Hybrid Ablation Plus Medical Therapy for Persistent Atrial Fibrillation (HYBRID-AF)

ClinicalTrials.gov ID: **NCT04190186**

March 03, 2025

Statistical Analysis Plan for the HYBRID-AF Trial

1. Introduction This Statistical Analysis Plan (SAP) outlines the planned statistical analyses for the HYBRID-AF Trial, which has concluded.

2. Study Objectives The HYBRID-AF Trial evaluates the effectiveness of Biotronik ICM-guided intervention in reducing atrial fibrillation (AF) burden in patients with symptomatic persistent AF post-ablation. The primary objective is to compare AF burden between months 3 and 15 post-ablation between the Biotronik ICM-guided arm and the conventional AF management arm.

3. Study Design

- Randomized, controlled trial with 90 subjects assigned 1:1 to either conventional AF management or Biotronik ICM-guided management.
- Follow-up assessments at 3, 6, 9, 12, and 15 months post-randomization.
- Primary and secondary endpoints will be analyzed according to the intent-to-treat (ITT) principle.

4. Endpoints

Primary Endpoint:

- AF burden, defined as the percentage of time a subject experiences AF between months 3 and 15 post-ablation, measured by the Biotronik ICM.

Secondary Endpoints:

1. Composite endpoint of:
    - Clinically significant (>30 min) atrial arrhythmia (AF, atrial flutter, or atrial tachycardia) detected by Biotronik ICM post-index ablation.
    - Symptomatic AF recurrence (any duration).
    - Repeat AF ablation.
    - Cardiac hospitalization.
    - Death.
    - Healthcare utilization (hospitalization, ED visits, unplanned office visits).
2. Incidence of atrial flutter or tachycardia post-ablation.
3. Incidence of repeat procedures.
4. Major adverse events requiring rehospitalization.
5. Quality of life (QOL) assessment.

5. Sample Size Justification Based on prior studies and preliminary data, AF burden is expected to be 25% in the conventional group and 16% in the intervention group, with a standard deviation of 15%. A Wilcoxon rank-sum test at a two-sided alpha level of 0.05 and 80% power determined that 90 subjects (with a 10% dropout rate) were required.

6. Statistical Methods

Primary Analysis:

- AF burden comparison between groups using the Wilcoxon rank-sum test.
- Descriptive statistics for median and interquartile range (IQR) of AF burden.
- Sensitivity analysis for missing data using multiple imputation.

Secondary Analyses:

- Kaplan-Meier survival analysis for time to first atrial arrhythmia event.
- Cox proportional hazards regression for risk factors associated with AF recurrence.
- Poisson regression for healthcare utilization.
- Mixed-effects models for QOL changes over time.

Subgroup Analyses:

- Stratification by baseline AF burden, age, and sex.
- Sensitivity analysis excluding early dropout subjects.

7. Data Handling

- All analyses will follow an ITT approach.
- Missing data will be addressed using multiple imputation and sensitivity analyses.
- Data management will be conducted per Good Clinical Practice (GCP) guidelines.

8. Reporting and Interpretation

- All results will be reported with 95% confidence intervals and p-values.
- Statistical significance is defined as $p<0.05$.
- Study findings will be presented in accordance with CONSORT guidelines.

9. Conclusion This SAP ensures rigorous and transparent statistical analyses for the HYBRID-AF Trial, aligning with ClinicalTrials.gov reporting requirements.

Hybrid Ablation Plus Medical Therapy for Persistent Atrial Fibrillation

Lead Principal Investigator: David T. Huang, MD

1. PURPOSE OF STUDY

To prospectively investigate the efficacy of an insertable cardiac monitor-guided atrial fibrillation (AF) management in reducing subsequent atrial arrhythmia burden in patients with persistent AF undergoing ablation. This is a Phase 4 study, and we are comparing two management strategies that are currently employed in clinical practice.

2. BACKGROUND AND RATIONALE

Percutaneous catheter ablation to achieve pulmonary vein electrical isolation is an effective and recommended treatment for paroxysmal atrial fibrillation. Catheter ablation for persistent AF is more complex, often may involve ablation of additional targets that maintain AF. Nevertheless, recurrence rate after a single ablation procedure in patients with persistent AF is in the range of 50%-70% at 1-year, and 70%-90% at 2-years. Accordingly, catheter ablation for persistent AF has been associated with less favorable outcomes. Continued antiarrhythmic drug (AAD) use, or redo AF ablation procedures often can improve outcomes in persistent AF patient's further substrate deterioration if sub-clinical AF recurrences are detected by an insertable cardiac monitor. Thereby, we propose utilizing the Biotronik ICM (BioMonitor3® or future generation of Biotronik ICM) in persistent AF patients following AF ablation to guide post ablation strategies of AAD treatment and/or repeat AF ablation and to continuously post-AF ablation to reduce the burden of atrial arrhythmia. However, these management strategies are currently limited to a subset of patients who present with symptomatic AF post-AF ablation, possibly late in the clinical course, due to lack of appropriate continuous monitoring tools following the procedure. With the Biotronik insertable cardiac monitor (ICM) in persistent AF patient's post-AF ablation, one may be able to provide patient-specific tailored management, and to identify those who may benefit from early intervention to prevent monitor AF burden. We hypothesize that early patient-specific intervention, guided by the Biotronik ICM, will be associated with a significant reduction in AF-burden at 15 months following ablation for persistent AF.
Of note contemporary referral for ablation among patients with persistent AF does not require failure of at least one AAD. Recent clinical trials have demonstrated the utility of ablation as first line therapy for patients with atrial fibrillation. Therefore, many patients with persistent AF are referred for AF ablation today without being on an AAD (Calkins, et al. Heart Rhythm, Vol 14, No 10, October 2017), thereby leading to higher recurrence rates in this population.

