REACT-AF: The **R**hythm **E**valuation for **A**nti**C**oagula**T**ion with Continuous Monitoring of **A**trial **F**ibrillation

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REACT- AF

AGREEMENT ON THE PROTOCOL

By signing below, I confirm that:

1) I have read the protocol and it contains all the necessary details for conducting this study

AND

2) I agree to conduct the trial in compliance with this protocol and to adhere to all regulations that govern the conduct of the study.

Investigator's Printed Name

Investigator's Signature

Date

Investigator's Institution

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	**2.0 (March 6, 2023)**	**See attached document**	**Y**
2	**3.0 (May 8, 2023)**	**See attached document**	**Y**
3	**4.0 (February 29, 2024)**	**See attached documents**	**Y**
4	**5.0 (October 18, 2024)**	**See attached documents**	**Y**
5	**6.0 (April 28, 2025)**	**See attached documents**	**Y**

ABBREVIATIONS/ DEFINITIONS

ACC	American College of Cardiology
AE	Adverse Event
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect of Quality of Life
AFSS	Atrial Fibrillation Severity Score
AFSW	AF-sensing Smart Watch
BID	Twice a day
CAPA	Corrective and Preventative Action
CCC	Clinical Coordinating Center
CDMP	Clinical Data Management Plan
CEC	Clinical Event Committee
CMS	Center for Medicare and Medicaid Services
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CT	Computerized Tomography
DASS	Duke Anticoagulation Satisfaction Scale
DBP	Diastolic Blood Pressure
DCC	Data Coordinating Center
DOAC	Direct Oral Anticoagulation
DSMB	Data and Safety Monitoring Board
DVT	Deep Vein Thrombosis
EC	Executive Committee
ECFoR-AF	East Carolina Fear of AF Recurrence Scale
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eTMF	Electronic Trial Master File
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEMS	Global Electronic trial Management
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
ICD	Implantable Cardioverter-Defibrillator
ICF	Informed Consent Form
ICM	Implantable Cardiac Monitors
INR	International Normalized Ratio
IQRMP	Integrated Quality and Risk Management Plan
ISTH	International Society on Thrombosis and Haemostasias
JHU	Johns Hopkins University
KRI	Key Risk Indicator
LTFU	Lost to Follow Up
MEOI	Medical Event of Interest
MR	Magnetic Resonance
mRS	Modified Rankin Scale
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NSAID	Non-Steroidal Anti-Inflammatory Drug
NU	Northwestern University

OAC	Oral Anticoagulant
PE	Pulmonary Embolism
PHI	Protected Health Information
PPG	Proprietary Photoplethysmography
QA/QC	Quality Assurance/ Quality Control
RBM	Risk-Based Monitoring
RIC	Recruitment Innovation Center
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Steering Committee
SDV	Source Document Verification
SIRB	Single Institutional Review Board
SOC	Standard of Care
SOP	Standard Operating Procedures
SU	Stanford University
TIA	Transient Ischemic Attack
UADE	Unanticipated Adverse Device Effect
VKA	Vitamin-K Antagonists

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1 STUDY SYNOPSIS

Study Title
REACT-AF: Rhythm **E**valuation for **A**nti**C**oagula**T**ion with Continuous Monitoring of **A**trial **F**ibrillation

Objectives
Primary Objective (Efficacy): To assess whether AFSW-guided, time-delimited DOAC therapy is non-inferior to continuous DOAC therapy for a composite endpoint that includes: (1) Ischemic stroke; (2) Systemic embolism; (3) All-cause mortality.

Secondary Objectives (Safety): To assess whether AFSW-guided, time-delimited DOAC therapy significantly reduces major bleeding events compared to continuous DOAC therapy.

Design and Outcomes
REACT-AF is a multicenter prospective, randomized, open-label, blinded endpoint (PROBE design), controlled trial comparing the current SOC of continuous DOAC use versus time-delimited (1 month) DOAC guided by an AFSW in participants with a history of non-permanent AFAF and low-to-moderate stroke risk (CHA_2DS_2-VASc score 1-4 for men, 2-4 for women). Follow-up time will be 3-5 years. The study will be conducted in approximately 100 centers targeting two-thirds academic and one-third private practices, with academic practices also enrolling from affiliated community sites.

Interventions and Duration
Participants randomized (1:1) to the experimental arm (AFSW-guided DOAC) will only take their DOAC for 30 consecutive days following a qualifying AF episode (i.e., >1 hour) detected by their AFSW if no further AF is detected. Participants randomized to the standard of care arm will remain on continuous DOAC throughout the study. The trial is expected to take approximately two years to enroll, and each participant will be followed for three to five years.

Sample size and Power
An enrollment of 5350 participants is planned. We anticipate evaluating 7643 consented individuals with external monitoring to ensure that a low-burden population will be randomized.

2 STUDY OBJECTIVES

Atrial fibrillation (AF) is the most common sustained arrhythmia and is a major cause of stroke. Continuous oral anticoagulation (OAC) reduces stroke risk but can cause bleeding, thus limiting its use. These competing risks have made stroke prevention among the most challenging aspects of AF management and underscore the need for innovative approaches. Studies show that stroke risk is temporally related to AF onset and duration, but bleeding risk continues throughout OAC exposure, even during long AF-free periods when stroke risk is low. The advent of rapid onset direct OACs (DOACs) paired with AF-sensing smartwatches (AFSW) allows for precision-targeted, time-delimited anticoagulation given only in response to a prolonged AF episode. The Rhythm Evaluation for AntiCoagulaTion with Continuous Monitoring for AF (REACT-AF) trial will compare the efficacy and safety of two treatment strategies for stroke prevention in AF: the current standard of continuous DOAC versus a novel strategy of precision, time-delimited DOAC given only for 30 days in response to a >1-hour AF episode detected by an AFSW. AFSW-guided, time-delimited DOAC treatment is expected to reduce bleeding events while maintaining stroke protection and has potential to improve major clinical outcomes and quality of life while reducing health care utilization.

2.1 Primary Aim

The primary objective (efficacy objective) of the REACT-AF trial is to assess whether AFSW-guided, time-delimited DOAC therapy is non-inferior to continuous DOAC therapy for a composite endpoint that includes: (1) Ischemic stroke; (2) Systemic embolism; and (3) All-cause mortality.

2.2 Secondary Aim

The secondary objective (safety objective) is to assess whether AFSW-guided, time-delimited DOAC therapy significantly reduces major bleeding events compared to continuous DOAC therapy.

2.3 Exploratory Aims

The exploratory aims are to first compare overall satisfaction with anticoagulation management between the study arms. We will also be comparing estimates of health-related resource utilization in participants randomized to the control arm versus the experimental arm. Given the reduced drug burden anticipated in the experimental group, this outcome measure is a means to test whether AFSW-guided, time-delimited DOAC therapy improves health-related outcomes and cost.

3 BACKGROUND

3.1 Rationale

Atrial fibrillation (AF), the most common sustained heart rhythm disorder, affects 2.9-7.7 million Americans, carries a lifetime risk of 25-33%, and costs the US healthcare system $6 billion a year.[1-7] The aging population and rising prevalence of AF-related risk factors, including obesity and diabetes, are contributing to an “epidemic” of AF that is projected to affect as many as 15.9 million Americans by the year 2050.[8,9] Clinical consequences of AF are varied and serious. Symptoms may include incapacitating palpitations and dyspnea, but many patients are entirely asymptomatic or feel only a minority of their episodes.[10,11]

Regardless of symptoms, AF is associated with congestive heart failure, dementia, premature death, and most importantly, a 3- to 5-fold higher risk of stroke, the most feared outcome of the arrhythmia.[3,12-19] The attributable risk of stroke increases with age so that nearly a quarter of all

strokes in those >80 years old are due to AF.[20,21] Strokes due to AF are more likely to be fatal or severely debilitating, underscoring the critical importance of preventive strategies.[23] Continuous oral anticoagulation (OAC) reduces stroke risk effectively, but exposes the patient to sustained and significant risk of major and minor bleeds even during prolonged periods of sinus rhythm when the stroke rate appears to be low. [24,25] These risks have resulted in OAC use in only 50-60% of eligible patients and discontinuation rates as high as 50% even when prescribed.[26-28]

Current Limitations and Alternative Strategies

Clinical characteristics influence stroke risk in AF patients, often characterized using the CHA_2DS_2-VASc risk stratification scoring system. This simple calculated point score is based on the presence of congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or TIA or thromboembolism (doubled), vascular disease, age 65 to 74 years, and female sex (Table 1).[3,29] Standard of care (SOC) for reducing stroke risk is through lifelong administration of oral anticoagulants, including vitamin-K antagonists (VKA) and direct oral anticoagulants (DOAC). Anti-coagulation prevents the formation and propagation of thrombi in the left atrium that can embolize to the brain or periphery.[13, 31] US treatment guidelines recommend continuous anticoagulation in patients with a CHA_2DS_2-VASc score ≥2 (Class I recommendation), while OAC can be considered for a score of 1 (Class IIb recommendation). [3, 13, 32, 33] European guidelines extend the recommendation for OAC to those with a score of 1.[34]. An estimated 80% of AF patients have an indication for continuous OAC.[35] Despite the high efficacy rate of these drugs (≥65% relative risk reduction in stroke), bleeding is a dominant limitation. [3, 13, 29, 36, 37] Bleeding of any severity occurs at an annual rate of 14.2–18.1% and major bleeding events occur at a rate of 2.1–3.6% on both DOACs and VKAs.[38-41] The incidence of intracranial hemorrhage is lower with DOACs (0.7% vs. 1.5% on warfarin), while the risk of major GI bleeding is higher (2.6% vs. 2.0% on warfarin), and both can result in serious morbidity and mortality.[39,40] Patients with OAC-related major bleeding incur a mean additional healthcare cost of $28,298 per year.[44] These issues limit clinical utility of anticoagulation by creating a need to balance stroke prevention with bleeding risk. Indeed, both major and minor bleeding events and concerns surrounding them are major causes for failure to initiate or continue anticoagulant treatment.[28, 38, 39, 45-48]

Table 1: CHA2DS2-VASC Score and Yearly Stroke Risk

Score	Stroke Rate (%/Year)
0	0
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

It is important to recognize that risk stratification for stroke in AF is currently applied equally to those with paroxysmal AF (AF that terminates spontaneously or with intervention in < 7 days), persistent AF (AF that fails to self-terminate within 7 days), or permanent AF (persistent AF where a joint decision has been made to no longer pursue a rhythm control strategy). In addition, the derivation and validation of all AF-related stroke risk scores are based on a clinical diagnosis of AF (usually based on claims data) rather than a minimum AF duration and/or burden (e.g., percent of time spent in AF). Therefore, all patients with any history of clinical AF and other stroke risk factors are currently treated in an identical manner with lifelong anticoagulation, regardless of how much AF is present, or even if the AF has been quiescent for long periods or eliminated altogether as the result of rhythm control interventions including antiarrhythmic drugs, ablation, or risk factor modification. [49]

The possibility of discontinuing anticoagulation following rhythm control strategy has been of great interest to clinicians and patients. However, randomized studies including AFFIRM and RACE, published more than 20 years ago, demonstrated that routine discontinuation of anticoagulation in those treated with antiarrhythmic drugs exposed the patient to stroke risk. [50, 51] This issue has also been addressed in the contemporary era of more effective maintenance of sinus rhythm with ablation, but with conflicting results. In one multicenter observational study, researchers found no

significant difference in stroke risk when anticoagulation was discontinued.[52,53] In contrast, analyses from a large US administrative claims database and the Swedish National Health Registry found an approximate 2.5 to 4.5-fold increase in the hazard ratio for stroke when anticoagulation was discontinued post-ablation in patients with a CHA_2DS_2-VASc score ≥ 2.[54, 55, 56] These results may be due to asymptomatic AF recurrences that remain un-anticoagulated due to an absence of ongoing rhythm assessment. Though it has been observed that CHA_2DS_2-VASc score alone predicts stroke even in the absence of known AF, there is no evidence that routine use of anticoagulation reduces stroke risk in those with vascular risk factors and no known history of arrhythmia.[57-59] These data, therefore, do not support routine cessation of anticoagulation in the setting of apparent rhythm control with either drugs or ablation, nor is such practice supported by guidelines.[49]

Studies of prolonged rhythm monitoring have clearly demonstrated that both AF duration and burden are associated with stroke risk.[60-68] These data, however, have not been incorporated into decision making regarding stroke prevention in AF based on several important considerations, including: (1) modest long-term efficacy of rhythm control interventions; (2) the unreliability of symptoms to detect presence or absence of AF; (3) complexity of data surrounding the temporal association between AF episodes and stroke; (4) the inability to easily and continuously monitor patients over long time periods for AF recurrence with previously available technologies; and (5) the prior inability to acutely anticoagulate patients following an AF episode with a rapid-onset oral drug.

Recent developments have potential to change this critical aspect of AF management. First, data on implanted cardiac rhythm management devices demonstrate that hours of AF, perhaps as much as 24 hours, are needed to increase stroke risk.[61, 63, 66, 69] Second, implantable devices and smartwatches capable of detecting AF allow for continuous or frequent intermittent remote monitoring regardless of symptoms. Third, unlike warfarin, DOACs provide rapid onset anticoagulation within 1-4 hours of a single dose. Fourth, stroke risk is low during prolonged periods of sinus rhythm, particularly in low-to-moderate risk individuals. [24, 25, 70-73] Finally, we and others have shown in pilot studies that a targeted, time-delimited approach to OAC is feasible and safe. [74-76]

Together, these data provide a strong rationale for testing whether an inexpensive, accurate AF-sensing smartwatch can direct DOAC therapy in a personalized, precise, time-delimited manner. This novel strategy enables rapid anticoagulation only in response to a clinically meaningful AF episode and enables patients to be rapidly and therapeutically anticoagulated only during the high-risk window for stroke, thus avoiding continuous anticoagulation and consequent bleeding events during prolonged periods of sinus rhythm when the risk of cardioembolic stroke is likely low.

<u>AF Duration and Stroke Risk: Rationale for Anticoagulating Based on AF Duration</u>

Current guidelines imply that 48 hours of AF are required for left atrial thrombus formation.[77, 78] This “48-hour rule” guides current practice and allows for cardioversion from AF of <48 hours duration without the need for ≥3 weeks of anticoagulation or transesophageal echocardiography to “rule out” intracardiac thrombus.[3] Studies enrolling patients with dual chamber pacemakers or defibrillators (ICDs) capable of recording atrial high-rate episodes (AHRE), composed mostly of AF, also provide robust evidence for choosing an actionable threshold for AF duration.[61, 63, 69, 79-82] These findings suggest device-detected, “sub-clinical” AHRE lasting 6 minutes to 24 hours is associated with minimal absolute increased stroke risk (i.e., 1.5% per year in ASSERT; 0.59% per year in TRENDS), which are considerably lower than expected based on clinical risk factors alone.[57, 73] In fact, AHRE used in conjunction with clinical risk factors may better predict stroke risk than AF duration alone, as patients with fewer risk factors required longer durations of AF before stroke risk increased.[68, 73] Whether those with subclinical AHRE lasting <24 hours benefit from anticoagulation is still under study. However, a post-hoc analysis of the ASSERT data demonstrated that only those patients with ≥24 hours of AHRE had a stroke risk commensurate

with their CHA2DS2-VASc score and that those with <24 hours of AF were as unlikely to suffer a stroke as those without any AF.[69, 83, 84] Given these data, there is a strong justification for anticoagulation only in response to a ≥1-hour episode of AF in a low-to-moderate risk (i.e., CHA_2DS_2-VASc 1-4 for men, 2-4 for women) AF population, as proposed in this protocol.

