University of California, San Francisco
Baylis Medical

WIRE IT (Wire Instrumentation using Radiofrequency Energy to Impact Transseptal Efficiency)

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
BAYLIS MEDICAL
Clinical Research Protocol
WIRE IT (Wire Instrumentation using Radiofrequency Energy to Impact Transseptal Efficiency)

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Principal Investigator:	Name: Gregory M Marcus, MD, MAS Telephone: (415) 476-3450 Fax: (415) 353-9190 E-mail: greg.marcus@ucsf.edu

Approval:

PI or Sponsor Signature (Name and Title) *Date*

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing Baylis Medical with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Title: **WIRE IT (Wire Instrumentation using Radiofrequency Energy to Impact Transseptal Efficiency)**

Protocol Date: 08/26/20

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LIST OF ABBREVIATIONS

AE	adverse event
CRF	case report form
AF	atrial fibrillation
AFEQT Questionnaire	Atrial Fibrillation Effect on QualiTy-of-life Questionnaire

1. BACKGROUND

Transseptal puncture is a common procedure performed in the electrophysiology lab to facilitate catheter access and ablation in the left atrium or ventricle. This procedure is most commonly used for atrial fibrillation ablation, which requires two sheaths/catheters to be inserted into the left atrium. Puncture through the interatrial septum is typically facilitated using a needle, which is pushed through the fossa ovalis and into the left atrium. The major risk of transseptal puncture is inadvertent injury to the wall of the left atrium by the advancing needle and sheath assembly, potentially resulting in pericardial bleeding, cardiac tamponade, and even death.

2. STUDY RATIONALE

Prior studies have shown that a radiofrequency (RF) transseptal needle is superior to a standard, manual needle with regard to left atrial access time. Recently, a novel RF wire system has been developed to further enhance the speed and safety of transseptal access. With this technique, an atruamatic RF wire can be used to both traverse the fossa ovalis and shield the left atrial wall from traumatic injury secondary to the advancing sheath. While this new RF wire system has recently become clinically available, there is no data substantiating its enhanced efficacy and safety compared to standard needle-based transseptal techniques.

3. STUDY OBJECTIVES

Primary Objective: To determine if the Baylis Versacross RF wire results in a shorter time to successful transseptal puncture compared to the conventional Baylis RF needle.

Secondary Objectives:

To determine if the Baylis Versacross RF wire results in greater first attempt transseptal puncture success compared to the conventional Baylis RF needle.

To determine if the Baylis Versacross RF wire results in less complications compared to the conventional Baylis RF needle.

To determine if the Baylis Versacross RF wire results in less right atrial needle/wire exchanges compared to the conventional Baylis RF needle.

4. STUDY DESIGN

This is a randomized, single blinded clinical trial comparing transseptal access using the Baylis Versacross RF wire versus the conventional Baylis RF needle among individuals undergoing atrial fibrillation catheter ablation.

Sedation, intubation, vascular access, and catheter ablation will be performed according to usual clinical care. Transseptal puncture will be performed using intracardiac ultrasound guidance. Each patient will undergo two transseptal punctures.

For participants randomized to the RF wire access system, the following equipment will be used:

- VersaCross™ RF Wire (Baylis, Montreal, Canada)
- VersaCross™ Transseptal Sheath (Baylis, Montreal, Canada)*
- VersaCross™ Steerable Sheath (Baylis, Montreal, Canada)*

*Because the transseptal wire does not provide the same mechanical support as a RF needle, these sheaths and their accompanying dilators must be used with the RF wire.

For participants randomized to the RF needle, the following equipment will be used:

- NRG® transseptal needle (Baylis, Montreal, Canada)
- SL1 sheath (Abbott Medical, Santa Clara, California).
- Agilis steerable sheath (Abbott Medical, Santa Clara, California)

The primary endpoint is time to complete transseptal puncture. Timing will start when the transseptal sheath wire is inserted into the femoral vein short sheath and will stop when the transseptal dilator is removed from the long sheath after placement in the left atrium. For each transseptal, the number of unsuccessful attempts requiring rewiring will be recorded. Fluoroscopy time, fluoroscopy dose, number of RF applications, procedural complications, and total procedural time will also be determined.

