Patients will be excluded in the event that cardioversion is unsuccessful.

4.3 Participant Withdrawals

Each participant will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time without effect on subsequent medical treatment or relationship with the treating physician. Participants who discontinue follow-up at any time after randomization will be included in the ITT analyses.

4.4 Other Early Terminations

Participants who discontinue follow-up at any time after randomization will be included in the ITT analyses.

Lost to Follow-Up: If a participant is unable to be contacted via phone for follow-up (i.e. participants who become lost to follow up and whose status is unclear because they fail to appear for study visits without stating an intention to withdraw) for any other reason, the participant will be designated an early termination. The clinical site Principal Investigator should show "due diligence" by documenting in the source documents, all steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc.

In the absence of a stated intention to withdraw, the physician or other healthcare professional of participants will be contacted in an attempt to ascertain the presence or absence of AF recurrence.

Principal Investigator Determination: Participants should also be early terminated at any time if the Principal Investigator concludes that it would be in the participant's best interest for any reason. Protocol deviations should not lead to early termination unless they indicate a significant risk to the participant's safety.

Early Study Closure: The study may be terminated due to safety concerns by the Data Safety Monitoring Board. Should this be necessary, participants currently in follow-up will be early terminated and scheduled for a Close-Out

Visit, as soon as possible. The Principal Investigator will be responsible for informing the appropriate local Institutional Review Board of the early study termination.

5.0 STUDY PROCEDURES

Table 2 provides an overview of the evaluations to be performed at each study visit/follow-up. See also Figure 1, the study flow diagram, for details on timing of these evaluations.

Table 2. Schedule of Evaluations and Visits

	Screening	Baseline	Phone	Follow-Up Phone Calls		
	Visits 1a-1b	**Visit 1c**	**Visit 2**	**Visit 3**	**Visit 3**	**Visit 4**
			Day 1	Month 3	Month 6	Month 12
		Cardioversion				
Initial inclusion/exclusion evaluation	X					
Screen for coffee consumption habits	X					
Screen for significant other caffeinated product consumption	X					
Informed consent	X					
Assessment of clinically available pre-cardioversion ECG		X				
Assessment of clinically available post-cardioversion ECG		X				
Randomization		X				
Reinforce randomization and answer any questions			X			
Detailed history of coffee consumption habits		X		X	X	X
Detailed history of other caffeinated product consumption		X		X	X	X
Detailed medical history		X				
Targeted medication history		X		X	X	X
		X				
Vital signs		X				
Adverse events/serious adverse events evaluation				X	X	X
AF Symptoms		X		X	X	X
Health related quality of life (SF-36) and physical activity questinnnaires		X				
Assessment of AliveCor KardiaMobile or Apple Watch ECG strip if required				X	X	X
Assessment of clinically available ECG or ambulatory ECG monitoring from				X	X	X

physician/healthcare provider if required						
Occurrence of other arrhythmias				X	X	X
Targeted medical care utilization				X	X	X

5.1 Screening for Inclusion/Exclusion Criteria

Each potential participant's medical record will be briefly reviewed for available inclusion and exclusion criteria data. Potentially eligible patients will be subsequently approached to ascertain interest and coffee/other caffeinated product consumption. After informed consent is obtained, pre- and post-cardioversion ECGs will be documented to record AF and sinus (or other appropriate non-AF underlying) rhythm respectively. Once this is confirmed, randomization will be undertaken.

5.5 Electrocardiogram (ECG)

Pre- and post-cardioversion electrocardiogram (ECG) data will be collected at baseline. Results from the ECG test will be entered onto the CRF.

5.6 Physical Examination and Medical History

The screening evaluation will collect medical history data for assessment of inclusion/exclusion criteria, including coffee/other caffeinated product consumption history.

5.7 Health-related Quality of Life (hrQOL) and Physical Activity (PA)

Health-related quality of life outcomes will be assessed using a self-administered SF-36 Health Survey (in English) at baseline, month 6, and month 12 (completed questionnaires may be collected by mail or email). Participants will also complete a self-administered International Physical Activity Questionnaire (IPAQ) short format questionnaire. Changes in QOL and PA measures between baseline and during follow-up will be assessed.