Rationale for Time-Delimited Anticoagulation after Conversion to Sinus Rhythm

The temporal relationship between AF episodes and cardioembolic stroke is complex. Clinical studies using dual chamber rhythm management devices with AF-sensing algorithms including TRENDS,[62] ASSERT,[79] and IMPACT[85] showed that many stroke events occurred in the absence of AF altogether or with an inconsistent temporal relationship between AF and stroke. Several hypotheses may explain these observations. First, AF may simply serve as a marker for an underlying atrial myopathy and pro-thrombotic state that can cause stroke independent of AF.[86-90] Second, AF episodes lasting minutes to hours may be too short to result in thrombus formation, and therefore no relationship with stroke can be expected in these cases. A third explanation is that AF is one of many causes of stroke, and patients with multiple additional stroke risk factors can have an ischemic event even in the absence of AF. This last point is exemplified by the ASSERT study of 2580 patients where the mean age of those with stroke was 78 ±7 years and the mean CHA_2DS_2-VASc score was 5.[114] To control for these potential confounders, two separate case-crossover analyses of patients with implanted devices and acute stroke have been performed. These demonstrated that the relative risk of stroke was 3 to 5-fold higher within the first 3 weeks following an episode of AF of ≥5.5 hours duration when compared to a control period without AF .[24, 25] The relative risk was amplified in those off OAC and attenuated to non-significance in those treated with OAC. A temporal association was also seen in ASSERT, with a 5.6-fold greater risk of cardioembolic stroke within 30 days following an AF episode lasting ≥24 hours.[69, 92, 93] Guidelines for duration of anticoagulation following cardioversion recommend a 4-week course to reduce stroke risk.[3] This recommendation is supported by observational studies, including one of 16,274 patients undergoing cardioversion where the risk of stroke was 2- to 4-fold higher during the first 30 days post-conversion.[115]

In sum, the weight of evidence supports a temporal association between AF and cardioembolic stroke and question the need for anticoagulation during prolonged periods of sinus rhythm when stroke risk appears to be low, particularly in patients with few vascular risk factors as defined by low-to-moderate CHA_2DS_2-VASc scores. In addition to addressing this issue, the Rhythm Evaluation for AntiCoagulaTion with Continuous Monitoring of Atrial Fibrillation (REACT-AF) trial will provide invaluable insights into the causal association between AF and cardioembolic stroke in a low-burden AF population with few additional stroke risk factors who will be intensively monitored for AF over a long timeframe.

3.2 Rationale for Study

The highest levels of scientific evidence, a randomized clinical trial, will be required to support a transformative change in practice. We have designed a two-phase hybrid trial with an initial explanatory phase (phase I) for the first 1000 participants and a phase II with pragmatic elements that will enroll 4350 participants. This design allows us to assess key components, including protocol compliance, event rates, and functionality of hardware and software components, prior to initiating the pragmatic elements in phase II. This hybrid approach will also ensure study integrity while providing generalizability and rapid adoption into the clinical arena if supported by the results. A study of this kind has not been undertaken before in AF.

The experimental arm will use a study-compatible Apple Watch (Apple Inc., Cupertino CA) as the AF detection device (AF-sensing smartwatch (AFSW)). There is an optional capability to record a single lead, 30-second ECG (K201525) with automated analysis. A study-specific application

will be installed on the participant's iPhone that will allow the AF algorithm to be installed on the Apple Watch. The AF-detection algorithms that serve as a basis for the one that will be used in REACT-AF received FDA 510K clearance in October 2021 (K212516) and June 2022 (K213971). However, the study method of monitoring and intended use was not the subject of FDA clearance. The device is designed to detect 85% of 6-hour episodes and 98% of 12-hour episodes based on internal data held by Apple. These specifications were not included in the studies conducted to support the 510(k) clearances cited above.

Rationale for Proposed Study Population:

An AF population with a CHA_2DS_2-VASc score of 1-4 for men and 2-4 for women was chosen as an entry criterion as these patients constitute 72% of the AF population and are more likely than others to receive a rhythm control strategy including antiarrhythmic drugs or ablation.[96, 103] Those with pacemakers or ICDs are excluded because the presence of ventricular pacing would prevent R-R irregularities that are the basis of the AF detection algorithm on the AFSW. Patients with prior stroke or TIA are excluded, as guidelines and clinical data strongly favor chronic anticoagulation in these individuals, particularly post-stroke, even in the setting of an apparently effective rhythm control strategy.[56, 106, 107]

Rationale for Key Study Criteria:

This study is limited to DOACs as the antithrombotic of choice given their rapid onset of action (1-4 hours vs. ~40 hours for warfarin) and the lack of need for INR monitoring. All FDA-approved DOACs will be used to increase the generalizability of the results, though two DOACs (apixaban and rivaroxaban) have 93% of the US market. Initial observations from the early DOAC trials in AF raised concerns about a possible rebound effect. Expert consensus is that this observation was due to study design factors in the clinical trial setting and an American College of Cardiology (ACC) Expert Analysis concluded that "there are no data showing a rebound effect exists on cessation of [DOACs]".[108-113]

A 1-hour AF threshold was chosen to trigger the initiation of DOAC for several reasons including: (1) evidence that only AF episodes considerably longer than 1 hour increase stroke risk[63, 69]; (2) the successful use of a 1-hour threshold in the REACT.COM pilot study and a second pilot study using ICMs to restart anticoagulation post ablation[74, 114]; (3) the expected high false-positive rate for short duration episodes in a device without the capability of recording direct atrial activity; and (4) the need to take into account the "worst case" scenario of a patient who goes into AF during sleep during which they have chosen to not wear the AFSW and could be notified one hour after resuming monitoring on awakening during a multi-hour AF episode. Participants will be continued on anticoagulants for a 30-day rolling window that begins following termination of an AF episode, The duration of anticoagulation is based on current guidelines following cardioversion (COR I, LOE B-R). Whether more abbreviated durations of anticoagulation or even no anticoagulation can be used for shorter duration AF episodes is beyond the scope of this study.

Stroke and systemic embolism were chosen as part of the primary composite endpoint given their recognized pathophysiologic and epidemiologic associations with AF and the severity of their clinical impact. We are not including TIAs given the challenges in diagnosis and post-hoc adjudication and note that this was not an endpoint in the landmark trials of DOACs. Inclusion of all-cause mortality in our efficacy endpoint is consistent with the consensus statement on outcome parameters for trials in AF that recommended including deaths in the safety outcome due to the complex consequences of this arrhythmia and the association between AF and premature mortality.[117,] We included all cause death in the composite endpoint to account for the acknowledged uncertainties in assigning cause of death based on clinical history alone (for example, in an individual who suffers sudden death, the diagnosis of intracranial hemorrhage or

massive stroke may be impossible to confirm without autopsy). We included only major bleeds requiring hospitalization as a primary safety outcome since minor bleeds often do not come to medical attention and are unlikely to play a dominant role in a decision to move a future positive result of this trial into clinical practice.

4 STUDY PROCEDURES

4.1 Study Design Overview

REACT-AF is a prospective, unblinded, randomized (1:1 allocation), multi-center, investigational clinical trial of men and women aged 22-85 with a documented history of history of non-permanent atrial fibrillation (AF) and a moderate risk of stroke (CHA2DS2-VASc score 1-4 for men, 2-4 for women). Participants randomized to the experimental arm (on demand DOAC) will take their DOAC for 30 consecutive days following a qualifying AF episode (i.e., >1 hour) detected by the AFSW. Participants randomized to the standard of care (control) arm will remain on their previously prescribed continuous DOAC throughout the study (Figure 1).

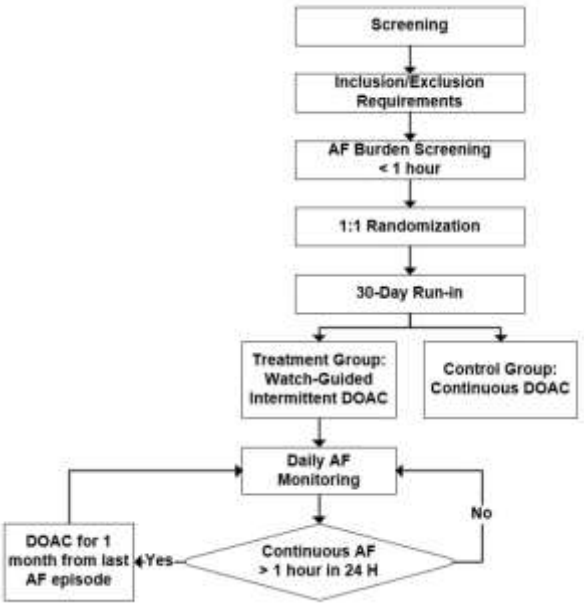

Figure 1: REACT-AF Study Schema

total of 5350 participants will be enrolled across approximately 100 study sites targeting two-thirds academic and one-third private practices, with academic practices also enrolling from affiliated community sites. We anticipate evaluating 7643 consented individuals with external monitoring to ensure that a low AF burden population will be randomized. Participation will last up to 60 months.

<u>Study Arms:</u>
Eligible participants will be randomized (1:1) to either the Control or Experimental arm:

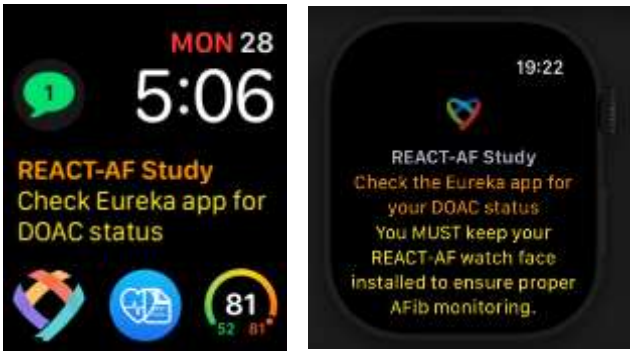

Figure 2: Eureka App Watch Face

Experimental Arm (AFSW Guided DOAC)
All participants randomized to the experimental arm will be provided with an AFSW that will be linked to their smartphone and the secure **REACT-AF app** within the Eureka cloud (Figure 2). The AFSW will intermittently (Q 15 minutes) and passively attempt to assess for rhythm irregularities consistent with AF and notify the wearer and coordinating center if a threshold AF event has occurred. A 30-second automatically interpreted lead I ECG can be performed on the AFSW in response to a notification or symptoms but will not be used for clinical decision making.

Throughout the study, the experimental group will have daily AF monitoring through their smartwatch with a suggested wear time of a minimum of 14 hours per day. The PPG-based algorithm attempts to assess the rhythm for one minute every 15 minutes during watch wear. Participants will receive an automatic notification alert within an hour when an AF event of qualifying duration (>1 hour) is detected and asked about any contradictions to anticoagulation

(i.e., recent surgery, recent trauma, or acute bleed). If a contraindication is reported, the participant will receive a notification to contact their treating physician. Notification times are expected to occur within 3 hours but may take up to 12 hours in rare cases. If no contraindications are reported, participants will be instructed to initiate their previously prescribed DOAC daily or twice daily (depending on DOAC). Reminders will be sent to take the prescribed DOAC for the next 30 consecutive days. A watch complication will also be used to signal to the participant whether or not they should be taking the DOAC. If the participant is already taking a 30-day course of DOAC and experiences a new qualifying AF episode, automated reminders will add another 30 days of DOAC treatment.

This REACT-AF study notification process will optimize AFSW-guided intermittent DOAC treatment through enhanced communication between the device, the participant, and the Johns Hopkins Brain Injury Outcomes (BIOS) coordinating center to ensure timely initiation of DOAC therapy when warranted.

Control Arm (Continuous DOAC therapy)
All participants randomized to the control arm will remain on their previously prescribed FDA-approved DOAC regimen as indicated by current practice standards. These participants will continuously take their DOAC through the course of the study as prescribed by their primary physician unless otherwise contraindicated. Participants in the control arm will also use the REACT-AF mobile app within the Eureka platform via their smartphone for study follow-up activities, but they will not receive an AFSW and any personally owned Apple Watch will not be loaded with the customized REACT-AF detection algorithm nor participant notification apps.

All DOACs approved by the FDA for stroke prevention in non-valvular AF will be eligible for use in the study. Dose adjustments in both study arms will be made at the discretion of the treating physician, but standard FDA-approved doses based on age, weight, and renal function (according to DOAC) will be strongly recommended.

This study will be divided into two phases:

<u>Phase I: Experimental Explanatory Phase:</u>
The first 1,000 participants (500 in the experimental arm) will be enrolled under Phase I. This phase is designed to provide an opportunity to assess the critical design and logistical issues, including estimates of crossovers, discontinuations and withdrawals, prior to the initiation of the pragmatic elements in Phase II. In addition, during Phase I, participant compliance, response rates, and times of notifications will be assessed. Functionality of the REACT-AF app and study platforms will also be confirmed during this time.

During Phase I, once a qualifying AF event is detected, participants will receive a push notification alert and text messages to restart their previously prescribed DOAC for 30 consecutive days. These alerts will be repeated until participant acknowledgment occurs. Failure to acknowledge the notifications will trigger robo-calls via Eureka. The DCC will contact participants who do not acknowledge any of the notifications within 2 days of report receipt.

The DCC will also be alerted for prolonged periods of non-adherence with wearing the AFSW, based on the device's activity and heart rate tracker and to any instances of removing the Apple Study App (needed for the AF detection algorithm) when there is a lack of “heartbeat” signal from the App to the Eureka backend. DCC will contact participants after 48 hours of non-compliance during Phase I. If the DCC cannot contact the participant or their designated alternative, the

Stanford CCC will be notified of the non-compliance by the DCC. The Stanford CCC will alert the study site of participant non-compliance.

All necessary changes will be implemented before the transition to prevent deficiencies from jeopardizing Phase II.

Phase II: Explanatory Phase with Pragmatic Elements:
Phase II is an explanatory phase with pragmatic elements to assess the novel intervention under close to routine clinical conditions with nearly full participant autonomy. Any changes based on findings from Phase I will be implemented before the initiation of Phase II. As in Phase I, if a participant has an AF event >1 hour, they will receive a push notification alert and text messages to restart their previously prescribed DOAC for 30 consecutive days. Failure to acknowledge the notifications will trigger robo-calls via Eureka.

The difference in Phase II is the DCC will contact participants after 72 hours, instead of 48, when notifications are not acknowledged and non-compliance with wearing the AFSW. Key differences between Phase I and Phase II can be seen in **Table 2**.

Table 2: Key Distinctions: Phase I and Phase II

Phase I: Explanatory Phase	Phase II: Explanatory Phase with Pragmatic Elements
Assess adherence to ASFSW wear times/contacts for non-adherence > 48 hours	Contact participants for non-adherence > 72 hours
Assess response rates and times to push notifications	No assessments performed
Contact participants only if no acknowledgement ≥ 48 hours after threshold AF event	Contact participants only if no acknowledgement ≥ 72hours after threshold AF event

4.2 Study Objectives

Primary Aim 1 Efficacy Objective:
To assess whether AFSW-guided, time-delimited DOAC therapy is non-inferior to continuous DOAC therapy for a composite endpoint that includes: (1) ischemic stroke, (2) systemic embolism, and (3) all-cause mortality. AF is associated with ischemic stroke, systemic embolism, and increased mortality. The intervention is not expected to significantly increase or decrease the event rate of the composite endpoint, and therefore the trial is powered as a non-inferiority trial for the primary efficacy endpoint.

Primary Aim 2 Safety Objective:
To assess whether AFSW-guided, time-delimited DOAC therapy significantly reduces major bleeding events compared to continuous DOAC therapy. Oral anticoagulation carries a risk of major bleeding, including life-threatening hemorrhage, the intervention is expected to reduce the safety endpoint, major bleeding, by > 35%, and the study is powered for the superiority of the safety endpoint.

Exploratory Aim 1:
To compare overall satisfaction with anticoagulation management between the study arms. Participant satisfaction with anticoagulation management will be superior in participants randomized to AFSW-guided, time-delimited DOAC therapy compared to participants receiving

continuous DOAC therapy. Given the reduced drug burden anticipated in the test group, this outcome measure is a means to evaluate whether AFSW-guided, time-delimited DOAC therapy improves health-related outcomes.

Exploratory Aim 2:
To compare estimates of health-related resource utilization in participants randomized to the control versus experimental arm. Health-related resource utilization will be lower in participants randomized to the AFSW-guided, time-delimited DOAC therapy compared to participants receiving continuous DOAC therapy. Given the reduced drug burden anticipated in the test group, this outcome measure is a means to evaluate whether AFSW-guided, time-delimited DOAC therapy improves health-related resource utilization.