Patients with persistent atrial fibrillation remain a challenging population in terms of achieving and maintaining sinus rhythm. Recent studies (Heart Rhythm. 2018 Mar; 15(3):363-368) have reported pulmonary vein isolation ablation to be a "safe, effective, and efficient" treatment. However, even with extensive ablation of PV isolation plus other targets, the recurrence of atrial arrhythmia post ablation for persistent AF ranged from at

least 41 to 54% with periodic ambulatory ECG monitors (Schreiber, et al. Circ Arrhythm Electrophysiol 2015; 8:308–317.; Verma, et al. N Engl J Med 2015; 372:1812–1822.). Most clinicians suspect the recurrence rates to be substantially higher if more robust surveillance is obtained. We had previously reported on the efficacy of hybrid therapy combining ablation of atrial flutter circuit and medical therapy for patients with atrial fibrillation who converted to atrial flutter with medical antiarrhythmics (Huang, et al., JCE May 1998, 9(5):462-469), and noted the importance of maintaining medical antiarrhythmic therapy to achieve long term substrate modification leading to sinus rhythm. A recent study reported >90% patients who experience AF events during the typical 3 months blanking period actually develop recurrent atrial arrhythmia by 1 year (Willems et al. Circ Arrhythm Electrophysiol 2016;9(8). Early recurrence of AF during the post ablation blanking period may be more aggressively treated to help reduce risk of late recurrence of AF. Therefore, in our study, we propose to initiate monitoring AF events during the blanking period, starting from the first month post-AF ablation (to allow sufficient time for post ablation healing). On the other hand, it is postulated that a subgroup of patients with persistent AF may respond well to repeat ablation alone, similar to patients with paroxysmal AF (Kirchhof, Calkins. European Heart Journal, 2017 Jan; 38(1):20–2). Thus, a management strategy of uniform continued AAD post ablation for persistent AF will result in unnecessary medical therapy in responders to the procedure. We therefore hypothesize that a patient-specific management strategy that incorporates continuous monitoring with Biotronik ICM will result in improved outcomes and resource utilization compared to conventional management in this high-risk population.

3. ADMINISTRATIVE ORGANIZATION

The University of Rochester is the Coordination and Data Center (CDC) for the multisite study. The University of Rochester Medical Center, Rochester Regional Health, Michigan Heart and the Cardiology Research Associates will be the participating centers in this trial. Each site will obtain separate local IRB approvals. The University of Rochester CDC will provide each site with the study protocol and a model consent form, along other relevant subject study materials. As the Coordination and Data Center (CDC), the University of Rochester will provide comprehensive training on the study protocol, study operations, and the electronic data capture system (TrialMaster). All training will be documented for each enrolling site.

The University of Rochester is the Study Sponsor and is receiving funding from BIOTRONIK for conducting this research study.

4. STUDY DESIGN

This is a multi-site, randomized clinical trial of approximately 90 subjects with 45 subjects in each arm randomized (1:1) to conventional AF management vs. Biotronik ICM-guided AF management following ablation for persistent AF. The study subject population will include subjects with history of persistent atrial fibrillation (sustained AF episode lasting more than 7 days, but less than 1 year), according to current guideline indications for persistent AF ablation and ICM (Biotronik ICM) implantation. Clinical and functional data will be

captured related to: activity, heart rate, blood pressure, weight, quality of life status, and clinical events.

A total of 4 high-volume sites will be enrolling subjects for this study. Estimated enrollment will be 1-2 subjects per study site per month. Patients will be enrolled at the time of the AF ablation and will be followed for 15 months after a 3 month blanking period following AF ablation. The planned study startup period is 3 months with an enrollment period of 10 months, a follow-up period of 15 months, and 2 months for closeout and analysis for a total of 30 months (2.5 years).

The CDC is responsible for data management, analysis, and coordination of logistics. The enrolling sites will manage all subject recruitment activity and data collection per protocol as well as interact with the CDC and enrolling site study team regarding study operations. The CDC will be responsible for overall study management, data management, data reporting, and center communications for the study.

Primary Endpoint

The primary endpoint is atrial fibrillation (AF) burden between months 3 and 15 after the ablation procedure (to exclude the first 3 month blanking period) by the Biotronik ICM in the conventional AF management versus the of Biotronik ICM-guided AF management arm.