At three months, six months, and one year after the ablation, study coordinators will follow up with participants and ask a series of questions remotely over the phone, or in-person if participants are coming to UCSF for clinical care. Total duration of subject participation will be one year.

5. CRITERIA FOR EVALUATION

Primary Efficacy Endpoint

- Time to completion of transseptal puncture

Secondary Efficacy Endpoints

- Efficacy of transseptal puncture
- Number of right atrial needle/wire exchanges
- Procedural complications including:
    i. Hemodynamically significant pericardial effusion
    ii. Bleeding requiring surgical intervention or transfusion
    iii. Hypotension regarding prolonged pressor support after the procedure
    iv. Prolonged intubation required
    v. Air embolism
    vi. Peripheral embolic event
    vii. Stroke
    viii. TIA
    ix. Pseudoaneurysm
    x. AV fistula
    xi. Hematoma
    xii. Myocardial infarction
    xiii. Death
    xiv. Migraine
- Efficacy of catheter ablation procedures: time to first clinically evident sustained AF after employing a 3 month blanking period.

- Safety Evaluations: incidence of adverse events

6. SUBJECT SELECTION

a. Study Population

Subjects with a diagnosis of atrial fibrillation or atrial flutter undergoing endocardial left atrial catheter ablation procedures who meet the inclusion and exclusion criteria will be eligible for participation in this study.

b. Inclusion Criteria

1. Age ≥ 18 years
2. Patients undergoing endocardial left atrial catheter ablation procedures using radiofrequency ablation catheters for atrial fibrillation or atrial flutter ablation procedures at UCSF
3. Willing and able to provide written informed consent in English.
4. Willing and able to comply with scheduled remote follow-up visits (through Year 1)

c. Exclusion Criteria

1. Presence of a patent foramen ovale closure device or atrial septal defect closure device.
2. Cryoballoon ablation
3. IVC filter
4. Deemed not suitable by study personnel.

7. CONCURRENT MEDICATIONS

a. Allowed Medications and Treatments

Standard pharmacologic therapy for atrial fibrillation or atrial flutter is allowed. There are no prohibited medications.

8. STUDY TREATMENTS

a. Method of Assigning Subjects to Treatment Groups

Up to 72 eligible patients will be randomly assigned to either the (1) RF wire group or (2) RF needle group for transseptal puncture. The randomization codes will be generated prior to the start of enrollment using a computer program to create randomization assignments to either group 1 or group 2, using blocks of 6.

Blinding

The randomization assignments will not be known to patients. However, due to the nature

of the study, investigators and research staff will need to know the randomization

assignments since investigators will be performing the ablation procedures using devices specific to each randomization group.

9. STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities.

a. Clinical Assessments

i. Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

ii. Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at Screening.

iii. Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates and times), severity/grade, outcome, and treatment will be recorded on the case report form (CRF).

10. EVALUATIONS BY VISIT

Visit 1: Screening

1. Review the study with the subject and obtain informed consent and HIPAA authorization and assent through written paper form or DocuSign.
2. Assign the subject a unique screening number.
3. Record demographics data.
4. Record medical history.
5. Record medications subject is currently taking.
6. Administer Atrial Fibrillation Effect on QualiTy-of-life questionnaire.
7. Ask questions about migraines using CRFs.
8. Randomize subject after completion of this visit, 1 day before ablation procedure.

Visit 2: Ablation Procedure Day

1. Ablation procedure performed using assigned randomization group.
2. Collect intraoperative data using CRFs.
3. Record any adverse events.

Visit 3: Month 3 (post-study ablation)

1. Record any adverse events.
2. Record medications subject is currently taking.
3. Ask follow-up questions about migraines using CRFs.