4.3 Study Procedures

Clinical data is collected at designated time points throughout the study. The requirements for data collection and study procedures by visit are summarized in **Table 3 and 4 (Schedule of Events for the Coordinator and Participant)**.

Screening/ Baseline Visit
Single IRB approval of the Clinical Investigation Plan and Informed Consent Form and reliance agreements at each site must be obtained prior to any enrollments. All participants must provide informed consent before participating in any study-related activities. After informed consent is obtained, the participant will receive a unique identification number in VISION EDC and Eureka. These identification numbers will use acrostics to link the participant across the platforms.

The participant must have an iPhone that supports the latest shipping iOS and active cellphone service are required to participate in this study. After informed consent is provided, the site investigator or authorized personnel will review demographics, and medical history. During this visit, detailed contact information will be obtained, and the site will capture this information in VISION EDC.

Cardiac Monitoring for AF Burden
During the screening visit, individuals should be carefully screened for presence of frequent (i.e.lasting ≥1 hour per month over the last 90 days) episodes of AF and/or >5% of atrial or ventricular premature ectopy at the time of enrollment.

For those with cardiac monitoring performed in the last 90 days, only those who did not experience any AF episodes ≥1 hour of PAC or PVC burden > 5% will be eligible for randomization.

Patients can be re-considered for enrollment at a later time if; (1) they have subsequently undergone a change in antiarrhythmic therapy or ablation, and (2) have a clinically indicated follow-up cardiac monitor meeting inclusion/exclusion criteria.

Enrollment/ Randomization Visit
Authorized personnel will confirm participant still meets eligibility requirements and review of concomitant medications, including verification of the current prescribed DOAC. Once eligibility is confirmed, sites will use the VISION EDC system to randomize (1:1) participants to an AFSW-guided intermittent DOAC (experimental arm) or continuous DOAC therapy (control arm).

Randomization for this trial will be stratified by study site, prior ablation (yes, no), and CHA_2DS_2-VASc score (1-2, 3-4) to ensure the two study arms are balanced with respect to these

characteristics. A dynamic randomization scheme will be used to ensure this balance is achieved across three stratification variables. Participants randomized to the experimental arm will receive an AFSW during this visit, and research personnel will provide instructions on use. Participants in both groups will be required to install the Eureka app on their smartphone during this visit. The Eureka app is a UCSF-based, HIPAA-compliant, IDE-approved, IRB-approved clinical research platform built largely with NIH support that hosts many studies simultaneously. The REACT-AF study will be one of these studies. For those randomized to the intervention group, there will also be a REACT-AF-specific Apple Watch app ("complication") that communicates via secure linkage with the Eureka app in order to run the study (ie: detect AFib episodes and provide follow-up instructions and activities according to an individual's randomization assignment). Open Epic is a module within the Eureka app that allows consenting participants to optionally authorize a connection to their MyChart account(s) so that they can share EHR data with the REACT-AF study in accordance with the US 21st Century Cures Act (2016). Geofencing is also a module built within the Eureka app that allows participants to optionally allow the app to access their phone's GPS for the sole purpose of detecting putative hospitalizations. When a participant's phone crosses a virtual "geofence" into a known healthcare provider's location for a given amount of time, Eureka can record that as a potential hospitalization event and trigger activities/surveys for the participant to confirm healthcare utilization and gather additional pertinent information as needed. Geofencing data within Eureka will only be collected when a participant moves to a new location. This new location is called "visits"; if the participant is present at that location for 14 or more hours this will be considered a "visit". Geolocation coordinates for visits are stored in an encrypted Realm Database on the participants iPhone. Eureka uses GooglePlaces API to map the coordinates onto hospitals to trigger the hospitalization visit. The data (including the location coordinates) is transmitted to the Eureka backend as encrypted data and stored in Eureka in our secure database (behind a virtual private network with controlled access) and once transmitted to the Eureka backend it is deleted from the phone. Eureka also collects one "event" per day even if not triggered by location to ensure that data is flowing properly, and permissions are turned on. Eureka only collects coordinates when a participant has a new visit (ie. moves from one location to another). This approach results in minimal impact on battery life and minimizes the amount of data transmissions.

Participants will remain under their clinician's care for all treatment, including DOAC dose adjustments and temporary or permanent discontinuation as needed. No study-specific office visits are planned after randomization. Participants in both arms will receive online contact via a study-specific app on their smartphone for study-related issues, including medication compliance assessment, device data review, study-related surveys, adverse events, a computer/ technology survey and the skin-tone survey. The skin-tone survey will be collected for secondary analyses and will be optional for participants.

30-Day Run-In Period

After randomization, participants in both study arms will enter a 30-day start-up period of continued anticoagulation. The run-in aims to account for the possibility of a prolonged, asymptomatic, AF episode between the time of screening and randomization. A 30-day start-up phase of anticoagulation will ensure participants in the experimental arm receive anticoagulation during this period of potential stroke risk. Technical issues affecting virtual follow-up will also be resolved during this period. Participants in whom remediation of AFSW or related technical issues is not possible will be crossed over to the control arm at the end of the run-in period for safety.

<u>Experimental arm</u>

At the end of the 30-day run-in phase, participants in the experimental arm confirmed to be free of a qualifying AF episode via the AFSW will receive a "STOP DOAC" notification. If the participant

fails to acknowledge the notification, they will be contacted by the DCC. If a qualifying AF episode occurs during the run-in phase, they will be notified to continue DOAC for another 30 days for up to 6 months.

Continuous DOAC (Control Arm)
The control group will continue taking their prescribed anticoagulation medication during the run-in period. At the end of 30 days, participants will continue to take DOAC as their treating physician prescribes.

At the end of the 30-Day run-in, participants in both study arms will receive a Duke Anticoagulation Satisfaction Scale (DASS) questionnaire, a CARDIA Anticoagulation Medication adherence survey, and a survey's regarding hospitalization, adverse events, changes in medication, and inquire about any technical issues the participant may have encountered with the software or hardware.

Follow-Up Period
Clinic visits for both arms will take place per standard of care for treatment of AF; no study visits are required after randomization. Data in this trial is being directly collected from each patient via various questionnaires on the REACT-AF (Eureka) mobile app.

Experimental Arm Only
Throughout the study, the experimental group will have opportunistic rhythm monitoring every 15 minutes through their smartwatch. We will encourage participants to maximize their watch wear time, educate them on the importance of wearing the watch as much as possible, even during sleep, and minimize the time they are not wearing the watch by taking advantage of the rapid (1-2 hour) charge times of the device. Participants will be asked to wear their watch for a suggested minimum of 14 hours a day and during sleep. If an enrollee has a qualifying AF episode within a 24-hour time-period, they will restart their DOAC for one month. If they have another qualifying episode while on their DOAC within those 30 days, this will be the new start date for another 30-day cycle of DOAC. Individuals in this arm will be instructed to have one dose of DOAC accessible at all times. Participants in whom rhythm monitoring is expected to be unavailable for $\geq$ 72 hours (i.e. no access to cell or WiFi service) will be instructed to resume DOAC therapy for 30 days from the time monitoring resumes.

Participants randomized to the experimental arm who remain on DOAC for six consecutive months due to recurrent AF with no plans for additional rhythm control will crossover to the control arm under the direction of the DCC with site communication by the Stanford CCC. Participants who transition to continuous DOAC therapy on the recommendation of their treating physician will also be considered crossovers.
Both Study Arms
Follow-up for this study will be completed virtually through Eureka. Participants in both groups will be asked to complete online surveys to evaluate outcomes of interest outlined in **Section 4.5.** In the event of a stroke, the participant will be contacted by the DCC within 90- 120 days to complete an mRS (modified Rankin Scale) assessment if not obtained during routine post-stroke clinical care.

During the follow-up period, optional geofencing will also supplement notifying the Stanford CCC of any potential inpatient or outpatient office or hospital visits. Smartphone-based geofencing allows real-time tracking of medical visits and reduces the measurement error of retrospective reporting. The "fence" does not require continuous tracking of location, which would impinge on

privacy and therefore limit acceptance. Instead, a location is identified only when the healthcare facility “fence” is crossed. Permission to request medical records, including inpatient and outpatient records, throughout the study period will be obtained as part of the consent process.

The CCC will reach out to sites to obtain further information, including medical records, source documents, images, and more, for safety reporting. Sites will be expected to upload this information into the EDC, and sites will be required to notify the Stanford CCC of any clinical endpoints or medical events of interest.

Help desks at the CCC, DCC, Eureka, and Apple will be available to the sites for study-related issues.

4.4 Study Duration

A total of 5350 participants will be enrolled across up to 100 study sites over two years. Participation will last up to 60 months, with the last enrolled patient followed for 36 months.

4.5 Study Schedule of Events

Table 3: Schedule of Events for the Coordinators
REACT-AF Coordinator Responsibilities completed in VISION EDC.

VISION EDC-Coordinator Completion	Screening/ Baseline Visit	Enrollment/ Randomization Visit (Day 0)	30 Day Run-In (Day 30)	Follow-up
Inclusion/Exclusion	X	X		
Demographics	X			
Informed consent	X			
Complete Contact Form	X			
Medical History	X			
AF Assessment (7-day Cardiac Monitor)[a]	X			
Randomization		X		
Skin-Tone Survey		X		
Install Eureka Study App		X		
Dispense Smart Watch [b]		X		

Discontinue Chronic Anticoagulation [b]			X	
Site Reporting of Clinical Endpoints and MEOIs to CCC[c]				X
Targeted Annual Medical Record Review				X
Complete Case Report Forms (CRFs)	X	X		X

PRN = as needed

[a] Individuals with a cardiac monitor within the past 90 days that did not experience any AF episodes ≥1 hour will be eligible for randomization. [b.] Treatment group (AFSW-guided DOAC) only. [c.] Obtained during routine clinic visits and targeted annual EMR Review.

Table 4: Schedule of Events for the Participants

REACT-AF Participant Surveys completed in the Eureka App.

EUREKA- Participant Completion	Enrollment/ Randomization Visit (Day 0)	30 Day Run-In (Day 30)	Quarterly Follow-up	Annual Follow-up	End of Study
Health Kit Activity	X				
Open Epic Activity	X			X	
Geolocation Permission Activity	X				
Address Collection Activity	X			X	
Contact Information	X			X	
Social Demographics	X				
Medications Activity	X	X	X	X	
Medical Conditions	X			X	
AF Severity Scale (AFSS)	X			X	
Atrial Fibrillation Effect of Quality of Life (AFEQT)	X			X	
EuroQol EQ-5D	X			X	

East Carolina Fear of AF Recurrence Scale (ECFoR-AF)	X			X	
CARDIA Anticoagulation Medication Adherence Survey		X	X	X	
Computer/ Technology Literacy Survey	X				
Geofence Hospitalization Survey (if participants allow geolocation)	X	X	X	X	
Hospitalization Survey		X	X	X	
Adverse Events Survey		X	X	X	
Duke Anticoagulation Satisfaction Scale (DASS)		X		X	
Afib Follow-up Survey			X	X	
Device Perception on Health Survey					X

4.6 Study Blinding

Unblinded

Participants and sites will not be blinded to which arm a participant is randomized. A DCC unblinded statistician will provide consultative outcomes support to the DSMB, compiling the data for the unblinded report according to the approved template.

Blinded

The Clinical Event Committee (CEC), Neuroimaging Adjudication Committee (NAC), Executive Committee, Steering Committee, and the DCC lead statistician and staff will support data compilation and advise the study Executive Committee while remaining blinded to treatment assignment.

4.7 Study Completion

End of Study

Study completion will occur at the end of three (minimum) to five years (maximum) of follow-up unless a participant is withdrawn prior. Participants who withdraw before completing the study will be asked to return their watch. The site in the EDC system will complete an end-of-study form, and patients will be instructed to continue routine care with their physician.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to regulatory authorities' queries. Minimal information includes demography and screen failure details.

Individuals who do not meet the criteria for participation in this trial because of an AF burden ≥1 hour during pre-randomization may be rescreened if a change in rhythm control strategy has been

implemented in the interim;. Rescreened participants will need to have a new subject number in VISION EDC. Participants may be rescreened if there is an update to their eligibility criteria.

Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

4.8 Participant Crossover

Participants who are in the study intervention arm may be crossed over to the control arm. Participants may choose to cross over to the control arm but must notify their site and return the watch provided by the study. The site will then notify the Stanford CCC and DCC. The reason for participant crossover will be recorded in the Eureka App by the participant and by the study coordinator in VISION EDC. The reasons for crossover are as follows:

- Participants who remain on DOAC for six consecutive months due to recurrent AF with no plans for additional rhythm control.
- Participants in whom watch-wear noncompliance reaches the crossover threshold.
- Participants who transition to continuous DOAC therapy on the recommendation of their treating physician.
- Inadequate number of tachograms despite wearing the watch and technical troubleshooting.
- Not responding to reminders.
- The site PI would like to crossover for participant safety.
- Participant would like to crossover from the intervention arm to the control arm.

4.9 Participant Discontinuation/ Withdraw from the Study

Participants are free to discontinue or withdraw from the study at any time upon request. Participant discontinuation is defined as any participant who qualifies for discontinuation due to one or more of the reasons listed below but who agrees to continue study follow-up. Participant withdrawal is defined as the participant revoking consent to access any additional study-related follow-up information.

The study may be modified or discontinued at any time by the IRB, or other government agencies as part of their duties to ensure that research participants are protected. An investigator may also discontinue or withdraw a participant from the study for the reasons below. The reason for participant discontinuation or withdrawal from the study will be recorded on the REACT-AF Case Report Forms (CRFs).

- Pregnancy
- Any clinical adverse event, laboratory abnormality, or other medical condition such that continued participation in the study would not be in the participant's best interest.
- Disease progression that requires discontinuation or withdrawal of the study intervention.
- Participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The participant is unable to take DOAC for 30 consecutive days.
- The participant develops a need for chronic anticoagulation for reasons other than AF.
- Development of a contraindication to DOAC use or the introduction of an intervention that obviates the need for anticoagulation (i.e., left atrial appendage occlusion).

4.10 Significant Non-Compliance:

Potential barriers to adherence and designated solutions are listed in **Table 5,** along with expected solutions.

Participants may also be removed for non-compliance with study activities, including:

- Not responding to medication reminders for more than 48 - 72 hours on two or more consecutive episodes of AF.
- Not wearing the study watch for > 72 hours on more than five occasions a year.
- Participants from either arm miss two or more consecutive quarterly follow-ups.

App/Watch Adherence

Trials relying on wearable device technology depend on participant adherence to the protocol and adherence to the use of the device. REACT-AF DCC will augment high retention and maximize protocol adherence through a patient-centered call center and automated notifications from the Eureka application. After a period of 36 hours with <5 tachograms, Eureka may send an automated SMS message to help resolve the low tachogram number issue. In addition, after a period of 72 hours with <5 tachograms, the call center at the DCC will contact the participant. The DCC call center will combine the trial's technology with experienced, trained staff to provide high-quality trial support. Fast access via wearable technology combined with personal interaction between the participant and the study team will increase the participant's interest and comfort level. Easy access to support staff will enhance participation and aid in retention. In parallel to this escalation process participants are instructed to resume their DOAC after 48 hours of no watch data being received.

As part of the participant engagement team, the call center research specialists will be responsible for monitoring participant compliance with study-required procedures. The specialists will contact study participants who are non-compliant or nonresponsive to study notifications and are available to answer participant questions or direct them to a problem-appropriate team member who will mitigate the participant's issue. Replacements will be provided for one lost or broken AFSW per enrollee within the first three years of enrollment and at the discretion of the enrolling site and the participant will be instructed to resume DOAC therapy while awaiting the replacement.

Call center personnel will have access to participant contact information and be notified of participants who are not responding to study notifications or are otherwise in need of contact. Systems are in place to keep personal information and conversations private and confidential.