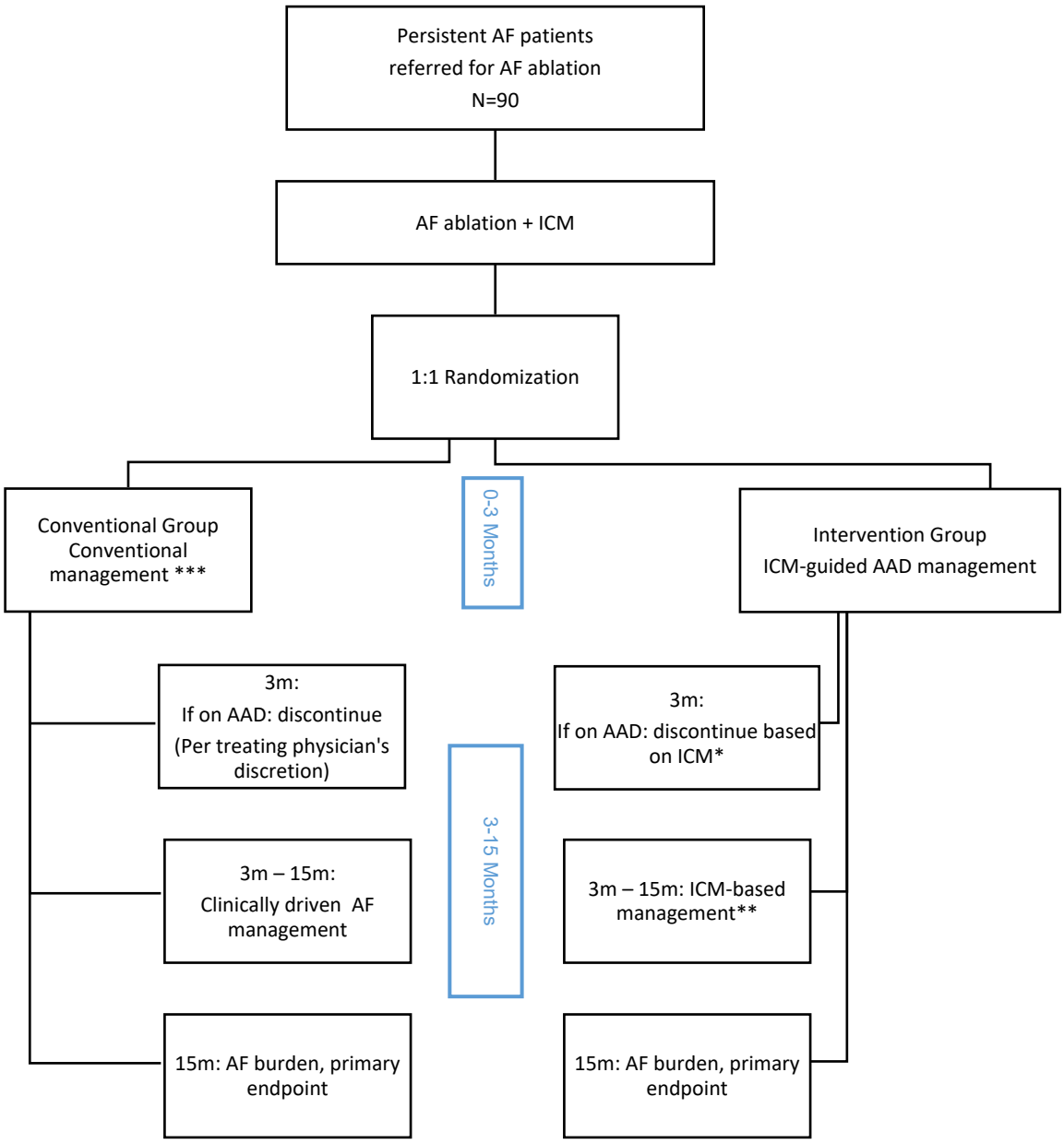
Secondary Endpoints

1. Composite end point of:
    - clinically significant (>30 min) atrial arrhythmia (atrial fibrillation, atrial flutter or atrial tachycardia) as detected and documented by Biotronik ICM after the performance of the index AF ablation procedure (excluding the initial 3-month blanking period), or
    - symptomatic AF recurrence (regardless of duration), or
    - repeat AF ablation, or
    - cardiac hospitalization, or
    - death
    - healthcare utilization, defined as hospitalization for any cause, ED visits, and unplanned office visits

For the primary outcome, no episode of AF occurring within the initial 3-month blanking period after ablation will be counted, although these will be tracked.

2. Incidence of atrial flutter or tachycardia after the index ablation procedure
3. Incidence of repeat procedures
4. Major adverse events requiring rehospitalization during follow-up
5. Quality of life (QOL) as assessed by Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) questionnaire

Figure 1: Study Design



* Based on Biotronik ICM data after 1st Month
** Escalate to medical therapy or repeat AF Ablation based on current treatment (i.e. no treatment will be escalated to the AAD or repeat ablation, and if on AAD will be escalated to AF ablation).
*** Biotronik ICM data on subclinical AF will not be provided to the treating physician

As detailed in Figure 1 subjects who agree to participate in the study by signing the IRB-approved informed consent are randomized 1:1 into:

The Intervention ICM-based AF management Arm

- In the intervention arm, the ICM obtained data will be actively used to guide and monitor treatment (See Figure 2A and B). A report of AF data (comprising the total number of episodes, duration, average heart rate response, and correlation with patient-reported symptoms) will be provided to the treating physician/nurse at monthly intervals, starting from the first month post-AF ablation from the study team comprised of electrophysiologists and cardiologists. A general recommendation for early intervention with AAD continuation/resumption or redo AF ablation will be provided to the treating physician if recurrent AF episodes are detected by the ICM (≥2 episodes at a duration of ≥ 6 minutes each), even without the presence of clinical symptoms. However, the final decision regarding management will be left to the discretion of the treating physician.

    - Management during the blanking period: Treatment with AAD after ablation will be left to the discretion of the treating physician per standard of care. If the patient is on an AAD after ablation, medical therapy with AADs in the intervention arm will continue for 3 months after the index CA procedure arm. Symptomatic AF recurrences during the blanking period will be treated with cardioversion. If, either SCAF (as defined above and in Figure 2A) is detected by the ICM or symptomatic AF recurrence occurs after one-month post-ablation (i.e. during the second or third months), AAD therapy will not be discontinued at 3 months per protocol (or will be initiated for those not treated with an AAD after ablation). AF recurrence during the blanking period will not be an indication for re-ablation.