Visit 4: Month 6 (post-study ablation)

1. Record medications subject is currently taking.
2. Ask follow-up questions about ablation procedure effectiveness using CRFs.
3. Administer AFEQT questionnaire.
4. Ask follow-up questions about migraines using CRFs.

Visit 5: Month 12 (post-study ablation)

1. Record medications subject is currently taking.
2. Ask follow-up questions about ablation procedure effectiveness using CRFs.
3. Administer AFEQT Questionnaire.

11. ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

a. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient. It does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study intervention, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

b. Serious Adverse Experiences (SAE)

An SAE is defined as any AE that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

i. Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study intervention) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC. All AEs and SAEs will also be reported to Baylis Medical.

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.4 Replacement of Subjects

Subjects who do not undergo the study ablation procedure will be replaced.

12. PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

Failure to meet inclusion/exclusion criteria

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. A copy of the form will be filed in the site's regulatory binder.

13. STATISTICAL METHODS AND CONSIDERATIONS

a. Data Sets Analyzed

All subjects who undergo a transseptal puncture during their study ablation procedure will be included in the analysis.

b. Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized*:* race, biological sex, gender, age, height and weight.

c. Analysis of Primary Endpoint

The primary endpoint (transseptal time, in minutes) will be analyzed using a t-test if time is normally distributed and a Wilxocon rank sum test if it exhibits a skewed distribution.

d. Sample Size and Randomization

The sample size of seventy-two patients will provide 99% power to detect a stastically significant difference in time assuming mean transseptal time of 5 minutes and standard deviation of 5 minutes using a two-tailed alpha of 0.05.

Up to 72 eligible patients will be randomly assigned to either the (1) RF wire group or (2) RF needle group for their transseptal puncture. The randomization codes will be generated prior to the start of enrollment using a computer program to create randomization assignments to either group 1 or group 2, using blocks of 6.

DATA COLLECTION, RETENTION AND MONITORING

e. Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject number and initials.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

f. Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

g. Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis.

h. Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

i. Availability and Retention of Investigational Records

The Investigator will make study data accessible to the IRB/IEC and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

14. ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. The Investigator will also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

a. Protocol Amendments

Any amendment to the protocol will be written by the Principal Investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

b. Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

c. Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

A properly executed informed consent will be obtained from each subject via a written consent document or DocuSign consent prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

d. Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the Principal Investigator and Baylis. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

e. Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol, except when to protect the safety, rights or welfare of subjects.

2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the IRB AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62.
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1: SCHEDULE OF STUDY VISITS

	VISIT 1 (Screening)	VISIT 2 (Ablation Procedure Day)	VISIT 3 (3 Month (post-study ablation))	VISIT 4 (6 Months (post-study ablation))	VISIT 5 (1 Year (post-study ablation))
Informed Consent	**X**				
Medical History	**X**				
Complete Physical Exam					
Abbreviated Physical Exam					
Height					
Weight					
Vital Signs					
Oximetry					
Spirometry					
Pharmacokinetics					
Chemistry					
Pregnancy Test (Urine or Serum)					
Hematology					
ESR					
C-Reactive Protein					
Urinalysis					
Randomization	**X (DAY BEFORE ABLATION)**				
Dispensing or Administration of Study Drug					
Counting of Returned Study Drug					
Initiate Subject Diary					
Subject Diary Review					
Concomitant Medication Review					

Adverse Experiences		X	X	X	X
AFEQT	X			X	X

[a] □2 days

1. Marcus GM, Ren X, Tseng ZH, et al. Repeat transseptal catheterization after ablation for atrial fibrillation. *J Cardiovasc Electrophysiol.* 2007;18(1):55-59.
2. Ross J, Jr. Transseptal left heart catheterization a 50-year odyssey. *J Am Coll Cardiol.* 2008;51(22):2107-2115.
3. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm.* 2017;14(10):e275-e444.
4. Hsu JC, Badhwar N, Gerstenfeld EP, et al. Randomized trial of conventional transseptal needle versus radiofrequency energy needle puncture for left atrial access (the TRAVERSE-LA study). *J Am Heart Assoc.* 2013;2(5):e000428.