Table 5: Potential Barriers to Non-Compliance

Potential Barriers	Solutions	Responsible party
Participants are encouraged to wear the AFSW on average of 14 hours a day.	The DCC will be alerted for prolonged (i.e. > 72 hours.) periods with < 5 tachograms per day. The DCC will follow up with a call center representative phoning the participant to ensure the app/watch is working properly and the participant is continuing in the study.	DCC Call Center, Participant Participant's Enrolling Physician
Reminder DOAC (based on prior prescription) will be delivered for the 30-day DOAC treatment period	The DCC will be alerted and phone participants for threshold events that are not acknowledged (i.e. > 72 hours.)	DCC Call Center, Participant, Participant's Physician

Participants are required to complete brief questionnaires every three months. A participant may be prompted to complete the questionnaire but not respond	If a participant does not respond to two consecutive quarterly questionnaires after notifications, a call center representative will call the participant to ensure the participant is continuing in the study and adhering to the study requirements.	DCC Call Center, Participant

4.11 Lost-to-Follow-Up

Participants will be considered LTFU if the DCC and site cannot contact participants or designated contact as documented by three unsuccessful attempts on three different days over a period of a minimum of 1 month by the DCC/site.

When the participant or the alternative designated contact cannot be reached, attempts will be made to ascertain the vital status of the participant by searching the appropriate national or regional vital status registry or other relevant databases, where available and allowable by local law. Depending on the local law, this search will be conducted by the enrolling physician, his/her designee at the study site, or the DCC.

5 ENROLLMENT AND RETENTION

Individuals ages 22-85 will be eligible for enrollment in REACT-AF Children (<18 years) will not be included in the study because AF is extremely rare in children, and the safety and effectiveness of the DOACs being used in this study have not been established in pediatric patients with AF. Individuals < 22 years are also excluded as the basis of the AF-detection algorithm on the Apple Watch being used in the study have not been tested in those < 22. Individuals >85 will be excluded due to the anticipated competing risks of death over the expected 3-5 years follow-up duration of the trial.

This study will enroll Medicare beneficiaries that qualify based on the inclusion and exclusion criteria below. This study will adhere to all standards of Medicare coverage and clinical trial coverage policies of the Center for Medicare and Medicaid Services (CMS). Risks described in section 11 RISKS, describes how all enrolled participants, including Medicare Beneficiaries, may be affected by the clinical trial. Participants are enrolled in this study are expected to be generalizable to the Medicare population.

5.1 Inclusion and Exclusion Criteria

Inclusion Criteria:

1. 22-85 years of age.
2. English speaking participants*
3. History of non-permanent atrial fibrillation.
4. CHA_2DS_2-VASC score of 1-4 for men and 2-4 for women without prior stroke or TIA**
5. The participant is on a DOAC at the time of screening and willing to stay on DOAC for duration of study.
6. Willing and able to comply with the protocol, including:
    - Possession of a smartwatch-compatible smartphone (iPhone that supports the latest shipping iOS) with a cellular service plan

- Be willing to wear the smartwatch for the suggested minimum of 14 hours a day
- Expected to be within cellular service range at least 80% of the time
- Be willing to answer PROs

7. Willing and able to discontinue DOAC
8. The participant is willing and able to provide informed consent.

Exclusion Criteria:

1. Valvular or permanent atrial fibrillation.
2. Current treatment with warfarin and unwilling or unable to take a DOAC.
3. The participant is a woman who is pregnant or nursing.
4. The participant is being treated with chronic daily NSAIDS and is unwilling or unable to discontinue use for the study duration.
5. Existing cardiac rhythm device or indication for a permanent pacemaker, ICD or CRT device or planned insertable cardiac monitor. Insertable cardiac monitors are permitted unless they are being used to guide anticoagulation treatment.
6. Known or suspected symptomatic or asymptomatic atrial fibrillation lasting ≥ 1 hour in each month over the last 3 months.
7. Any documented single AF episode lasting ≥ 1 hour on a cardiac monitor performed within 90 days prior to randomization.**
8. Ablation for AF within last month (participants may be consented at the time of ablation and enrolled/ randomized as early as 30 days after an AF ablation).
9. Prior or anticipated left atrial appendage occlusion or ligation.
10. Mechanical prosthetic valve(s) or severe valve disease.
11. Hypertrophic cardiomyopathy.
12. Participant needs DOAC for reasons other than preventing stroke or arterial embolism resulting from AF (i.e., preventing DVT or PE) or needs permanent OAC (i.e., congenital heart defects, prosthetic heart valve).
13. Participants deemed high risk for non-cardioembolic stroke (i.e., significant carotid artery disease defined as stenosis $\geq$ 75%) based on the investigator's discretion.
14. The participant is enrolled, has participated within the last 30 days, or is planning to participate in a concurrent drug and/or device study during the course of this clinical trial. Co-enrollment in concurrent trials is only allowed with documented pre-approval from the study manager; there is no concern that co-enrollment could confound the results of this trial.
15. The participant has a tattoo, birthmark, or surgical scar over the dorsal wrist area on the ipsilateral side that the AFSW may be worn.
16. The participant has a tremor on their ipsilateral side that the AFSW may be worn.
17. Any concomitant condition that, in the investigator's opinion, would not allow safe participation in the study (e.g., drug addiction, alcohol abuse).
18. Known hypersensitivity or contraindication to direct oral anticoagulants.
19. Documented prior stroke (ischemic or hemorrhagic) or transient ischemic attack.
20. Reversible causes of AF (e.g., cardiac surgery, pulmonary embolism, untreated hyperthyroidism). AF ablation does not constitute reversible AF.
21. > 5% burden of premature atrial or ventricular depolarizations on cardiac monitoring.
22. History of ECG-documented, sustained atrial flutter that has not been treated with ablation (participants with atrial flutter who have been ablated are eligible for enrollment)
23. Stage 4 or 5 chronic kidney disease.
24. Conditions associated with an increased risk of bleeding:
    - Major surgery in the previous month

- Planned surgery or intervention in the next three months that would require cessation of anticoagulation > 2 weeks.
- History of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding
- Gastrointestinal hemorrhage within the past year unless the cause has been permanently eliminated (e.g., by surgery)
- Symptomatic or endoscopically documented gastroduodenal ulcer disease in the previous 30 days
- Hemorrhagic disorder or bleeding diathesis
- Need for anticoagulant treatment for disorders other than AF
- Uncontrolled hypertension (SBP >180 mmHg and/or DBP >100 mmHg)

*Spanish-only speakers may be included in the future at select sites where consent forms are appropriately translated.

** Congestive heart failure defined as: The presence of signs and symptoms of either right (elevated central venous pressure, hepatomegaly, dependent edema) or left ventricular failure (exertional dyspnea, cough, fatigue, orthopnea, paroxysmal nocturnal dyspnea, cardiac enlargement, rales, gallop rhythm, pulmonary venous congestion) or both, confirmed by non-invasive or invasive measurements demonstrating objective evidence of cardiac dysfunction and/or ejection fraction < 40%.

5.2 Recruitment

Sites will be responsible for participant recruitment. All sites will participate in regular conference calls during the start-up phase to discuss site-specific recruitment.

To proactively address recruitment, each site manager will provide weekly enrollment status reports to the Recruitment and Retention Committee/Group and the Clinical Coordinating Center, creating and updating a master enrollment log. The information will be proactively acted upon to address enrollment timelines.

Training for recruiting racial and ethnic minority populations: Sites located in areas with higher populations of racial and ethnic minorities will receive additional training for cultural sensitivity/humility. These sites will provide recommendations for other sites.

Sites experienced with building rapport with participants, engaging women and minorities, increasing awareness, and enrolling the study population will share successful strategies with less experienced sites.

5.3 Retention

The study will use the Eureka Research Platform as a participant contact point. Eureka is a non-profit resource built by researchers at the University of California San Francisco with support from the National Institutes of Health. The Eureka Research Platform is designed to help investigators conduct direct-to-participant longitudinal research, including cohort studies and randomized controlled trials. The platform uses technology developed for the *Health eHeart* Study and enables online surveys, data collection from wearable sensors, devices, and smartphones, and flexible messaging for reminders and behavioral interventions. The functionality will be developed specifically for REACT-AF with the launch of a study-specific app. The app will capture participant/patient-reported outcomes. Participants will complete tasks and have access to informational pages and contacts. The real-time interaction will also support study retention.

Regular reports accessible to sites and the DCC will generate lists of participants who have not been compliant with key patient reported outcomes (i.e.. response to notifications about starting anticoagulation, regular reporting of hospitalizations, stroke or bleeding events). The DCC will contact those participants to complete the patient reported outcomes or to complete them via proxy data entry during a phone interview. Participants will also provide additional contacts (next of kin, emergency contacts) and those will be contacted in the event the DCC is unable to reach the participant.

6 STUDY INTERVENTIONS

6.1 Study Interventions and Supplies

Direct Oral Anticoagulant (DOAC)

DOACs will be prescribed to patients according to the treating healthcare provider(s) according to labeling instructions. All DOACs approved by the FDA for stroke prevention in non-valvular AF will be eligible for use in the study.

Study Device (AF-sensing smartwatch (AFSW))

Stanford CCC will oversee the distribution the AFSW to study sites. Devices shall be securely maintained, controlled, and used only in this clinical study. The device inventory log will track participants' device allocations during the study.

The Stanford CCC will maintain records to document the physical location of all smartwatches from shipment to the investigation sites. The study devices should be kept in a secure room with room temperature maintained at 20-30 degrees Celsius, and access to devices should be limited to authorized study personnel.

Records shall be kept by trained site personnel to document the physical location and conditions of storage of all equipment. The principal investigator or an authorized designee shall keep records documenting the receipt, use, return, and disposal of the devices, which shall include the following:

- Date of receipt
- Identification of each device (batch number or unique code)
- Expiry date, as applicable
- Date dispensed
- Participant identification
- Date device was returned from the participant, if applicable
- Date of return (and number) of unused, expired, or malfunctioning devices

6.2 Concomitant Medications

Selected concomitant medications will be collected at randomization, throughout treatment, and follow-up using the Eureka Medication tool—a simple-to-use tool linked to RxNorm database with “autofill” functionality to ensure accurate data input. The number and percentage of participants who received each type of medication at randomization and follow-up will be presented for all randomized participants.

Medication Adherence will be assessed using three questions adapted from the Coronary Artery Risk Development in YOung Adults (CARDIA) study [118] : (1) 'In the past month, how often did you take your medications as the doctor prescribed?' with the response options of 'All of the time (100%)', 'Nearly all of the time (90%)', 'Most of the time (75%)', 'About half the time (50%)' and 'Less than half the time (<50%)'; (2) 'In the past month, how often did you forget to take one or more of your prescribed medications?' with the response options of 'Never', 'Once', '2–3 times', 'Once per week', 'Several times per week' and 'Nearly every day'; and (3) 'In the past month, how often did you decide to skip one or more of your prescribed mediations' with the same response options as question two. Medication non-adherence was defined as either (a) response to question one of "most of the time (75%)" or less, (b) response to question two of "once per week" or more, or (c) response to question three of "once per week" or more, based on previously validated definitions of non-adherence[119]. Participants in the intervention arm will be asked about DOAC compliance at the end of their 30-day "on treatment period".

7 CLINICAL ENDPOINTS, MEDICAL EVENTS OF INTEREST, ADVERSE EVENTS AND EVENT ADJUDICATION

7.1 Event Definitions

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

A study-related adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: 1) death, a life-threatening adverse event, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. 2) Device-related: Having a connection to the device, such as the Apple Watch, one of the two study applications, or cessation of DOAC use. 3) Unexpected: An event that is not anticipated by the study team.

Events are categorized into Adverse Events (AEs), Clinical Endpoints, and Medical Events of Interest (MEOI).The Clinical Events Committee (CEC) will review and adjudicate all clinical endpoints. The Medical Events of Interest and associated medical records will be collected, but not adjudicated. The MEOI event reports will be available if future secondary analyses require their adjudication. The clinical sites might discover some Endpoints, MEOI, and AE's during routine standard-of-care patient visits; sites will be instructed to notify the CCC immediately of any CEC adjudicating study endpoints for review and will otherwise be instructed to perform targeted annual reviews of participant medical records for clinical endpoints and MEOI's .

All clinical endpoints and MEOI's will be collected from the Screening/Baseline Visit through follow-up or study discontinuation, whichever occurs first.

7.2 Clinical Endpoints

Clinical endpoints will be ascertained from the following sources: (1) PRO triggered by geofencing; (2) Quarterly PRO; (3) Targeted annual site review of enrolled patients. The following will be considered clinical endpoints:

- Ischemic stroke
- Systemic embolism
- All-cause mortality
- Major bleeds requiring hospitalization

7.3 Clinical Endpoint Definitions:

Study Endpoints Definitions: The CEC charter will provide detailed definitions to the site investigators. An overview is provided below with details provided in Appendix A.

Stroke: Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

Classification:

A. Ischemic Stroke
   Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.
   Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.
B. Hemorrhagic Stroke
   Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.
C. Undetermined Stroke
   Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

Stroke will be categorized by the DCC as ischemic, hemorrhagic, or cause unknown based on CT or MR scanning or autopsy. Sites will be expected to upload this information into the EDC. The DCC will use imaging and their interpretations in the EDC as resolved by the Neuroimaging Adjudication Committee (NAC) process. A telephonic, modified Rankin Score will assess the stroke severity at hospital discharge and three to four months later. A fatal stroke will be defined as death from any cause within 30 days of a stroke.

Systemic embolism will be defined as an acute vascular occlusion of the extremities or any organ and must be documented by angiography, surgery, scintigraphy, or autopsy and require hospitalization.

All-cause mortality. The primary cause will be defined as the underlying disease or injury that initiates the train of events resulting in death. Cardiovascular deaths will include deaths that result from acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, and death due to other cardiovascular causes. The proposed categories for classifying a specific cardiovascular cause of death are based on the primary cause rather than the mode of death or an intervening cause.

The death of any participant due to any cause and adverse events will be expeditiously submitted to the CEC. In addition, the National Death Index and/or the Social Security Death Index will be reviewed annually for all participants in whom there was no known contact throughout that year.

Major bleeding will be defined as requiring hospitalization and by ≥1 of the following International Society on Thrombosis and Haemostasis (ISTH) criteria: (1) Bleeding associated with a reduction in hemoglobin level of at least 2.0 g/dL; (2) Bleeding leading to transfusion of at least two units of blood or packed cells; or (3) Symptomatic bleeding in a critical area or organ such as intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding, or pericardial bleeding. A major bleed is classified as life-threatening if it meets ≥1 of these criteria: (1) Fatal, symptomatic intracranial bleed; (2) Reduction in hemoglobin level of at least 5.0 g/L; (3) Transfusion of at least 4 U of blood or packed cells; and (4) Associated with hypotension requiring use of intravenous inotropic agents; (5) Necessitated surgical intervention.[134]

7.4 Medical Events of Interest

Medical events of interest (MEOI's) will be ascertained from the following sources: (1) PRO triggered by geofencing; (2) Quarterly PRO; (3) Targeted annual site review of enrolled patients. The following will be considered MEOIs:

- Myocardial Infarction
- Pulmonary Embolus

7.5 Medical Events of Interest Definitions:

Myocardial Infarction will be defined when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

Pulmonary Embolus will be defined as the obstruction of the pulmonary artery or one of its branches by material originating elsewhere in the body. The diagnosis requires a clinical history consistent with an acute loss of blood flow to the lungs supported by evidence of embolism from surgical specimens, autopsy, angiography, vascular imaging, or another objective testing.

7.6 Event Review and Adjudication

These clinical endpoints will be reviewed by the CEC at Stanford, using VISION medical monitoring and endpoint adjudication tools by a dedicated safety and endpoint team (led by Stanford), with each clinical endpoint being adjudicated by an appropriate panel of physicians and therapeutic experts. These events will be compiled, undergo validation checks, and be presented

at each Data and Safety Monitoring Board (DSMB) meeting, with appropriate statistical analyses highlighting trends or other safety signals.

The CEC will comprise seven board-eligible physician reviewers (members) with cardiology and neurology expertise unaffiliated with any other aspect of the study. Of the seven members, one member will be designated the CEC chairman. CEC clinical endpoint review will consist of two physician reviewers independently adjudicating each event using the criteria in the CEC charter. According to the charter, the members will review endpoint events that occur post-randomization and adjudicate them in a consistent and unbiased manner.