    - Management after the blanking period: If SCAF recurrences detected by the ICM (as defined above and in Figure 2B) or if clinical recurrence occurs after the blanking period, treatment will be escalated as follows:

        - If the patient is not on an AAD after the blanking period, treatment with an AAD will be resumed (to the same drug discontinued at 3 months) or initiated (type of AAD will be left to the decision of the treating physician as per standard of care). Alternatively, if the patient does not tolerate or does not wish treatment with an AAD, the patient can be referred for repeat AF ablation.

        - If AF recurrence occurs on AAD, the e patient will be referred for re-ablation.

        - The ICM-derived heart rate monitoring data will also be used for improved rate control (with a target mean heart rate of <80-100 bpm) regardless of atrial rhythm.

- An ad hoc adjudication committee will be formed to review and review all ICM interrogations. The committee will consist of Drs. Goldenberg, Kutyifa, Zareba, and Aktas. The final adjudication of each arrhythmic event will be captured in the study database for the analysis of study endpoints and will not be used to guide management.

- The ICM report of AF data (comprising the total number of episodes, duration, average heart rate response, and correlation with subject-reported symptoms) will be provided to the treating physician/nurse at monthly intervals, starting from the first month post-AF ablation.
- In-clinic follow up visits as scheduled for subjects per standard of care and will occur at 3, 9, and 15 months. These visits will include a medical assessment and subjects will be questioned about clinical and unexpected medical (adverse) events.
- Phone follow-up visits will be conducted by the study team at 6 and 12 months as part of the study. The study team will perform a medical assessment, and ask questions about medication changes, along with clinical and unexpected medical (adverse) events as part of these follow-up phone calls.
- Chart reviews will be performed by the study team at each time point and include data about clinical history, medications, ablation procedure, device implantation, and follow-up data will be collected from the medical record.
- Quality of life questionnaire will be completed on paper by the patient at baseline and 15 months as part of the research study activities.
- ECGs performed as standard of care at Baseline, 3 month, 9 month, and 15 month.
- Endpoint assessment defined as AF burden, quality of life, and healthcare utilization (comprising the total of unplanned clinic visits, hospitalizations, repeat ablations, or death at 15 months.

Figure 2A: Management protocol for AF recurrence at Months 2 or 3 Post Ablation in the Intervention Arm*

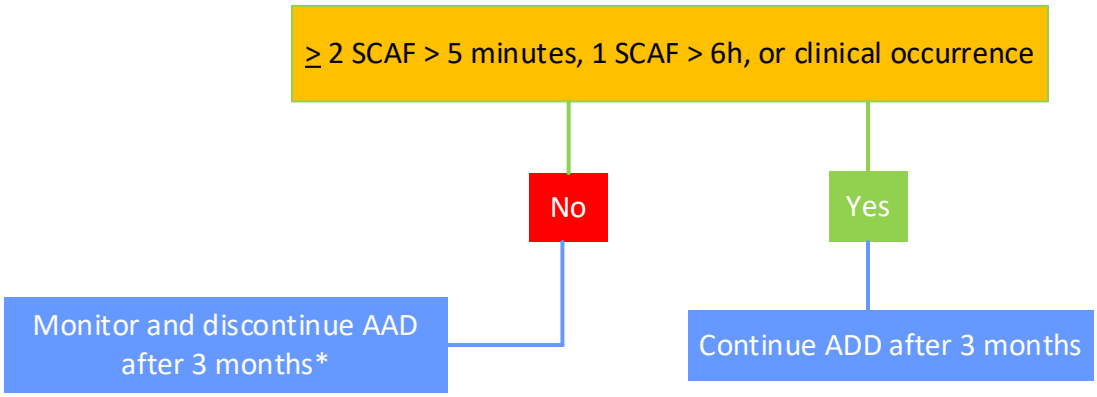
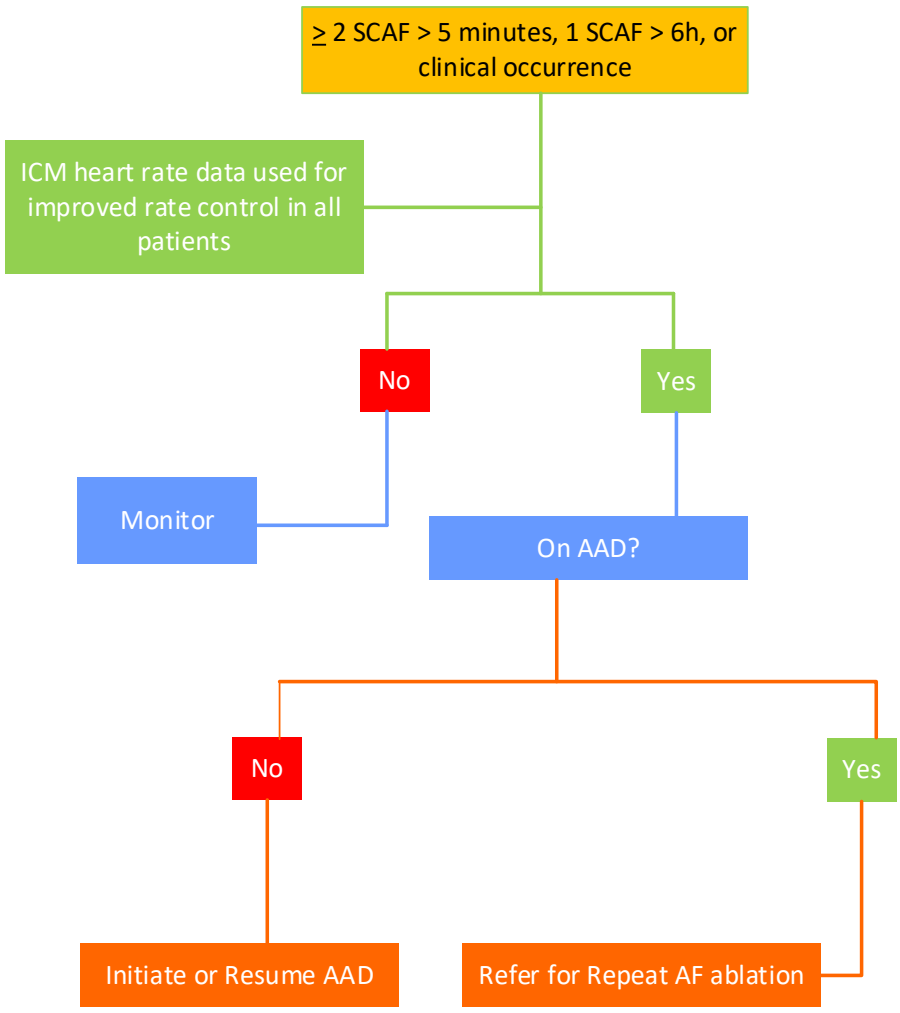