5.8 Targeted Medication Inventory

Current/regular use (since the last study follow up) of a specific list of concomitant medications/therapies will be documented at baseline (post cardioversion) and at all follow-up visits. Medication data will be collected by self-report on a CRF and will include type of medication, frequency, and dosage. The list of targeted medications/therapies, includes AF-related medications (e.g., anticoagulants, antiarrhythmics, negative chronotropic agents).

5.9 Targeted Medical Care Utilization

The occurrence of targeted medical care utilization (primarily cardiac-care) will be collected at all follow-up visits by self-report. At each study visit, participants will be queried on the occurrence (since the last study visit) of change in symptoms specific to AF and specific cardiovascular-related procedures, emergency room visits, and hospitalizations.

5.10 Adverse Event (AE) and Serious Adverse Event (SAE) Evaluation

After cardioversion (at the baseline visit) and at all follow-up visits, safety evaluations will include monitoring for targeted adverse events and recording all serious adverse events for the assessment of the secondary exploratory study objective (i.e., symptoms or other adverse events from coffee abstinetion).

Serious adverse event occurrences will be reported to the local Institutional Review Board (IRB) per IRB/EC policy. Copies of each report and documentation of IRB notification and receipt will be kept on file.

5.10.1 Targeted Adverse Events Reporting

An adverse event is any undesirable sign, symptom or medical condition occurring after initiation of the study allocation even if the event is not considered to be related to study allocation. Medical conditions/diseases present before starting study allocation are only considered AEs if they worsen after starting study allocation (or any procedures specified in the study protocol). Specified AEs occurring before study allocation, but after signing the informed consent form, should be recorded on the Medical History CRF during screening.

At each study visit, participants will be queried on the occurrence (since their last study follow up) of specific AEs. The list of targeted AEs includes possible cardiovascular-related events and events that are known to occur in relation to coffee or caffeine abstinence/withdrawal.

Information about targeted adverse events, whether volunteered by the subject, discovered by Principal Investigator questioning, or other means, will be collected and recorded on the Adverse Event CRF and followed as appropriate. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, or are considered clinically significant for any reason, in which case they are recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them.

As possible, each targeted adverse event will be described by:
- duration (start and end dates),
- severity grade (mild, moderate, severe),
- relationship to study allocation (suspected/ not suspected),
- action(s) taken and, as relevant, the outcome.

5.10.1.1 Adjudication of Specific AEs

If any of the following AEs are reported, additional documentation will be collected for event adjudication:
1. Any death
2. Myocardial infarction
3. Stroke/TIA
4. Cardiovascular hospitalization

If a death occurs, a questionnaire assessing circumstances of the event will be completed, and a copy of the death certificate will be obtained, if possible, in addition to other related documentation. At each follow-up, participants will be queried as to whether any of the specific AEs have occurred since the last visit. For each of these reported clinical events, a questionnaire assessing circumstances of the event, a copy of any hospital discharge summary, and other related documentation may be collected, as appropriate. The UCSF CC Endpoints Group will review and adjudicate these specific adverse event reports, blinded to treatment assignment, as per the STOP-COFFEE Adjudication Guidelines. Only those events which can be confirmed will be included in analyses.

5.10.2 Serious Adverse Event Reporting

Principal Investigators and clinical site staff must conform to the AE/SAE reporting timelines, formats and requirements of the various entities to which they are responsible. Information about all serious adverse events will be collected and recorded on the Serious Adverse Event Report CRF. Any SAE, irrespective of causality, occurring in a participant after providing informed consent and until 30 days after ending study visits/participation must be reported. To ensure patient safety, each SAE must also be reported to UCSF CC (by notification email, see STOP-COFFEE Operations Manual for full instructions) of learning of its occurrence. The SAE Report CRF and any supporting documentation should then be immediately sent to the UCSF CC as per the guidelines detailed in the STOP-COFFEE Operations Manual.

An SAE is an undesirable sign, symptom or medical condition which:
1. is fatal or life-threatening;
2. required or prolonged hospitalization;
3. results in persistent or significant disability/incapacity;
4. constitutes a congenital anomaly or a birth defect; and/or
5. is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

When an SAE is followed by reports of recurrent episodes, re-exposure, complications or progression of the initial SAE, all such reports must be reported as follow-up to the original episode. If a new SAE occurring at a different time interval is considered completely non-associated to a previously reported one, a new SAE CRF should be submitted as an initial report. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation in the study is not the cause. SAEs that are still ongoing at the end of the study period must be followed up to determine the final outcome.