Members will remain blinded to treatment assignment throughout the adjudication process and for the duration of the study. Their reviews will be based on information submitted from the VISION eCRF, event narratives, and other outcome event supportive documents. If there is a disagreement between initial reviewers, there will be teleconference meetings for the CEC chair, reviewers, and operations staff to discuss and finalize a consensus decision.

The CEC adjudication will include grading the severity of the clinical endpoint and their relationship to the study intervention. These events will be compiled, undergo validation checks, and be presented at each Data and Safety Monitoring Board (DSMB) meeting, with appropriate statistical analyses highlighting trends or other safety signals.

7.7 Adverse Events

The following study related Adverse Events will be reported by participants through regular PRO surveys or additional surveys triggered by optional geofencing.

- Minor bleeds
- Cardiovascular hospitalizations due to atrial fibrillation or heart failure
- Changes in AF-related treatment such as:
    - Cardioversions (with/without TEE)
    - Ablations for atrial fibrillation or atrial flutter
    - Change in antiarrhythmic therapy
- New congestive heart failure diagnosis
- Skin rash on the wrist due to wearing the Apple Watch
- Anxiety related to the study questions, receipt of results, and/or follow-up discussions
- Anxiety related to irregular pulse notifications from the REACT-AF Study App

7.8 AE Definitions:

Cardioversions will be defined as the restoration from atrial fibrillation to sinus rhythm using direct current or antiarrhythmic drugs

Cardiac Ablation is defined as a procedure intended to eliminate or modify a focus or re-entry circuit that causes arrhythmia in the heart.

Congestive Heart failure will be characterized by impaired ventricular performance, elevated diastolic filling pressures, and diminished exercise capacity. Patients with heart failure and ventricular disease may have a low ventricular ejection fraction (systolic dysfunction) or normal ejection fraction (diastolic dysfunction).

Cardiovascular hospitalizations due to atrial fibrillation or heart failure will include hospitalizations to monitor or initiate or titrate medical treatment for either of these cardiovascular events.

7.9 Ascertainment of Events (Table 6)

We will use a variety of approaches to ascertain clinical endpoints, MEOI's and AEs. As part of Eureka, participants will be asked to turn on geolocation in which we can record when someone has been in a hospital for ≥14 hours through geofencing. Once detected, the location and date of the event is stored in the Eureka data for that participant and a survey is triggered to confirm that they were hospitalized and for what medical problems. In addition, participants will receive quarterly surveys asking if they have been hospitalized in the past month and to provide some additional details of the hospitalization. For participants who do not answer these surveys, the DCC will contact the participant about intervening hospitalizations. For those that reported a hospitalization, the DCC will work with the sites to obtain relevant documentation needed for review and adjudication. As an adjunct, participants will also be asked to connect their medical record to the study using the Eureka Open Epic app. Sites will also be asked to complete a targeted review the medical records of study participants on a yearly basis for clinical endpoints and MEOIs. AEs will be ascertained through PRO surveys in Eureka.

Table 6: Ascertainment of Events

Event	Event type	Ascertainment Method	Frequency	Trigger	Adjudication
Stroke/Systemic Embolism	Clinical Endpoint	P, DCC, S	Geo+ Quarterly PRO /Annual SR	Geo, PRO, SR	CEC
All-cause mortality	Clinical Endpoint	DCC, S	Geo+ Quarterly PRO /Annual SR	Geo, SR	CEC
Major bleeding requiring hospitalization	Clinical Endpoint	P, DCC, S	Geo+ Quarterly PRO /Annual SR	Geo, PRO, SR	CEC
Myocardial Infarction	MEOI	P, DCC, S	Geo+ Quarterly PRO /Annual SR	Geo, PRO, SR	None, collect for future review
Pulmonary Embolus	MEOI	P, DCC, S	Geo+ Quarterly PRO /Annual SR	Geo, PRO, SR	None, collect for future review
Minor bleeds	AE	P	Quarterly	PRO	None
CV Hosp/AF or HF	AE	P	Quarterly + Geo	PRO	None
∆ AF treatment	AE	P	Quarterly + Geo	PRO	None
New HF dx	AE	P	Quarterly	PRO	None
Skin rash	AE	P	Quarterly	PRO	None
Anxiety to questions	AE	P	Quarterly	PRO	None

Anxiety from app	AE	P	Quarterly	PRO	None

MEOI= Medical Event of Interest
AE = Study related adverse events
P = participant (via Eureka PRO)
S = site
PRO = patient reported outcomes
Geo = geofencing
SR = Site review
CEC = clinical events committee
DCC= Call center at the Data Coordinating Center

8 STATISTICAL CONSIDERATIONS

Specific Aim 1: The primary aim of this multi-center, randomized, open-label study is to assess whether atrial fibrillation-sensing smartwatch (AFSW)-guided, time-delimited direct oral anticoagulant (DOAC) therapy is non-inferior to continuous DOAC therapy for a composite endpoint that includes:
1. Ischemic stroke
2. Arterial (systemic) embolism
3. All-cause mortality

Statistical Hypothesis 1:
The null (H_0) and alternative (H_a) hypotheses are:

- H_0: HR ≥ δ
- H_a: HR < δ
- Where HR is the ratio of hazards of the composite endpoint for the AFSW-guided, time-delimited DOAC therapy group and the control arm (continuous DOAC) over up to 60 months of follow-up, and δ = 1.45 is the non-inferiority margin.

Specific Aim 1 Primary Outcome. The primary outcome for testing the efficacy of AFSW-guided DOAC will be a composite endpoint of ischemic stroke, arterial (systemic) embolism, and all-cause mortality. Accordingly, approximately 2677 AFSW devices will be used in the study for participants randomized to the novel strategy arm. To ensure data generalizability, minimize site bias in study results, and ensure sites will be able to manage and follow enrolled participants, the maximum number of randomized participants allowed at a single site is 200. The enrollment period is expected to last approximately 24 months. Participants will be followed for up to 60 months and then exited. Follow-up will be per standard of care; no study-specific visits are required after randomization. Participants will report events via the smartphone-based Eureka system, and sites will report events via the electronic data capture (EDC) system. Source documents related to these events will be uploaded to the EDC for adjudication.

Definitions of Analysis Samples

ITT Set. ITT set includes all participants randomized to either AFSW-guided, time-delimited DOAC therapy or to continuous DOAC therapy. Participants randomized to the AFSW-guided, time-delimited DOAC therapy will be instructed to take targeted, time-delimited DOAC for 30 days only in response to a prolonged (i.e., >1 hour) AF episode detected by an AF-sensing smartwatch (AFSW) for up to 60 months following randomization; participants randomized to the continuous DOAC therapy will receive their previously prescribed current standard of care of continuous

anticoagulation with DOAC for up to 60 months following randomization. All follow-up data will be included in the ITT statistical analyses regardless of adherence to instructions assigned by randomization.

Safety Analysis Set. The safety population includes all participants who signed informed consent and are exposed to the study interventions. Participants will be analyzed for the safety endpoints according to the treatment randomization they received, adjusting for participants who crossover from the on-demand DOAC strategy to the continous DOAC arm.

Per Protocol Set. The Per Protocol Set will include the follow-up for all participants randomized to the intervention and control arms with no major protocol violations, study arm crossover, or drop-out prior to a primary endpoint event.

Multiplicity. The primary analysis population is the Per Protocol set, and the analysis will compare the AFSW-guided, time-delimited DOAC therapy group with the continuous DOAC group.

Secondary (safety) hypothesis will also be tested on the Per Protocol sample. A hierarchical testing strategy will be used, and the primary safety endpoint (major bleeding event) will only be formally evaluated if non-inferiority is demonstrated for the efficacy endpoint (combined stroke, systemic embolism, and alll-cause death). In addition, a test of superiority of the on-demand DOACAFSW guided treatment vs continuous DOAC will be performed only if non-inferiority is demonstrated. No multiplicity adjustment is required per the recommendations in International Conference on Harmonisation guidance E9: Statistical Principles for Clinical Trials (ICH E9).[5]

8.1 Primary Efficacy Analysis

The primary analyses will use Per Protocol approach to compare the distribution functions of survival free of the composite endpoint between the participants randomized to the AFSW-guided, time-delimited DOAC therapy arm versus those randomized to the continuous DOAC arm who had no major protocol violations, study arm crossover, or drop-out prior to a primary endpoint event. First, we will use the stratified log-rank test, where the strata are clinical site, prior ablation (yes/no), and CHA_2DS_2-VASc score category (1-2/3-4). Inverse Probability (IP)-weighted survival estimates will be calculated and the study will be considered a success for AFSW-guided, time-delimited DOAC therapy if this novel therapy is shown to yield non-inferior composite event rates to the continuous DOAC arm at a one-sided significance level of 0.025. Participants not achieving the composite endpoint during the up to 60 months of follow-up will be censored in the analysis at the time of last known contact or the end of study follow-up or crossover, whichever is earlier.[23] The IP-weighted hazard ratio and two-sided 95% confidence intervals (AFSW-guided vs. continuous DOAC) of the hazard ratio will be estimated using g-methods to adjust for pre- and post-randomization covariates.[24] In addition, if the inferiority hypothesis is rejected, then a test of superiority for the secondary safety endpoint will be performed without multiplicity adjustment.

Analytic Considerations. A per-protocol analysis for the primary efficacy and safety endpoints is most conservative for a non-inferiority trial since factors such as crossovers, protocol non-adherence, and the type and extent of missing data will tend to bias the results towards rejecting the null. The per protocol analysis is based on data generated by the participants who complied with the protocol sufficiently and without crossover or dropout (participants will be censored at time of crossover or dropout) to ensure exposure to the randomized study treatment strategies and provide availability of measurements for adjudicating endpoints in the absence of major protocol violations.[19] In the per protocol analysis, the participants will be censored after they

become non-adherent to the AF management strategy. There are three potential components of non-adherence: 1) non-compliance with watch-wearing time (intervention arm only), 2) lack of response to notifications (intervention arm only) and 3) non-adherence to DOAC as defined by the protocol (both study arms). A modified per protocol analysis will include censored participants.

It must be emphasized that REACT-AF is comparing two competing *strategies* for stroke prevention. Inherent in this study design is the assumption that DOAC non-adherence may not be uncommon but is difficult to assess, particularly in a largely pragmatic and virtual study such as REACT-AF.[20] Furthermore, any attempt to surveil the control arm for DOAC adherence would depart from the standard of care and potentially exacerbate a Hawthorne effect above and beyond that induced by study inclusion alone.

In contrast to the challenges in assessing DOAC adherence, adherence to the intervention arm's smartwatch guidance can be objectively, accurately, and remotely assessed through "wristwear" times (i.e. combining activity and heart rate data) and responses to push notifications concerning rhythm status. Given these considerations, non-adherence will be defined as follows:

Intervention arm:

- Not wearing watch for more than 72 hours on more than 5 occasions a year
- Missing two or more consecutive quarterly follow-ups and failing to respond
- Not responding to the AF notification ("you are in AF") or not responding "I plan to take DOACs now".

Standard arm:
Missing two or more consecutive quarterly follow-ups and failing to respond

The participants who qualify as "non-adherent" based on the above definitions, will be censored at the time of becoming non-adherent. We will use a 'Per Protocol' approach to analyze the assigned intervention as the primary treatment variable. The stroke and bleeding events that occur after non-adherence time point will be excluded in the primary analysis data set. Thus, utilizing data censored at time of crossover, we will only analyze the period that participants are exposed to the intervention to which they were randomly assigned. This will allow us to measure the effect of the intervention without "regression to the mean" which would result from contamination in the ITT population by a group of crossover study participants who, despite randomization to the intervention arm, crossover to continuous DOAC exposure. We will record crossover data, as well as the factors that might predict crossover. A separate ITT analysis will control for these factors, some of which might be time- and/or assigned treatment-dependent, using Inverse Probability weighting[21,22] . Overall, this form of censoring is the most conservative approach, preserves the effects of randomization, and maintains the assumptions around non-inferiority testing in the trial. In addition, it protects the safety analysis by producing an analytic population that has maximal exposure to the AFSW strategy.

Secondary analyses will also be conducted using the "As Treated" approach with time-varying treatment information (i.e. initial randomized exposure period and the "crossover" treatment after the crossover). Follow-up information for all participants will be collected according to the intention-to-treat principle, whether or not they continue with therapy/remain compliant. Sensitivity analyses will be performed for dropouts by imputing the data under the null hypothesis of inferiority as recommended in the FDA guideline for non-inferiority studies. Additional analyses will be performed on an ITT population.

Specific Aim 2: Aim 2 is to assess whether AFSW-guided, time-delimited DOAC therapy significantly reduces major bleeding events compared to continuous DOAC therapy.

Statistical Hypothesis 2:
The null (H_0) and alternative (H_a) hypotheses are:

- H_0 : HR = 1
- H_a : HR ≠ 1
- Where HR is the true hazard ratio of major bleeding of the AFSW-guided DOAC vs. continuous DOAC therapy.

Specific Aim 2 Outcome: The primary safety endpoint will be time to first occurrence of major bleeding during the treatment period. Time-to-event methods will be used to estimate cumulative risk of major bleeding. Participants without events during the follow-up period will be censored. Sensitivity analyses will be performed.

Exploratory Aim 1: To compare overall satisfaction with anticoagulation management between the two study arms.

Exploratory Aim 1 Outcome. The primary quality of life outcome measure will be the Duke Anticoagulation Satisfaction Scale (DASS).

Exploratory Aim 2: To compare estimates of health-related resource utilization in participants randomized to control versus experimental arms.

Exploratory Aim 2 Outcome. The primary resource utilization outcome will be the costs and quality-adjusted life years (QALYs) utilizing the quality of life questionnaires.

Handling of Missing Data
The primary endpoint analyses will use all available data. Sensitivity analysis using simple and multiple imputation methods and tipping point analyses will be performed to evaluate the impact of the missing values on study conclusions.

8.2 Statistical Power

Justification of the composite endpoint. The efficacy endpoint of REACT-AF is a combination of ischemic stroke, systemic embolization, and all-cause mortality. Disease-related (i.e. cardiovascular) mortality is often used to assess the effects of an intervention within a 'mechanistic paradigm' for phase 3 randomized clinical trials as detailed trial monitoring is directed to detect the effects of the experimental intervention which is presumably not diluted by events unrelated to the disease. However, all-cause mortality remains a reliable and patient-centered primary outcome in most circumstances.[1-3] To determine disease related mortality, an unbiased cause of death must be determined and deaths must be allocated in a standard manner to disease related, other causes, and unknown causes. These determinations are problematic.[4, 5] In fact, the Standardized Data Collection for Cardiovascular Trials Initiative, notes that "deaths of undetermined cause should be very few," and that "use of this category is discouraged and should be rare in well-run clinical trials in which adequate source documentation is assiduously sought by participating investigators.[6] "However, major cardiovascular trials demonstrate that CEC-adjudicated deaths of undetermined cause ranged from 7.0-21.7% across trials.[7] Thus, inherent limitations in adjudicating cause of death are unavoidable in clinical trials, and particularly likely to be worse in a predominantly virtual trial such as REACT-AF. Therefore, we have chosen to use

all-cause mortality in the co-primary endpoint while examining CEC-adjudicated cardiovascular mortality in an exploratory analysis.

Event rate. Event rates for the efficacy endpoints were estimated from analyses of the pivotal DOAC trials.[8-10] In ARISTOTLE,[10] 30% of participants had a $CHADS_2$ score ≥3. It is estimated approximately 15% of participants had a $CHADS_2$ score >4 (corresponding to a CHA_2DS_2-VASc score ≥5). This estimation is based on the distribution of $CHADS_2$ scores in Chiang et al.[11] The event rates in ARISTOTLE are therefore adjusted to account for the lower distribution of CHA_2DS_2-VASc scores in REACT-AF. The SPARCtool (sparctool.com/sparcnotes.htm) was employed to calculate the stroke risk by CHA_2DS_2-VASc score for participants using continuous DOAC therapy. Overall rate in ARISTOTLE for stroke/embolism was 1.28%. Using the SPARCtool, average rate for scores 5 or higher is 3.97%, averaged over all DOACs. Thus, rate of stroke or arterial embolism in DOAC-treated patients with CHA_2DS_2-VASc scores 4 or lower is estimated at 0.8% per year.