Figure 2B: Management Protocol for AF Recurrence after 3 Post Ablation in the Intervention Arm



***If the patient is not on an AAD after the ablation, AAD will be initiated during the blanking period and continued post-blanking if there is >=2 SCAF, 1 SCAF >6h or clinical recurrence. The type of AAD will left to the discretion of the treating physician as per standard of care. Repeat ablation can be offered if the patient does not tolerate or wish treatment with an AAD.**

Conventional AF Management Control Arm

- In the control arm, ICM data on SCAF recurrence will not be used to guide management. Management of clinical AF recurrence in the conventional management arm will be left to the discretion of the treating physician. The treating physician has access to all ICM data as standard of care and can use it per their discretion.

    - Management during the blanking period (ER): AAD management in the conventional arm, will be left to the discretion of the treating physician since

current guidelines do not provide specific recommendations (ref). Symptomatic AF recurrences during the blanking period will be treated with cardioversion and SCAF detected by the ICM will not drive management.

- Management after the blanking period (LR): If the patient was on medical therapy with an AAD, it will be discontinued after 3 months in the conventional arm, unless considered necessary by the treating physician. SCAF detected by the ICM will not drive management.

- Patients will attend scheduled in-clinic follow up visits at month 3, 9, and 15 as part of standard of care. These visits will include a medical assessment and questions about clinical and adverse events.
- Chart reviews will be performed by the study team at each time point and include data about clinical history, medications, ablation procedure device implantation, and follow-up data will be collected from medical record.
- Quality of life questionnaire complete on paper by the patient at baseline and 15 months as part of the research study activities.
- Phone follow-up visits will be conducted by the study team at 6 and 12 months. The study team will perform a medical assessment, and ask questions about medication changes, along with clinical and unexpected medical (adverse) events as part of these follow-up phone calls.
- ECGs performed as standard of care at Baseline, 3 months, 9 months, and 15 month.
- Endpoint assessment defined as AF burden, quality of life, unplanned clinic visits or hospitalizations, repeat ablation, death at 15 months.

4.1 SUBJECT POPULATION

The study population will include subjects with persistent atrial fibrillation (sustained AF episode lasting more than 7 days, but less than 1 year), according to current guideline indications for persistent AF ablation.

Approximately 90 subjects will be enrolled in this study following a 1:1 ratio (intervention: conventional). A total of 4 high-volume sites will be enrolling subjects for this study. Estimated enrollment will be 1-2 subject per study site per month. Patients will be randomized following AF ablation and ICM implant and will be followed for 12 months after a 3 month blanking period.

Gender and Age

Male and female subjects 18 years or older will be. We expect to enroll about 25% women.

Racial and Ethnic Origin

There are no restrictions on race or ethnicity in this study. We expect to enroll about 25% minority subjects.

Inclusion of Vulnerable Populations:

Vulnerable populations: Women of childbearing potential are included if they are currently on the medications to be optimized.

4.2 STUDY INTERVENTIONS

Please see section 8 entitled study procedures that includes further study interventions.

Devices
This study is not studying devices but will utilize data already clinically used and available from the Biotronik ICM. Before or at the time of ablation for persistent AF, all subjects will be implanted with a Biotronik ICM. The Biotronik ICM is FDA approved and will be used per the current FDA indications and is used as standard of care to monitor arrhythmias following AF ablation.

5. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

- 18 years of age or older
- History of persistent atrial fibrillation (sustained AF episode lasting more than 7 days, but less than a year)
- Planned to undergo **first** AF ablation with successful Biotronik ICM implant before or at time of ablation

Exclusion criteria

- Paroxysmal atrial fibrillation
- Long persistent atrial fibrillation (continuous atrial fibrillation that lasts more than 1 year)
- Permanent atrial fibrillation
- Left atrial diameter of 60 mm or greater
- Patients with CHF status prohibiting EP study and ablation, but may be re-considered for enrollment later after effective treatment
- Patients with metabolic derangements (e.g. renal/hepatic failure, electrolyte disturbance, etc.), prohibiting EP study and ablation or antiarrhythmic medical therapy (e.g. dofetilide, sotalol or amiodarone, etc.)
- Patients with an intra-cardiac thrombus, but may be re-considered for enrollment later after effective treatment
- Serious known concomitant disease with a life expectancy of < 1 year
- Pregnancy or nursing
- Unwilling or unable to give informed consent
- Existing CIED such as pacemaker or ICD

6. RECRUITMENT METHODS

Subjects will be recruited from ongoing local referrals of patients with persistent atrial fibrillation (sustained AF episode lasting more than 7 days, but less than 1 year), , according to current guideline indications for persistent AF ablation.