The Clinical Site will send all SAE reports and documentation to the UCSF CC for reporting to the medical authorities, as appropriate. After the initial report, any significant new information on ongoing SAEs should be provided promptly to the UCSF CC. If additional documentation for the SAE is required, the UCSF CC will follow-up directly with the clinical site.

5.10.3 Reporting: Regulatory Authorities and Study-Wide Principal Investigators

Reported serious adverse events will be submitted to the required regulatory authorities by the UCSF CC, as appropriate. It is also the responsibility of the UCSF CC to notify all participating Principal Investigators of any adverse event associated with the use of the study devices/treatment that is both serious and unexpected, if advised by the Data Safety and Monitoring Board (DSMB).

6.0 Risks and Benefits of the Study

6.1 Cardioversion Procedure

The cardioversion procedure involves several risks, but each of these participants would experience these risks whether or not they choose to participate in STOP-COFFEE or not, since inclusion is this trial requires already having a planned/scheduled cardioversion procedure. The known risks have been shown to occur in less than 1% of cases and include adverse reaction from administered medications for sedation/anesthesia, lack of success, induction of another arrhythmia, skin burn, or stroke/TIA. Potential benefits of cardioversion include reduction in symptoms (such as palpitations, shortness of breath, and dizzy spells), improvement in energy/well-being, and strengthening of heart function (if AF is a major cause or contributor to weakened function).

6.2 Coffee Abstinence or Continuation

Abstinence from coffee and other caffeine-related products may result in caffeine-withdrawal, symptoms of which can include headache, fatigue, anxiety, difficulty concentrating, depressed mood, irritability, tremors, and low energy. It is not clear what effect, if any, coffee has on AF and AF recurrence; this forms the rationale for the present study. Potential benefits of coffee abstention may therefore include a reduction in AF recurrence. Conversely, it may be possible that coffee consumption is beneficial and abstinence may result in a greater likelihood of AF recurrence.

7.0 STUDY ROLES

The STOP-COFFEE study has been developed by the Principal Investigator at the University of California, San Francisco (UCSF). The study investigators are committed to conducting this study in a uniform manner, adhering

to the study protocol and the operations manual. Standardization, supervision and coordination of all procedures will be enhanced through peer review and quality control mechanisms.

7.1 Administrative Organization

STOP-COFFEE is organized and conducted by the University of California San Francisco (UCSF) under the guidance of the Principal Investigator.

7.2 Enrolling Clinical Site

The study will be conducted only at the University of California, San Francisco.

7.2.1 Clinical Site Principal Investigator

This study protocol will be conducted by the Principal Investigator and his staff. The Principal Investigator has experience in and will be responsible for:

- Conducting the study protocol in accordance with the signed agreement with the UCSF, the study protocol, all applicable FDA regulations (21 CFR Parts 50, 54, 56, 812), GCP guidelines, and any conditions of approval imposed by the IRB
- Providing IRB Approval and an Approved Informed Consent
- Screening and selecting appropriate participants
- Collection and archiving of data obtained pursuant to the requirements of the study protocol during the course of the study and after the study has been completed

It is acceptable for the Principal Investigator to delegate one or more of the above functions to an associate or co-Investigator, however, the Principal Investigator remains responsible for the proper conduct of the study protocol, complying with the study protocol and collecting all required data.

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8.0 PROTOCOL DEVIATIONS

Principal Investigators are required to adhere to the study protocol, applicable federal (national) or state/local, laws and regulations, and any conditions required by the IRB or applicable regulatory authorities.

A protocol deviation is used to describe situations in which the clinical protocol was not followed. All major deviations from the study protocol will be reported on the Protocol Deviation CRF, as soon as possible, but no later than 10 working days of notification of the event. In addition, all major deviations will be reported to the local IRB as appropriate, per the IRB's reporting requirements.

9.0 QUALITY ASSURANCE AND DATA MANAGEMENT

9.1 Clinical Site Investigator and Coordinator Training

Each investigator and coordinator will be trained on the study protocol and procedures to ensure accurate and consistent study methods are used study-wide and throughout the entire study duration. Trainings will include review of the protocol, operations manual, CRFs, event reporting, and data management procedures.