All-cause mortality in DOAC-treated patients was 1.9% in ROCKET-AF, 3.6% in RE-LY, and 3.5% in ARISTOTLE. We conservatively estimate that all-cause mortality rate in those with a CHA_2DS_2-VASc score of 1-4, with additional discounting for anticipated younger age of our cohort and exclusion of high-risk comorbidities such as heart failure and prior stroke, to be 1.2%. Thus the overall event rate for stroke, systemic embolism, and all cause mortality in the REACT-AF trial is estimated as 2.0% per year (0.8% + 1.2%). We recognize that the studies cited were published a decade ago. However, together they enrolled >36,000 participants on DOACS and there have not been substantive changes in the AF population since then. We also reviewed 4 retrospective cohort studies enrolling > 400,000 DOAC patients. Our estimates for the primary combined endpoint of stroke, systemic embolization, and all-cause mortality are approximately 50% lower than that reported in these studies. This supports that our estimated event rates for lower-risk participants in REACT-AF trial are conservative. [12-16]

The sample size calculation assumes a one-sided type I error rate of 0.025 and a type II error rate of 0.10 or equivalently, power of 0.90 for the final analysis. The non-inferiority HR margin is 1.45, consistent with other major AF trials designed for FDA-approval including ROCKET-AF (NI margin 1.46), ARISTOTLE (NI margin 1.38), CHAMPION-AF (NI margin 1.4), CATALYST (NI margin 1.5), and PROTECT AF (NI margin 2.0). **Table 7** shows the required sample size based on these assumptions and accounting for a conservative 12% loss to follow-up per year and a 10% crossover rate per year (which will be considered discontinued from study at the time of crossover). The loss to follow-up and crossover rates are highly conservative compared to those observed in the major DOAC trials and other cardiology RCTs. Individuals randomized to the control arm will not have access to the AF-sensing smartwatch being used in this study as the customized software is not commercially available, thereby ensuring that crossovers will be unidirectional.

Dropouts are minimized by decreasing participants' burden and inconvenience during data-collection with limited number of assessments, collecting only necessary information, and user-friendly forms. We will provide extensive counseling to participants on all aspects of data collection. In a digital health anticoagulation adherence intervention randomized trial in an AF population, SmartADHERE, led by the Stanford collaborators, the trial saw no crossovers using these techniques.[17] Our "Engagement and Adherence" section details extensive plans to minimize dropout and crossover that the study team developed in close collaboration with the Recruitment Innovation Center (RIC) at Vanderbilt. Crossover from rhythm guided anticoagulation to daily therapy in the setting of AF progression or the development of chronic AF

is expected to be minimal, as data show that only a small minority of patients have significant progression of AF over 3.5 years of follow-up.[18]

Table 7: Sample Size requirements for 90% statistical power, 1.45 NI HR margin and one-sided alpha = 0.025

Cumulative Incidence (per year)	Monthly Hazard rate	Loss to Follow-up (per year)			N per arm	Total N
		DOAC	Intervention*	% crossover from intervention to DOAC		
2.0%	0.0017	12%	22%	10.0%	2675	5350
2.1%	0.0018	12%	22%	10.0%	2532	5064
2.3%	0.0019	12%	22%	10.0%	2404	4808

Note: * includes 12% assumed for DOAC + % for crossovers from intervention to DOAC

With a sample size of 5350 randomized participants and a non-inferiority test at an α = 0.025 (1-sided) significance, the power is 90% to reject the null hypothesis of inferiority in favor of the alternative hypothesis of non-inferiority of the proportion of participants with composite endpoint in the AFSW-guided DOAC arm compared to the continuous DOAC arm, when the composite endpoint rate in both groups is 2.0% per year over the 60 months follow-up period, a non-inferiority margin of 1.45, 12% loss to follow-up per year, 10% crossover from the AFSW-guided arm to the continous DOAC arm (who will be considered discontinued from study at the time of crossover), and 1:1 randomization. PASS 15 was used to compute the power, assuming the log-rank test for non-inferiority. Rejection of the null hypothesis will signify that the AFSW-guided experimental arm is non-inferior to the control arm (continuous DOAC) for the composite endpoint during the 60 months of follow-up.This study design is methodologically appropriate and the number of patients anticipated is adequate to confidently answer the questions asked.

Sample Size Re-estimation

Upon randomization of the 1000th and 4000th participant the lost-to-follow-up (LTFU), crossover, and observed event rate based on pooled, blinded accumulation of primary efficacy endpoint events will be calculated and plotted. If these analyses suggest the number of participants LTFU, crossing over from the AFSW-guided experimental arm to the continuous DOAC experimental arm, or with at least one adjudicated, primary event (and appropriately accounting for participants with potential primary events for which the adjudication process is then incomplete) is consistent with projections, the study could continue toward the protocol-specified target enrollment of 5350 participants. However, if the LTFU, crossovers or events appears inconsistent with projections, the REACT-AF leadership will consider, under blinded conditions and with documented approval of the NIH, the Steering Committee, and the Data Safety Monitoring Board, re-calculating the number of participants needed to achieve the target number of events within the desired timeline, increasing the number of sites, or extending the follow-up period. The timing of the 4000th participant reflects a meaningful accrual (i.e. 75% accrual) of trial participants as well as representing the latest possible timing to reassess event rates with trial operational considerations. We do not anticipate either timepoint (1000th or 4000th) reassessment to disrupt enrollment in the trial.

Because this procedure is blinded to treatment assignment, no meaningful inflation of the type-I error rate is expected.

The following limits will be adhered to when updating the sample size:

- The sample size will be updated only if the revised sample size is more than 10% larger than the planned value of 5354, i.e., greater than 5885.
- The updated sample size will not exceed 6500 participants.
- No decrease in the planned sample size will be allowed (outside of the direction of the DSMB).

These rules are in accord with guidelines suggested by Gould.[7]

9 DATA COLLECTION AND SITE MONITORING

9.1 Quality Management

The DCC will be responsible for quality assurance, including QA monitoring of compiled data and site compliance. In accordance with the March 2018 revision to FDA's E6r2 Good Clinical Practice standard, FDA's 2013 guidance on risk-based monitoring, the 2018 ISO 31000 standard, and the recommendations of TransCelerate and other industry consortiums and regulatory guidance, this study will be conducted using best-practice risk-based quality management system principles. The project team will conduct an in-depth assessment of risk, including safety-related risks to patients and general risks to successful project completion, shortly after project launch. This includes identifying and ranking the risks (so as to focus resources on those that matter the most), devising ways to prevent or at least mitigate those risks, determining methods of identifying trending risks, and planning suitable response strategies and procedures. A preliminary assessment of the project's risks and initial mitigation plans is presented later in this section. This formal Risk Assessment, as documented and expanded into an Integrated Quality and Risk Management Plan (IQRMP), will be used to develop other project plans, such as the Risk-Based Monitoring (RBM) Plan, the Safety Plan, and the Clinical Data Management Plan (CDMP). Quality and risk management assessment is always ongoing, and these plans will therefore be refined and enhanced throughout the study, both as new information becomes available and during pre-defined periodic reviews/audits and re-assessment of risk. Relevant information can come from many sources: monitoring and data management, safety surveillance, QA/QC audits, site management, etc.

QA/QC activities of this integrated Quality System will be implemented and maintained by the DCC for this trial. Specifically, selected data (excluding PHI) will be pulled from the electronic data capture (EDC) system to calculate daily metrics called Key Risk Indicators (KRIs). These metrics, using statistical point-in-time and trend analyses, are calculated daily to quantify the level of risk across sites, regions, and the overall study. Should a KRI exceed a predefined threshold (established during risk assessment) or is showing a discernable trend, the QA team (monitors and data managers) will be automatically notified by email. Project team members may also make manual entries, such as to document a quality/risk finding discovered during a site visit, a data listing review, or communication with a site. The project team, under the guidance of the Operations/Clinical Affairs Team, will then undertake appropriate corrective and preventative action (CAPA) to address these risks. Most responses are predefined during the risk assessment, but unanticipated or overtly egregious events may be referred to the Executive Committee (EC). These actions are then documented and archived. As an example, a predefined response might be to elevate the site to "Enhanced Monitoring," which would entail expanding the level of remote/central monitoring for that site and increasing management communications. A higher-level response might be to conduct a for-cause on-site visit to undertake a root-cause analysis

and implementation of a formal CAPA program. Compliance with the IQRMP is governed by SOPs, audited by the DCC manager, and enforced by leadership.

9.2 Monitoring Plan and Data Integrity

Risk-based monitoring is an important component of the Quality System for this trial and will be conducted in accordance with the DCC's monitoring SOP and a formal Monitoring Plan to be developed in consultation with the CCC. The DCC's team of monitors will conduct remote monitoring reviews on a patient-by-patient basis for both accuracy and completeness of the data and agreement with uploaded source medical records (e.g., remote source verification). Clinical sites will screen and randomize the study patients and transcribe this baseline data into the EDC from medical charts or data compilation worksheets. Site coordinators will scan and upload these "source documents" directly to the EDC under their log-in credentials, thereby creating certified copies for regulatory compliance and allowing the EDC to be used as the Electronic Trial Master File (eTMF). Sites will additionally be uploading hospital records for study related Serious Adverse Events and study endpoints (major bleeding, systemic emboli, death, stroke, etc.). Data discrepancies identified by the monitoring team while reviewing patient cases and verifying data entry against these uploaded source documents will be entered as "queries" in the VISION EDC platform, and the monitors will then work with the sites to obtain query resolution and data correction. The DCC QA monitors will review the online case forms for completeness, logic, and consistency, then verify the entered data against the uploaded source medical records and data collection worksheets. These reviews are continuous and ongoing over the course of the study and conducted promptly after each patient encounter ("visit"). The monitors are highly independent and skilled, and they have professional experience in monitoring regulated clinical trials. As monitors are regionally based, it also reduces the cost of on-site visits, should a visit for cause be required.

The data collected on the mobile platform (Eureka) is reported electronically directly by patients ("ePRO") meaning there is no source medical record for verification (i.e. Eureka data is the source documentation for these measures and outcomes). Also, this data will mostly entail "point-in-time" assessments, meaning there should not be "after-the-fact" changes. Nonetheless, the Eureka data can still be monitored by quality/consistency, and these monitoring findings will be documented as a quality control process.

For example, significant or repeated inconsistencies may require asking the site to follow up with the patient to ensure proper training, or if there are trends, the project team may redesign the forms to improve accuracy and compliance. Following the project team's quality-by-design principle, the proposed data collection form designs will undergo pre-testing that employs representative examples of potential study patients, as well as clinicians and mobile-interface experts. The goal will be intuitive, low-burden forms, both in Eureka and in VISION (the latter, for completion by site coordinators), that will produce high-quality data. Both systems will use automated feedback and quality checks to reduce error and ensure the user understands what to record. In this regard, the VISION EDC system, as well as the Eureka direct-patient-entry forms, will have robust field-level data quality checks executed at the time of data entry. This includes the standard validations available with most EDC systems, such as range checks and data format checks, plus sophisticated cross-form logic; for example, VISION can check if a site is on hold to prevent randomization of new patients, and Eureka can issue a notification via phone as a reminder to enter today's dosing information.

9.3 Quality Assurance (QA) and Quality Control (QC) Tools

Another critical aspect of quality is the data system itself. The data collection/retention systems (i.e., implementations of VISION and Eureka) and the data interchange programming (API

publishing/subscribing) in this study will be developed in accordance with detailed design specifications and thoroughly tested, both as individual systems (unit and functional tests) and as an integrated system, i.e., end-to-end (E2E), user acceptance testing (UAT), and automated load testing. The DCC system implementation team will follow a business-driven development (BDD) approach, writing E2E/UAT testing scenarios in Gherkin and conducting both manual and automated testing using web application testing tools such as Selenium. This will include simulating patient randomizations and subsequent visits using sham data. All documents will be completed prior to activation of the first site ("go-live"), with documentation retained in the Trial Master File. Any subsequent changes to the data systems must first undergo regression testing and re-validation prior to being moved into the production environment. All activities related to the data systems will be conducted in accordance with DCC standard operating procedures and undergo QA/QC auditing by the QA team. The IT management team will generate suitable QC documents to document its actions in accordance with the SOPs and applicable plans (Security Plan, Data Management Plan, etc.). As with other work teams, QA audits are conducted at least annually and as part of deliverables/milestones such as system go-live, and these reviews will include assessing the SOPs and project plans as well.

9.4 Data Integrity and QA Monitoring

The DCC will ensure data integrity, according to institute policies, by assuring that appropriate blinding and separation of all CCC and DCC functions are maintained, including data monitoring and management by the DCC. QA monitoring will be done remotely, saving money by reducing the need for frequent site visits. Once a potential participant is identified, a site coordinator will register the patient in the EDC system, triggering an automated alert to the DCC. Should the patient subsequently fail to qualify for the study, the basic demographic information and reason for screen failure will be assessed to identify recruitment barriers. The VISION EDC system has a set of field-level, data quality checks executed at the time of data entry at the investigational site. This includes standard validations available with most EDC systems such as range checks and data format checks. The DCC QA monitors will be responsible for near real-time review of the clinical data entered into our EDC system against source medical records (i.e., Source Document Verification or SDV) as well as generation and resolution of the associated data. The DCC QA monitors will review the online case forms for completeness, logic, and consistency, then verify the entered data against the uploaded source medical records and data collection worksheets.

VISION EDC system will reflect the FDA Guidance for Industry for Computerized Systems Used in Clinical Trials as well as the Electronic Records/Electronic Signatures rule (21 CFR part 11). A secure, computer generated, time-stamped electronic record allows reconstruction of the course of events relating to the creation, modification, and deletion of an electronic record. Security measures are in place to prevent unauthorized access to the system and data. To ensure that individuals have the authority to proceed with data entry, the system is designed to verify the electronic signature (user ID and password) at the start of a user session.

In addition to "remote" monitoring, the Quality System will incorporate "central" monitoring, which entails activities of site managers, data managers, statisticians, the safety team, and other staff (in addition to dedicated site monitors) in the review of clinical data. Central monitoring inputs and tools include the built-in data validations of the EDC, the offline "edit checks" run against the compiled data, various statistical data quality checks, periodic reviews of data listings, medical monitoring and ECG overreads by the Stanford team, the DSMB reviews, project management oversight, QA auditing, and the ongoing oversight by the single IRB (sIRB). A project statistician will be charged with conducting suitable analyses on the compiled data on periodic basis (appropriate for an analysis as determined during the risk assessment) to check for any

quality/safety, excessive site variation (outliers), or ensuring-risk issues that may span multiple sites or might have been missed by the monitoring team.

10 HUMAN PARTICIPANTS

10.1 Single IRB (SIRB)

The Johns Hopkins University School of Medicine (JHM) Institutional Review Board (IRB) will serve as the named sIRB for the REACT-AF trial.

JHM IRB is responsible for protecting the rights and welfare of human participants participating in research. The JHM IRB has been accredited by the Association for the Accreditation of Human Research Protection Programs since 2005, most recently receiving full reaccreditation as of June 2021. The JHM IRB includes six committees that meet weekly to review human participants' research projects and a seventh committee, located at Johns Hopkins All Children's Hospital in Florida, which meets monthly. The IRB has approximately 75 members with diverse disciplinary expertise and includes physicians, ethicists, pharmacy and therapeutics representatives, and community members.

JHM IRBs have diverse representation, including community representatives, with membership considerations given to race, gender, and cultural backgrounds to ensure all federal requirements for IRB membership under the U.S. Department of Health and Human Services and Food and Drug Administration regulations are met. The JHM IRBs are supported by 38 professional staff members, including a team of regulatory experts. On average, staff members have at least 7-10 years of experience in research and human participants' protections.

JHM IRB has served as the sIRB for many collaborative initiatives, including serving as the single IRB for the PaTH initiative, a multicenter collaborative partially funded by PCORI. JHM IRB routinely serves as the IRB of record for other academic institutions, hospitals and medical centers, and small community practices. In addition, since August 2017, the JHM IRB has taken on the role of sIRB for 100 + multisite studies ranging in number of relying sites from 5 to 45. This includes federally funded studies and studies that are industry-sponsored or foundation-funded.