Each enrolling site will follow their specific guidelines to determine patient eligibility for this clinical trial. If the patient meets inclusion/exclusion criteria, the study team will approach potential subjects for participation in the study based on the policies of each enrolling site.

7. CONSENT PROCESS

A model consent document as well as the study protocol will be provided to each site to obtain local IRB approval. Revisions to the model consent require approval from the Coordinating Center prior to submission of the consent to the participating site IRB.

The informed consent process will be conducted by the Principal Investigator or individual authorized to conduct the process and will follow the local applicable laws, rules, regulations and guidelines. The consent document will be used as a guide for discussion with the potential subject. The potential subject will be given sufficient time to ask questions and to consider their participation. Refusal to participate or withdrawal from the study will not interfere with future medical treatment. All participants will receive a copy of their signed informed consent and the original will be maintained at the enrolling site. Subject recruitment at an enrolling site may not begin until local IRB-approval is obtained related to the study protocol and consent.

8. STUDY PROCEDURES

After signing the informed consent and undergoing ICM implant prior to or at time of the AF ablation as part of standard of care, subjects will undergo randomization and the following procedures:

12 lead ECG performed as standard of care.

- Quality of life (QOL) questionnaire will be completed by the patients as part of the research study on a paper form and entered into an electronic database by the research coordinator. The questionnaire should take the patient approximately ten minutes to complete.

- Chart Review: Data regarding clinical history, medications, ablation procedure, device implantation, and follow-up data will be collected from electronic medical records prior to in-clinic or follow up calls with the patients.

- In-Clinic Visits: Per standard of care, patients will attend scheduled follow up visits at 3, 9, and 15 months. The study team will perform a medical assessment, and ask questions about adverse events.

- Follow-Up Phone Calls: Patients will receive follow-up calls from the study team at 6 and 12 months. The study team will ask questions about medication changes and any unexpected medical (adverse) events as part of research.

Method of Assigning Subjects to Treatment

Subjects will be randomized 1:1 to conventional AF management vs. ICM-guided AF management following ablation for persistent AF. Randomization will occur electronically using the electronic data collection system. TrialMaster that is available 24/7 to all study personnel.

Follow-up Schedule (See also Figure 1 and Table 1)

Following enrollment and randomization to an intervention arm ICM-based AF management vs. conventional AF management, all subjects will have scheduled follow-up visits (clinic or phone) by the study team at quarterly intervals following randomization. ICM data will be collected electronically at monthly intervals.

All subjects will be followed for a time-period of 15 months.

The following data will be collected at these time-points:

Randomization/Baseline: Baseline clinical characteristics, existing echocardiographic measures, labs, QOL questionnaire, and NYHA class will be recorded.

- *Monthly:*
    - Conventional and Interventional arm
        - Obtain ICM data remotely
- *3-months ±14 days from randomization:*
    - Conventional
        - Office visit for clinical assessment
        - Clinical and adverse events
            - Discontinue AAD after 3 months following the AF ablation procedure per treating physician discretion
    - Interventional arm
        - Office visit for clinical assessment
        - Clinical and adverse events
            - Decision on discontinuation of AAD after 3 months based on AF recurrences between 1-3 months detected by the ICM
- *6-months - 7 days/+21 days from randomization:*
    - Conventional
        - Phone follow up for medications
        - Clinical and adverse events
        - Resumption of AAD or repeat AF ablation based on clinical AF recurrence

- Interventional arm
    - Phone follow up for medications
    - Clinical and adverse events
    - Decision on resuming AAD or repeat AF ablation based on AF recurrences detected by the ICM.

- *9-months - 7 days/+21 days from randomization:*
    - Conventional
        - Office visit for clinical assessment
        - Clinical and adverse events
        - Resumption of AAD, repeat AF ablation, or no change in management based on clinical AF recurrence

    - Interventional arm
        - Office visit for clinical assessment
        - Clinical and adverse events
        - Decision on resume AAD or repeat AF ablation based on AF recurrences detected by the ICM.
- *12-months - 7 days/+21 days from randomization:*
    - Conventional
        - Phone follow up for medications
        - Clinical and adverse events
        - Resumption of AAD or repeat AF ablation based on clinical AF recurrence

    - Interventional arm
        - Phone follow up for medications
        - Clinical and adverse events
        - Decision on resume AAD or repeat AF ablation based on AF recurrences detected by the ICM

- *15-months - 7 days/+21 days from randomization:*
    - Conventional
        - Office visit for clinical assessment
        - Clinical and adverse events
        - Resumption of AAD or repeat AF ablation based on clinical AF recurrence
        - QOL questionnaire

    - Interventional arm
        - Phone follow up for medications
        - Clinical and adverse events
        - Decision on resume AAD or repeat AF ablation based on AF recurrences detected by the ICM
        - QOL questionnaire