9.2 Data Handling and Confidentiality

Information about study participants 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 patient authorization informing the patient of the following:

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

In the event that a participant revokes authorization to collect or use PHI, the Principal Investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants 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 participant is alive) at the end of their scheduled study follow-up.

9.3 Source Documents

Complete study files will be kept in a secure location. Participant files will include archives of completed CRFs and source documents. The case report forms (CRFs) are the primary data collection instrument for the study and are considered source documents. All data requested on the CRF will be recorded. Source data also include original records of clinical findings, observations, or study measurement results (e.g., hospital records, clinical and office charts, laboratory notes, dispensing records, recorded data from automated instruments, and patient files).

9.4 Data Collection and Management

The data will be compiled into the central study database at UCSF. The study data will be stored in the study database at UCSF and will be subjected to checks for completeness, consistency and validity. Data entry will occur in a timely manner.

9.5 Data Monitoring

The Steering Committee will be responsible for monitoring procedures related to study conduct and data collection/reporting to ensure the quality and integrity of the study data. A representative will check the completeness of participant study records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, as per the STOP-COFFEE Monitoring Guidelines.

To ensure data quality, we will perform the following Quality Assurance procedures: after the first two participants are randomized and the study intervention is performed, 100% of inclusion/exclusion criteria and key baseline data points will be reviewed against source documentation collected from the site (such as the participant's de-identified initial EP H&P, procedure note and first follow-up EP note). In addition, specified de-identified documentation will be requested from each site to perform source verification on a random 10% sample of key study data. If during the course of the study the error rate exceeds a 5% threshold, the percentage of source verification will increase until control is demonstrated.

10.0 STATISTICAL METHODS

10.1 Sample Size and Randomization

The goal of this pilot trial is the enroll a total of 200 participants (n=100 per treatment group).

This target sample size was chosen as it is deemed to be feasible for a single center to recruit this number in approximately one year and will be sufficient to provide estimates of effect size, acceptability (and thus compliance), and the proportion of enrolled individuals who have personally owned AliveCor KardiaMobile or Apple Watches that can be used to verify AF recurrence.

Assuming a 0.05 two-tailed alpha level, 1:1 randomization scheme, 50% recurrence rate in the absence of coffee, and potential 10% lost to follow-up, a sample size of n=200 (100 per arm) will provide approximately 80% power to detect a 1.63 times increased hazard of AF recurrence between the groups.

Randomization will be performed 1:1 with stratification and permuted block randomization by use of any anti-arrhythmic medication (including Amiodarone, Dronedarone, Flecainide, Dofetilide, Sotalol, and similar).

10.2 Intention-to-Treat (ITT)

The main intention-to-treat (ITT) analysis set will include all randomized participants, whether or not they are compliant with the treatment allocation for this trial. Every attempt will be made to collect data until the end of the follow-up period for all randomized participants and these data will be included as part of the main ITT analysis. The analyses for the primary objective will be performed using the ITT dataset.

Although substantial crossover is not anticipated, per protocol analyses will also be conducted if failure to comply with allocated treatment assignments occurs in more than 10% of cases or if there is a significantly different proportion of assignment adherence in one group compared to the other.

11.0 PUBLICATION

Any presentation/publication of any data from this study must be approved by the Principal Investigator prior to release.

12.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 812 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

12.1 Institutional Review Board (IRB) and Ethics Committee (EC) Approval

This protocol and any amendments will be submitted to a properly constituted independent IRB for each clinical site, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the Principal Investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The Principal Investigator should also provide a list of IRB members and their affiliate to the UCSF CC.

12.2 Informed Consent

The investigator must explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each participant must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the participant cannot read or sign the document, oral presentation may be made or signature given by the participant's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the participant could not read or sign the documents. No participant can enter the study before his/her informed consent has been obtained. (NOTE: consent by proxy is not allowed for this study as neurocognitive function is an endpoint in this trial)

The informed consent form must be submitted by the investigator for IRB approval. An informed consent template will be provided to all of the clinical sites for their use. Any changes to the template consent form suggested by the Investigator must be agreed to by the UCSF CC before submission to the local IRB, and a copy of the approved version must be provided to UCSF CC after IRB approval.

12.3 Declaration of Helsinki

The investigator must conduct the trial in accordance with the Declaration of Helsinki.

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