10.2 Informed Consent

As part of the Informed Consent (ICF) and its incorporated HIPAA release, study participants must agree to collect and share their study data and medical records with the project team prior to study participation, some of which will include PHI, as described above. Site personnel will provide participants with an overview of the study procedures. If the participant is interested in participating in the study, they will be asked to review the consent form, which outlines the purpose of the study, information to be collected, planned analyses, follow-up procedures, and protection of personal identifying information. The participant will be given sufficient time to decide whether they are interested in participating in the study. The site PI will be available to answer all participant questions during this time. All participants must be capable of providing informed consent. Once the participant has had time to carefully consider all the information on the written consent form and all questions have been answered, they will be asked to sign the consent form, which will be maintained by the study staff at the clinical sites. Site staff will provide participants with a copy of their signed consent form.

REACT-AF will utilize the VISION EDC platform for a direct-to-participant eConsent. VISION EDC uses a custom-built, multi-tenant HIPAA- complaint backend in the cloud that supports

synchronized web portal and mobile application participant interfaces and a study team interface for participant and study management. It features an eConsent system that can accommodate eSignatures.

As part of the Single IRB (sIRB) process, a master ICF will be developed, having an insert that allows customization by participating sites, as may be required by local regulations or organizational policy. As part of the Informed Consent (ICF) and its incorporated HIPAA release, study participants will agree to collect and share their study data and medical records with the project team prior to study participation, some of which will include PHI.

This ICF shall comply with 21 CFR Part 50 (Protection of Human Participants) and, in accordance with DCC SOPs, shall be collected and reviewed both by the JHU-Tufts sIRB coordinating /startup team and then by the JHU sIRB. Local site IRBs or research committees shall also review the informed consent during the “Local Context Review” portion of the sIRB process.

In addition, this study conforms with 21 CFR 56, and 812, and 45 CFR 46.

10.3 Recruitment of Minorities and Women

The study will comply with the NIH Policy on Inclusion of Women and Minorities as Participants in Clinical Research. The study population's anticipated gender, racial, and ethnic breakdown is included (**Table 8**). We anticipate enrolling a minimum of 40% women and 20% minorities in the trial. Special attention will be given to participants with lower health and computer literacy, and all participant-facing study materials will be communicated no higher than a 5th-grade reading level. Additionally, extra time will be allocated to study visits for participants to allow time for study team members to address computer/technology literacy barriers, help participants set up their new watch, guide them through usage and answer any questions. Additionally, a list of resources and help desk phone numbers will be sent home with each participant. Links to phone numbers and other resources will be provided via MyCap, text message, and available on the study website.

Table 8: Gender, racial, and ethnic enrollment

Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	171	257	428
Not Hispanic or Latino	1969	2953	4922
Ethnic Category: Total of All Subjects *	2140	3210	5350
Racial Categories			
American Indian/Alaska Native	21	32	53
Asian	43	64	107
Native Hawaiian or Other Pacific Islander	21	32	53
Black or African American	342	514	856
White	1713	2568	4281
Racial Categories: Total of All Subjects *	2140	3210	5350

11 RISKS

Chronic anticoagulation has been demonstrated to reduce the risk of thromboembolic events in participants with AF and other vascular risk factors; however, chronic anticoagulation may be unnecessary in patients with brief and/or infrequent episodes of AF, such as the patient population to be enrolled in this study.

While transitioning an individual from chronic anticoagulation to device-guided intermittent anticoagulation may expose patients to an increased risk of cardioembolic events including stroke, continuing anticoagulation when it may not be necessary carries a risk of anticoagulation-induced hemorrhage, particularly intracranial hemorrhage. The anticipated rate of cardioembolic events in the experimental arm is ≤ 1% per year. A reduction in the use of anticoagulation is expected to reduce the risk of major bleeding in the intervention arm by at least 35% but conversely exposes those in the standard of care (control) arm to an increased risk of bleeding. The use of anticoagulants in general are associated with bleeding events including life-threatening bleeds. The overall risk of major bleeding or hemorrhagic stroke in the standard of care arm is estimated from the four pivotal DOAC trials (and adjusted for CHA_2DS_2-VASc score 1-4 population) to be 2.1% per year. The purpose of the pragmatic phase is to reduce the level of oversight by the study team and assess the safety and efficacy of the novel intervention in a more "real world" setting. As there will be no study team to contact future patients who clinically adopt the REACT-AF strategy if the trial is positive, we believe it is important to evaluate the safety of this approach with less stringent guardrails in place. The 48-hour threshold for thrombus formation is a consensus opinion. This threshold will be informed by the data in Phase 1 of the study. The 72- hour threshold will not move forward without supporting data and approval of the DSMB and sIRB. Thus, the decision to extend the time to patient contact during the pragmatic phase to 72 hours is based less on the pathophysiology of thrombus formation during AF and more on the goal of expanding the generalizability of the novel approach while still providing the necessary oversight to ensure the safety of study participants. Importantly, we will not move to the pragmatic phase with the 72-hour threshold without supporting safety data and approval of the DSMB and sIRB.

In order to participate in this study, subjects must demonstrate that ability to tolerate an FDA-approved non-Coumadin oral anticoagulant (i.e., dabigatran, rivaroxaban, apixaban, or edoxaban) for at least 30 days. This inclusion criterion is expected to select for a patient population at a lower risk of bleeding and increased rate of medication compliance.

Side effects of intermittent non-Coumadin oral anticoagulants may also include the following:

- Hematoma
- Blood in the urine
- Blood in the stool
- Bruising
- Longer bleeding times
- Throwing up or spitting up blood
- Bleeding of the gums
- Bleeding around the eyes
- Nose-bleed
- Bleeding in the stomach
- Bleeding from the rectum
- Gastric upset or dyspepsia

Enrollment in this study may carry additional untoward risks. For those participants randomized to the treatment arm, the smartwatch may not detect all episodes of atrial fibrillation especially if the participant is not wearing their watch when the episode occurs. Failure to detect a prolonged episode of atrial fibrillation when the participant is not on blood thinners could increase the risk of stroke. The cessation of chronic anticoagulation may create adverse psychological effects on some patients, as may the daily assessment of their AF using the AFSW. Some of the questions on the surveys may be upsetting or may make the subject feel uncomfortable answering. If they do not wish to answer a question, they may skip it and go to the next question.

11.1 Protections Against Risk

Protection to minimize medical risks:
Every attempt will be made to minimize or eliminate potential risks to research participants. The measures planned include careful monitoring of the progress of the project by the Principal and Co-Investigators, frequent review of any adverse events by the study safety monitor, and prompt reporting of any such event to the IRB and DSMB.

The REACT-AF study will utilize custom software relying on the same machine learning model and operating point used in the Atrial Fibrillation (AFib) History Feature (cleared via K213971) for its functionality. This algorithm was trained on over 3 million tachograms from over 2500 subjects, representing a broad range of age, sex, BMI, race, and skin tones. The performance of this algorithm was reported in the clinical validation study included in the AFib History 510(k) submission to have a sensitivity and specificity of 92.6% and 98.8%, respectively.

The Eureka/AFSW notification process is designed to (1) ensure rapid communication between the AFSW and participant in the case of a threshold AF event for which DOAC should be re-initiated and (2) provide timely notification in the event a subject has not adhered to the notifications within a 48-hour period (or 72 hours in the pragmatic phase of the trial) or has been non-adherent to AFSW wearing for a 48-hour period (or 72 hours in the pragmatic phase of trial). In both cases, a push notification, SMS texts, and robocalls would be sent to the subject's smartphone that will be asked to respond to. If the subject has not adhered to the notifications , a DCC call center representative will reach out via phone to the participant and, if necessary, their contacts.

The Data Safety Monitoring Board will be convened with expertise in AF, stroke, clinical trials and/or statistical methodologies and will meet as directed by the NIH to review the overall progress of the project. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the Clinical Investigation Plan.

In addition, all study personnel will need to provide proof of suitable Human Subjects Protection (HSP) and Good Clinical Practices (GCP) training as a requirement of site qualification. The principles of GCP help assure the safety, integrity, and quality of clinical trials by addressing elements related to the design, conduct, and reporting of clinical trials and will be strictly adhered to throughout this trial. GCP training will be required for all study leadership and all site staff. The goals of GCP training are to ensure the rights, safety, and well-being of human subjects are protected, clinical trials are conducted in accordance with approved plans with rigor and integrity, and the data derived from clinical trials are reliable.

Protection against potential risks regarding subject confidentiality:

While there is a minimal risk to participants of privacy breaches, researchers will take all possible steps to maintain privacy by separating participant-identifying information from participant data. Only REACT-AF study researchers will have access to all data stored in study databases, which will be password protected; user logins and passwords will be required. In addition, sites will have access to only the data from their center and will not have access to data from other centers.

To further ensure privacy protection, pseudonymized patient numbers are used in the secondary data management systems (VISION) to limit the disclosure of direct patient identifiers (name, address, phone number, etc.) to project team members. As required under Good Clinical Practice guidelines (E6r2 8.3.21), the clinical sites must maintain a "Patient Identification Code List" that maps the patient number in the EDC back to the actual patient identity. For this study, that mapping will be maintained securely in VISION EDC rather than on a paper form and exposed only to select project staff (e.g., study monitors) on a strict need-to-know basis. Any study data for uncontrolled case-level release outside of the project team (e.g., clinicalTrials.gov, BioLINCC data repositories) will require full and complete anonymization, which mandates there be no direct or indirect way (such as a site or sponsor decoding list) to map data back to ANY patient identifier. For non-summary data, this requires permanently destroying (replacing with random numbers, using offset days rather than dates) any patient name, site names/numbers, EDC patient numbers, procedure dates, and similar identifiers.

All hard copies of study records will be kept in dedicated office space with appropriately secure locked file cabinets. Electronic data will be collected on password protected online database developed and managed by the DCC. Individual participants will be identifiable only by a unique study number, which bears no relationship to personal identifiers. We will use a central IRB tasked with assuring informed consent and other protection procedures comply with the requirements of individual state privacy laws and HIPAA and the requirements of separate local IRBs.

12 BENEFITS

12.1 Potential Benefits

The REACT-AF trial represents a potential paradigm shift in the treatment of AF. Individuals with AF have historically had two major options for stroke prevention; daily anticoagulation, which reduces stroke risk but exposes the individual to bleeding events, or no anticoagulation treatment, which minimizes bleeds but exposes the individual to the risk of stroke. If positive, this trial will offer a third option of personalized, targeted anticoagulation therapy taken only during a period of time when stroke risk is highest. This strategy may reduce bleeding events while still maintaining protection against stroke and may favorably affect the lives of millions of patients with AF worldwide. Thus, all participants will be contributing to medical science in a manner that will directly impact their treatment in the not-too-distant future.

For research participants, this randomized study offers a 50% chance of being randomized to the intervention arm, where anticoagulation is discontinued during long periods of sinus rhythm, albeit in a closely monitored setting. Individuals randomized to the intervention arm will also receive an AF-sensing smartwatch, another potential benefit. Patients randomized to the standard of care group will also be providing invaluable information to medical science, including our understanding of the relationship between AF and stroke. It will be emphasized to all participants that enrollment in clinical trials is generally associated with improved outcomes and that the results of this study will be immediately applicable to their own care. The risks to the study subjects are reasonable because we are enrolling only those with low- to moderate vascular risk factors

and a low burden of AF, a population in whom the current standard of care recommends chronic anticoagulation but in whom the risk of major bleeding events on therapy is expected to exceed the stroke risk without treatment.

12.2 Importance of the Knowledge to be Gained

The REACT-AF trial represents a novel, technology-guided application of low-cost, precision medicine to a serious and increasingly common problem in patients with AF. The study will focus on the growing population of AF patients with limited vascular risk factors and low-burden AF that still receive life-long anticoagulation by today's standard of care. Estimates show that the results of this study may apply to about half the AF population. By providing efficacious treatments targeted to patients only when they are at the highest risk for cardioembolic events while simultaneously minimizing the potential for bleeding, we intend to test a new treatment paradigm for this challenging aspect of AF management where efficacy is maximized while harm is minimized specifically for this low- to moderate-risk subgroup. There is clear clinical equipoise for testing the hypothesis that anticoagulation treatment for 30 days following a threshold (≥ 1 hour) AF event is sufficient, especially in light of the time-dependent benefits of these drugs, the uncertainty among physicians surrounding the need for lifelong anticoagulation in those with infrequent and short-lived AF episodes either spontaneously or as the result of a rhythm control intervention, and the strong desire of patients and their physicians to eliminate the need for continuous anticoagulation. In addition, this approach is likely to prove cost-effective in light of the drug's price and the cost of anticoagulation-related bleeding.

13 PAYMENT

13.1 Compensation for Participants

Participants will not be compensated for participating in this study. Patients randomized to the intervention arm will be provided with the AFSW free of charge and may keep the AFSW at the end of the study. Following enrollment, participants in both study arms will be followed virtually/remotely using the Eureka Research Platform, with all interactions via the Eureka mobile app on participants' iPhones. This will not require any in-person study-related visits, and clinic visits will only occur as per the standard of care for treating participants with AF and other stroke risk factors.

14 COSTS

14.1 Costs of Study Procedures to Participants

Direct Oral Anticoagulant (DOAC)

DOACs will be prescribed to patients according to the treating healthcare provider(s) according to labeling instructions. Participants will be required to cover the costs of their prescribed DOAC as per the standard of care.

External Cardiac Monitoring Patches

If needed, the study will provide external monitoring patches at no cost to the participant.

Study Device (AF-sensing smartwatch (AFSW))

The study will provide the AFSW study device at no cost to the participant. Participants may choose to use their device if they already own one, but the study will not compensate the participant if they choose to buy or use their own watch.

15 TRANSFER OF MATERIALS

Not Applicable- no biospecimens will be transferred for this study.

16 TRANSFER OF DATA

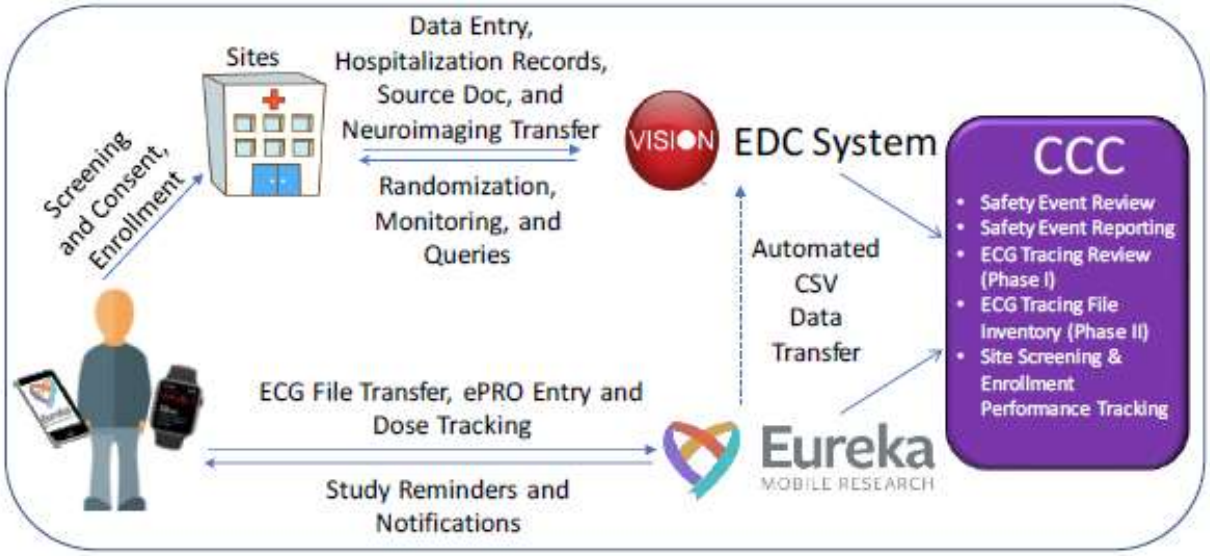

Figure 3: Electronic Systems and Data Flow

17 TRIAL ADMINISTRATIVE STRUCTURE

17.1 Overall Structure of the Study Teams

The REACT-AF trial brings three well-established research teams at Northwestern University (NU), Stanford University (SU), and Johns Hopkins University (JHU) into a new partnership.