Table 1: Data Collection Timepoints

	Screen/ Consent/ Random-ization	**FOLLOW-UP**					
Timeline		Monthly intervals after random-ization	3 calendar months from random-ization ± 14 days	6 calendar months from random-ization - 7/+21 days	9 calendar months from random-ization - 7/+21 days	12 calendar months from random-ization - 7/+21 days	15 calendar months from random-ization - 7/+21 days
Eligibility Confirmation/ Randomization	√						
Demographics, PE, Medical Hx/NYHA	√						
12 lead ECG (SOC)	√		√		√		√
Echocardiogram (SOC)	√						
Labs (SOC)	√						
Vitals (SOC)	√			√		√	√
CV Medication	√		√	√	√	√	√
Quality of Life	√						√
ICM Implant (SOC)	√						
Ablation Procedure	√						
In-person Visit (SOC)/Clinical Events			√		√		√
Phone Follow-Up/ Clinical Events				√		√	
ICM Remote Monitoring (SOC)		√					
Adverse Event	√	√	√	√	√	√	√
Protocol Deviation	√	√	√	√	√	√	√

Plans for return of research results:

Research results will not be provided directly to patients, but will be presented in national conferences and published in peer-reviewed papers after study completion. If requested by patients, we will send the published research results to patients.

9. RISKS TO SUBJECTS

This is a prospective study in subjects with persistent AF undergoing ablation and ICM implant prior to randomization. The study is not evaluating any medical device. The study includes the use of a currently available ICM to investigate the efficacy of an insertable cardiac monitor-guided atrial fibrillation (AF) management in reducing subsequent atrial arrhythmia burden.

There is some risk of associated with the use of any medication. It is important to note that in this study, we are using standard of care and recommended guideline directed medications already indicated in this population of patients; which are often associated with improved outcomes. We are not testing new medications. Medications inherently may be associated with side effects. The clinical research team is experienced in cardiovascular trials and the clinical management of patients with heart disease/heart failure and will be monitoring for any adverse effects and adjust medications accordingly. This is a Phase 4 study, and we are comparing two management strategies that are currently employed in clinical practice.

The risk to participating in this study may include a potential risk of a breach in confidentiality. Every effort will be made to keep the data confidential. To protect against this risk the information collected at each enrolling site will be entered by site personnel into a password protected electronic data capture (EDC) system. Subjects will be assigned a unique subject identification number at the time of registration, which is completed in the EDC system. The subject identification number is not connected with any PHI, such as date of birth or medical record. Each enrolling site will maintain an internal key linking the subject's name with the study data and will not be shared with anyone outside of the enrolling site.

10. POTENTIAL BENEFITS TO SUBJECTS

There are no potential benefits to subjects.

11. COSTS FOR PARTICIPATION

There are no additional costs to the subject. All office visit/procedures follows standard of care guidelines.

12. PAYMENT FOR PARTICIPATION

Subjects will be reimbursed per the institutional policies for each enrolling site (e.g., cash,

check, gift card).

13. SUBJECT WITHDRAWALS

Subjects enrolled in the study may be withdrawn prior to the study completion for a variety of reasons including:

- Subject withdraws consent for any reason;
- Subject is lost to follow up despite best efforts to locate the subject;
- Subject is withdrawn at study investigator discretion.

Subjects may be considered lost to follow up after missing two consecutive follow-up visits with documented efforts to contact the subject.

These subjects will not undergo any additional study activities after withdrawal. If a subject becomes pregnant during the course of a study, they will continue to be monitored but no longer be part of the interventional arm. Data collection will occur until the date of withdrawal and utilized in the study analysis.

Patients who complete fewer than 3 months of follow-up and thus will not complete the blanking period will be excluded from primary end-point analysis, but will be included for all secondary end-points. Withdrawn subjects who have been randomized will not be replaced.

14. PRIVACY AND CONFIDENTIALITY OF SUBJECTS AND RESEARCH DATA

Data collected during this study will be obtained for research purposes and derived from study procedures, study ICM device, subject records and subject visits. All study data will be stored in a password-protected database located at the CCRC per Section 15 and de-identified. To protect confidentiality and privacy, subject data will be assigned a code using a unique subject ID number at the time of randomization and linked to subject identifiers that are stored separately in a study log solely maintained by the enrolling site study coordinator. The electronic data will be directly entered and extracted from computer system for data collection using encryption and physical controls. There is no plan to share, transmit or transfer the data.

15. DATA/SAMPLE STORAGE FOR FUTURE USE

Study coordination, database management and statistical analysis will be performed by the Clinical Cardiovascular Research Center (CCRC) at the University of Rochester Medical Center (U of R) acting as the Coordinating Center for the study.

Data will be captured using TrialMaster, a HIPAA compliant secure web-based electronic data capture (EDC) system that is used to support the clinical research process. Data that are entered are validated against a set of rules to ensure the accuracy of the clinical data. The TrialMaster system is housed on CCRC servers that are housed behind the U of R firewall in

the U of R Primary Data Center, where physical access and environmental controls are in place to protect the data. All access to the data is through an authentication process provided by the system and over the encrypted, secured U of R network, which both provide the necessary controls to prohibit unauthorized access to the clinical data. Continuous availability of the data is provided by mirroring the databases to servers located in a physically separate Secondary Data Center. Additional details are in the Data Safety Monitoring section below.

Only enrolling site personnel authorized by the site Principal Investigator will have access to the EDC system. Study personnel at each site delegated with EDC permission will be required to complete EDC training before receiving access to the system. Site personnel with EDC permission will have access to the system 24/7 for data entry. Study personnel will initially enter all data related to the randomization and baseline data collection and will then complete data entry after each identified data collection timeframe per Table 1.

Data collected may be used for the development of future research studies. We will maintain the confidentiality of the data throughout the process. Only authorized research personnel working on the project will have access to the data.

16. DATA AND SAFETY MONITORING PLAN

Adverse Event Data

An adverse event is any unexpected symptom, sign, illness, or experience that develops or worsens during the course of the study and is possibly or definitely related to study procedures. All protocol-defined adverse events will be collected after subject randomization at all subject contacts as indicated in Table 1. Adverse event data will be captured in the electronic data capture system and investigators are responsible for reporting to and following local Institutional Review Board (IRB) guidelines.

Adverse Event Reporting

Investigators shall report to their local IRB per local reporting guidelines, and report in the electronic data collection system within five business days of PI awareness only real or suspected, serious and unanticipated adverse events that are related to participation in the study. Events related to standard of care such as medications side effects do not need to be reported unless severe as defined below. Death of a subject must be reported as an adverse event, per the serious adverse event definition below. The PI is aware that investigators are responsible for reporting to and following the guidance of any other applicable oversight bodies, including the Institutional Review Broad (IRB).

The CDC will be forwarding relevant documents to the Chair of DSMB for review and the Chair will determine whether individual case will require immediate assessment by the full DSMB committee or it could be assessed during electively scheduled DSMB meeting. The main point of assessment by DSMB will be to judge whether given adverse event could be related to ablation.

Serious Adverse Event Definition

This population is at increased risk of heart failure, death, and poor clinical outcomes. A serious adverse event (SAE) is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in permanent impairment of a body structure or a body function;
- requires medical or surgical intervention to prevent permanent impairment or damage;
- leads to fetal distress, fetal death or a congenital abnormality or birth defect.

Data Safety Monitoring Board

A data and safety monitoring board (DSMB) will be convened to independently monitor the conduct and the outcomes of the trial. The DSMB will be responsible for monitoring the safety and well-being of the patients participating in this study and ensuring the ethical conduct of the trial. The DSMB will be responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study. The DSMB will be an independent group advisory to the study principal investigator and will be asked to provide recommendations about starting, continuing, and stopping the study. In addition, the DSMB is asked to make recommendations, as appropriate, about:

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

Data on clinical events including procedural complications, hospitalizations, stroke, atrial tachyarrhythmias, and death will also be collected by the study and provided to DSMB for evaluation of risks associated with ablation in the study participants.

The board will be comprised of 3 independent members: (1) 1 statistician with experience in clinical trials; (2) 1 cardiologist with expertise in clinical trials; and (3) 1 electrophysiologist with expertise in ablation.

The DSMB will meet before trial commencement and 3 times after each group of 30 patients

is enrolled. It is anticipated that these meetings will take place via conference call. One of the clinical cardiologists will be selected to chair the committee and will serve as the principal representative of the group. The Chair of the committee will be informed monthly about adverse events and will monitor safety of the patients during interim time between formal meetings of DSMB.

Monthly reports will be sent by the CDC to the DSMB chair, to report data on expected and unexpected adverse events. The Chair of the DSMB will have the right to convene additional meetings with all DSMB members when needed. The DSMB will carefully consider if these events are consistent with anticipated clinical outcome, i.e. unrelated, or a consequence of the study procedure, i.e. related. Information on all these events will be sent to DSMB Chair on monthly basis and in addition, a full DSMB report will be prepared before every elective DSMB meeting.

Adverse events that will be judged by the DSMB Committee as related to repeat ablation will be described and reported to CDC IRB at University of Rochester as well as local IRBs.

17. DATA ANALYSIS PLAN

For the primary endpoint of AF burden, i.e. percentage of overall follow-up spent by the subject experiencing atrial arrhythmias, the Wilcoxon rank-sum test will be used to statistically compare the conventional group vs. the active treatment group.

For the secondary composite end point, we will perform longitudinal event-free survival analysis, defined by survival and freedom from atrial arrhythmias, re-ablation, and cardiac hospitalization. Event-free survival rates, as captured by the composite secondary endpoint, will be displayed using the method of Kaplan-Meier. We will use the log-rank test to non-parametrically compare the overall survival curves for the two treatments. The other secondary endpoints of atrial flutter/tachycardia recurrence, repeat ablation incidence, and major adverse events will be compared utilizing negative binomial regression tests to statistically compare the event rates in the two arms, using the natural log of follow-up time as an offset. Quality of life measures will be compared between the arms using the non-parametric Wilcoxon rank-sum test.
The estimate for the sample size necessary to compare AF burden at 12 months between the conventional AF management arm vs. the Bio-Monitor 3-guided repeat ablation arm will assume a 1:1 distribution of subjects between the two arms. Since most of the re-ablation procedures will be carried out based on ICM-detected subclinical AF recurrences, we conservatively expect a re-ablation rate of 50% in the intervention arm vs. 5% in the conventional arm (in which only clinical episodes will be treated and resumption of antiarrhythmic medical therapy is also allowed).

For the planned analysis of the primary end point of AF burden involving the Wilcoxon rank-sum test, a two-sided = 0.05 and power of 80% was assumed. Based on our preliminary data and our prior studies on AF burden (The HARMONY Trial, Circulation Arrhythmia and Electrophysiology, 2015), the 12 month primary outcome of AF burden is assumed to be 25% vs. 16% in the conventional group, with a standard deviation of 15% (a conservative estimates which allows for 10% drop-out). A reduction from 25% to 16% and 80% power,

with a drop-out rate of 10%, will result in a total sample of 90 patients.

18. COORDINATING CENTER TRACKING

Acting as Coordinating Center for the study, in order to ensure all required information is provided to the Sponsor IRB, a Coordinating Center Tracking Spreadsheet will be submitted at the time of each annual progress review.

19. REFERENCES

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