Northwestern CCC Team

Dr. Passman, NU, is the Principal Investigator and Study Chairman, leads the Executive and Steering Committees, and directs the scientific and financial operations. The NU team will administer the trial overall, lead application development and integration, and administer the financial aspects of the trial, specifically subawards, service agreements, and reimbursements. Dr. Passman will serve as contact PI and will maintain communication among PIs and key personnel through quarterly and monthly meetings. He will be responsible for communication with NIH and submission of annual reports.

Stanford CCC Team

Drs. Marco Perez and Ken Mahaffey will manage site performance, adjudicate non-neurologic endpoints, review study Clinical Endpoints and MEOIs, and monitor safety. Under the direction of an operations manager and key operational leaders with experience in site management, Apple watch performance, safety surveillance, and regulatory compliance, the three teams will manage site performance, AFSW device distribution to sites, the collection and review of AEs and non-neurologic event adjudication. Using the DCC systems for data collection and reporting, SU will

provide safety data for DSMB reporting and periodic trial progress updates. Stanford staff assignments include interdependent liaison relationships with the JHU DCC team.

JHU DCC Team

The DCC, led by Dr. Dan Hanley, will be the vital center for trial data management, data systems, randomization, QA/QC reporting, analysis, and human participant and data protection. The DCC will facilitate the communications and interactions of the coordinating centers (Northwestern and Stanford) with secure methods of collecting trial information, performance information, and historical transcripts of meetings and actions into its databases and website. For DSMB meetings, the DCC will organize the chairs, NHLBI-appointed DSMB, committees, and other stakeholders, with the NHLBI's assistance. DCC staff assignments include interdependent liaison relationships with Stanford. The Brain Injury Outcomes [BIOS] Clinical Trial Coordinating Center is serving as the Coordinating Center for this single IRB study. The BIOS Coordinating Center has an IRB approved protocol that describes their roles and responsibilities [NA_00010432]. The coordinating center will follow this approved protocol for the coordinating center functions it performs for this study.

UCSF-Eureka Technology Center Team

The Technology Center Team, led by Dr. Jeffrey Olgin, will be responsible for developing and deploying the REACT Study on the Eureka platform. This will include coding surveys, reminder messages and study flows within Eureka. The team will also be responsible for working with Apple to ensure vital transfer from the Apple App to Eureka. The UCSF Team, via Eureka, will also be responsible for working with Apple and the EC to develop strategy for the messaging around the intervention group (ie. to take DOAC when AFib is detected) within the Eureka app and platform. The UCSF Eureka team will provide a mechanism for the DCC to obtain/export data and reports from the Eureka system. The UCSF Eureka team will train the DCC and CCC on how to use the study admin portal and will provide technical assistance to the DCC and CCC to ensure that sites are adequately trained.

DCC Management Plan

The DCC activities to support the REACT-AF program require integrated data coordination across four domains (teams): 1) trial statistics (analysis and reporting team); 2) data management team; 3) clinical affairs team; 4) operations team. The DCC physically resides at Johns Hopkins and is part of the Trial Innovation Network (TIN). As contact PI, Dr. Hanley will take overall responsibility for the DCC activities and for coordinating the DCC activities with our NU and SU partners. Study-specific DCC SOPs will be developed to govern the DCC's overall function. The four DCC teams require seamless integration of activities, and the three PIs, Drs. Hanley, Yenokyan, and Thompson will ensure this is accomplished. Thus, the REACT-AF trial will be able to take advantage of the innovations and collective experience developed by the JHU Trial Innovation Center as part of the NCATS Trial Innovation Network. The PIs of the DCC, each with decades of experience, and a decade working together, will work synergistically with one other, performing complementary tasks in this manner, while each has a full understanding of overall DCC tasks.

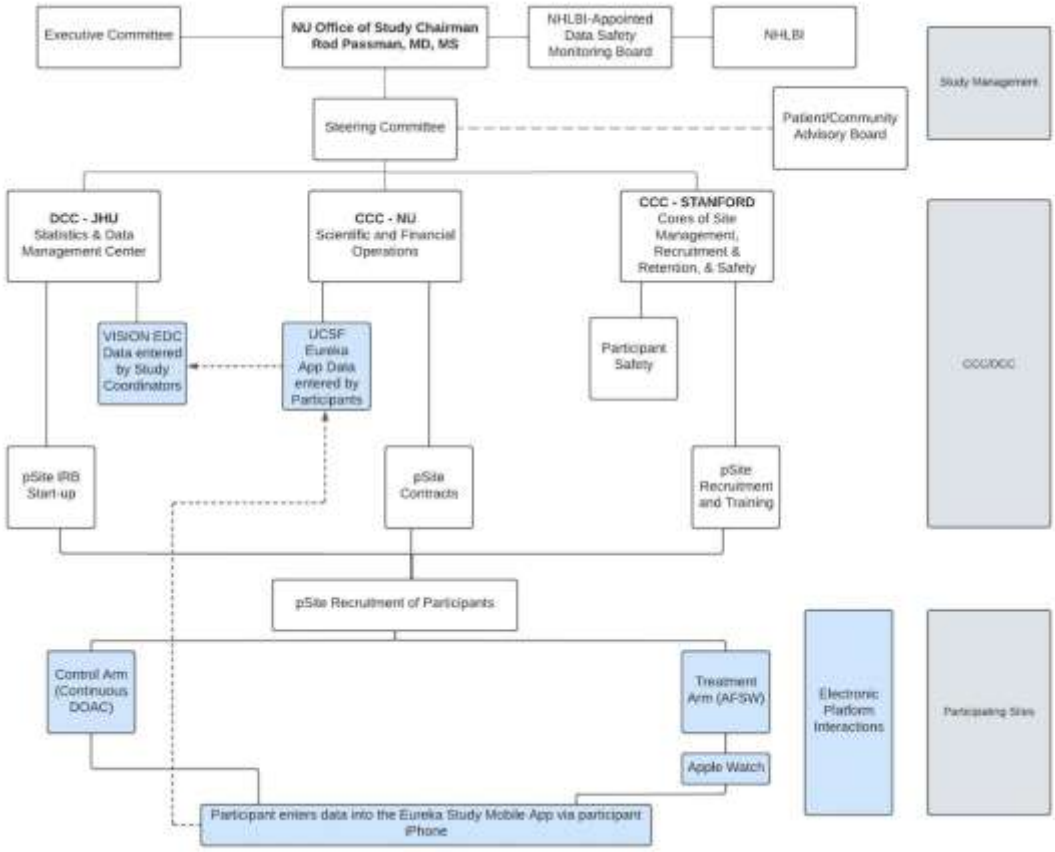

Figure 4: Study Management and Organization

17.2 Committees

Committees will provide leadership and oversight for the REACT-AF Trial. Each committee will consist of leadership from the three centers and members representing the enrolling sites. CCC/DCC faculty and staff will support and serve on each of the committees. Committee service will be done without any payment or compensation; service is voluntary.

Executive Committee (EC):

Working out of the Office of the Study Chairman at Northwestern University, Dr. Passman will provide the overall project management, organizational leadership, and fiduciary/budgetary controls. The JHU DCC will provide single IRB support and statistical leadership and oversee the data center. The DCC will also merge innovative practices with time-sensitive managerial stewardship of the trial. Stanford University will provide collaborative oversight of enrolling center performance, creative recruitment and retention innovations (coordinating with the recruitment and retention team and the call center), and a complementary expertise pool for monitoring safety events. As PI and Study Chairman, Dr. Passman will lead the Executive Committee (EC). The NHLBI Program Director shall be an ex-officio member of the EC. Should the need arise, Dr. Hanley (DCC PI) will chair meetings in Dr. Passman's absence.

The REACT-AF EC will review the trial strategy and process and monitor the trial's progress on a semiannual basis. The Executive Committee will meet in person in Chicago or using Web or teleconference modalities when necessary. In addition to the semi-annual, in-person meetings, the EC members will be charged with monthly agenda-driven, one-hour teleconferences for operational decisions that require more expeditious action or complex implementation than can

be achieved through the semi-annual EC meetings or the quarterly meetings of the Steering Committee.

Steering Committee:
The major leadership mechanism will be the REACT-AF Steering Committee (SC). The core group includes the EC, elected collaborating center investigators, and the DCC statistical leadership. The SC members have extensive clinical trial experience in the domains of digital health, stroke, anticoagulation, and AF. The Steering Committee will provide the framework for overseeing the CCC/DCC operations and coordinating management issues that cut across the centers. The SC will maintain four subcommittees: Administrative (finance, logistics), Adjudication, Application Development, and Innovations. A Publications Committee will be added in Year 2. The subcommittees will coordinate the activities mandated by the SC membership. The SC and subcommittees will include CCC and DCC faculty and staff. The SC will meet quarterly via Web or teleconferencing and/or at annual meetings. The NHLBI Program Director shall be an ex-officio member of the Steering Committee.

17.3 Data and Safety Monitoring Board (DSMB)

This study will utilize a DSMB organized by the NIH. Given its responsibility for the data management system, Hopkins will compile the DSMB reports according to a DSMB-approved template. The DCC lead statistician and staff will support data compilation and advise the study Executive Committee while remaining blinded to treatment assignment. A DCC unblinded statistician will provide consultative outcomes support to the DSMB, compiling the data for the unblinded report according to the approved template. In accordance with the charter approved by the DSMB prior to the start of patient enrollment, the DSMB will be responsible for monitoring patient safety and that there are no unexpected, study-related SAEs or medical problems that put patients at higher risk. This would include any operational issues such as issues related to patient confidentiality or well-being, inadequate data integrity, insufficient quality controls, or similar untoward situations that jeopardize participants, stakeholder reputations, or the success of the trial.

18 PUBLICATION OF RESEARCH FINDINGS

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results/information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. The results must be made public within 24 months of the end of data collection.

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. Any presentation, abstract, or manuscript will be made available for review by the NIH prior to submission.

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20 APPENDICES

20.1 Appendix A: Definition of Select Study- Related Significant Adverse Events

Definition of Cardiovascular Death

Cardiovascular death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

Classifying CV mortality more specifically (MI, sudden death etc.) is usually not needed for outcome trials. Moreover, such classification is difficult because the classifications refer both to underlying cause (e.g., acute MI, which can cause fatal arrhythmias or HF) and to mode of death (sudden/arrhythmic; HF, which can result from an MI or worsening HF), and they overlap substantially. The following definitions can, however, be used if desired.

1. **Death due to Acute Myocardial Infarction** refers to a death by any CV mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days[1] after a MI, related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. We note that there may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs ≤ 30 days of the MI, it will be considered a death due to MI.

   Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI (see Appendix 6) or by autopsy findings showing recent MI or recent coronary thrombosis.

   Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI.

   Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. **Sudden Cardiac Death** refers to a death that occurs unexpectedly and not within 30 days of an acute MI. Sudden cardiac death includes the following scenarios:

   a. Death witnessed and occurring without new or worsening symptoms

   b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI

[1]The 30 day cut-off is arbitrary.

c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)

d. Death after unsuccessful resuscitation from cardiac arrest (e.g., implantable cardioverter defibrillator (ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest)

e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology

f. Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

- Unless additional information suggests an alternate specific cause of death (e.g., Death due to Other Cardiovascular Causes), if a patient is seen alive ≤ 24 hours of being found dead, sudden cardiac death (criterion 2f) should be recorded. For patients who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (e.g., a subject found dead in bed, but who had not been seen by family for > 24 hours).

3. **Death due to Heart Failure** refers to a death in association with clinically worsening symptoms and/or signs of HF regardless of HF etiology (see Appendix 9). Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

4. **Death due to Stroke** refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke (see Appendix 8).

5. **Death due to Cardiovascular Procedures** refers to death caused by the immediate complications of a cardiac procedure.

6. **Death due to Cardiovascular Hemorrhage** refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (e.g., subdural hematoma) (see Appendix 8), non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. **Death due to Other Cardiovascular Causes** refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

Non-cardiovascular death is defined as any death with a specific cause that is not thought to be CV in nature, as listed in Appendix 3. Detailed recommendations on the classification of non-CV causes of death are beyond the scope of this document. The level of detail required and the optimum classification will depend on the nature of the study population and the anticipated number and type of non-CV deaths. Any specific anticipated safety concern should be included as a separate cause of death. The following is a suggested list of non-CV causes of death:

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory (e.g., Systemic Inflammatory Response Syndrome (SIRS) / Immune (including autoimmune) (may include anaphylaxis from environmental (e.g., food allergies))
- Hemorrhage that is neither CV bleeding or a stroke (see Appendix 3, Section 6, and Appendix 8)
- Non-CV procedure or surgery
- Trauma (includes homicide)
- Suicide
- Non-prescription drug reaction or overdose
- Prescription drug reaction or overdose (may include anaphylaxis)
- Neurological (non-CV) (excludes CV death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke or CV hemorrhage of central nervous system)
- Malignancy (e.g., leukemia, lymphoma, or other malignancy)
- Other non-CV, specify: _____

Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is “patient died”) or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few patients in well-run clinical trials.

A common analytic approach for cause of death analyses is to assume that all undetermined cases are included in the CV category (e.g., presumed CV death, specifically “death due to other CV causes”). Nevertheless, the appropriate classification and analysis of undetermined causes of death depends on the population, the intervention under investigation, the duration of follow-up, and the disease process (presuming CV death does not seem appropriate, for example, for people with late stage cancer, advanced pulmonary disease, long-standing infections, etc.). The approach should be prespecified and described in the protocol and other trial documentation such as the endpoint adjudication procedures and/or the statistical analysis plan.

Definition of Myocardial Infarction

Please also see the 2012 Third Universal Definition of Myocardial Infarction.

1. General Considerations
   The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

   In general, the diagnosis of MI requires the combination of:

   - Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
   - Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

   The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

2. Criteria for Myocardial Infarction
   a. Clinical Presentation
      The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with chronic or transient elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, HF, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

   b. Biomarker Elevations
      For cardiac biomarkers, the 99th percentile of the upper reference limit (URL) should be used. The URL is determined by the manufacturer of the assay and can be determined by an individual hospital that has studied a normal reference population. Because hospitals may use different URLs for the identical assay without studying a normal reference population and for reasons not evident to a Clinical Events Committee (CEC), variability in MI reporting due to the URL for specific assays may be reduced by using the manufacturer's recommended 99th percentile or a core biochemistry laboratory. An alternate approach would be to use the local laboratory value, but this may be less satisfactory if the local laboratory did not study a normal reference population.

      Cardiac troponins are the preferred biomarker to diagnose MI. If cTn values are not available, then CK-MB mass should be used.

For types 4a and 5 MI events, different biomarker elevations for cTn and CK-MB are required. The specific criteria will be referenced to the URL.

In many studies, particularly those in which patients present acutely to hospitals which are not participating sites, it is not practical to stipulate the use of a single biomarker or assay, and the locally available results will need to be used as the basis for adjudication unless the assay type can be determined. However, if possible, using the same cardiac biomarker assay and preferably, a core laboratory, for all measurements reduces inter-assay variability.

Since the prognostic significance of different types of myocardial infarctions (e.g., periprocedural MI versus spontaneous MI) may be different, MI subtypes should be reported separately, in addition to total number of MI events. Reporting the ratio of peak biomarker value observed/URL should be considered to provide a rough estimate of MI size.

c. Electrocardiogram (ECG) Changes
Electrocardiographic changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

- ECG manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):
  - ST elevation
    New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.

  - ST depression and T-wave changes
    New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or new T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1.

  The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- Criteria for pathological Q-wave

  - Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  - Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, and aVF)[a]

[a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal

plane lead grouping.

- ECG changes associated with prior myocardial infarction
  - Pathological Q-waves, as defined above
  - R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect
- Criteria for prior myocardial infarction (e.g., silent MI)
  Any one of the following criteria meets the diagnosis for prior MI:

  - Pathological Q waves with or without symptoms in the absence of non-ischemic causes
  - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
  - Pathological findings of a prior MI

may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- Criteria for pathological Q-wave
  - Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  - Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, and aVF)[a]

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  - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
  - Pathological findings of a prior MI

Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.