Guidance for Industry and FDA Staff

Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation

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Cardiac Electrophysiology and Monitoring Branch
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Office of Device Evaluation

Preface

Public Comment

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Introduction

Atrial fibrillation (AF) is a complex arrhythmia; its precise mechanisms remain unclear, and the clinical presentation, arrhythmia characteristics, and underlying pathophysiology are variable. The arrhythmia has been classified in various ways based on electrocardiography (ECG) or clinical criteria. Because ablation therapies proposed to date for treatment of atrial fibrillation are intended to prevent or reduce the recurrence of this arrhythmia, this document will use a rhythm classification scheme (Table 1), adapted from the American College of Cardiology/American Heart Association/ European Society of Cardiology (ACC/AHA/ESC) Guidelines for the Management of Patients with Atrial Fibrillation, based on arrhythmia recurrence pattern.[1] This general classification scheme may be useful when defining patient populations for inclusion in clinical studies and when selecting appropriate methods to evaluate treatment effectiveness in the selected patient populations.

Table 1. AF Rhythm Classification Scheme

Classification	AF Episodes
Paroxysmal	self-terminating
Persistent	not self-terminating but can be cardioverted with drugs or electricity
Permanent	not self-terminating and the arrhythmia cannot be cardioverted or recurs quickly following cardioversion
Recurrent	two or more documented episodes occur

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Scope

This guidance document addresses study design issues associated with catheter ablation devices intended for treatment of atrial fibrillation. These devices (product code, LPB, Electrode, Percutaneous, Conduction Tissue Ablation) are class III, requiring premarket approval applications before marketing (section 513(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360c(a))).

FDA believes that the devices addressed by this guidance document are significant risk devices as defined in 21 CFR 812.3(m).[i] In addition to the requirement of having an FDA-approved IDE (21 CFR Part 812), sponsors of such studies must comply with the regulations governing institutional review boards (21 CFR Part 56) and informed consent (21 CFR Part 50).

[i] Please refer to Blue Book Memorandum entitled "SIGNIFICANT RISK AND NONSIGNIFICANT RISK MEDICAL DEVICE STUDIES," http://www.fda.gov/cdrh/d861.html.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe should be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html

Study Design

FDA believes that, in general, randomized, controlled trials reflect the least burdensome means of collecting clinical data in support of safety and effectiveness for catheter devices intended to treat AF. In considering alternative study designs, FDA believes that using patients as their own control or using a historical control can complicate the demonstration of effectiveness in most investigations. Statistical concerns that underlie this recommendation include both general considerations, e.g., regression to the mean, and disease-specific considerations, e.g., the clustered, non-random AF recurrence pattern that has been described for patients with paroxysmal AF.[2,3] Additional considerations that suggest the use of a randomized control include the high degree of heterogeneity that exists in the potential patient population, in AF disease presentation, in potential ablation technologies, and in concomitant medical treatment.

Although FDA generally recommends a randomized, controlled trial for these reasons, you may use an alternative study design if it is scientifically sound and addresses the relevant safety and effectiveness questions. For example, a self-controlled study may be appropriate to evaluate treatment effectiveness among patients with truly refractory permanent AF, and a study with a sham control arm may be considered for a study involving subjective criteria such as perceived symptoms. FDA recognizes that there is no unique "best design" in catheter ablation investigations, but considers the elements discussed in this document as core features of reasonable studies. As noted earlier, we will consider alternative study designs, but we recommend that you explain the scientific arguments supporting your alternative design.

If you conduct a randomized, controlled study, you should select an appropriate control therapy. Selection of this control should depend on the:

- indications for use

- patient population
- device design considerations.

Potential control therapies include:

- best medical therapy with antiarrhythmic drugs
- therapy with approved medical device(s)
- patients as own controls
- sham therapy.

In the case where sponsors elect to utilize best medical therapy with antiarrhythmic drugs as the control therapy, FDA recognizes that drug regimens are tailored to individual circumstances and that no unique optimal regimen may exist. However, FDA recommends that any investigation with antiarrhythmic drugs utilize a pre-specified tiered protocol that delineates criteria for initial drug selection and for changes in drug therapy.

Control to a previously approved, atrial fibrillation device therapy may be a particularly desirable option because study design, patient enrollment and data analysis may all, potentially, be very straightforward. For example, if a catheter ablation system is approved for treatment of AF via pulmonary vein isolation, then it might be both simple and appropriate to use a randomized study to compare the safety and effectiveness of a new ablation device versus the safety and effectiveness of the previously approved device.

Sham controlled studies allow the sponsor to evaluate for procedure/placebo effect and to mask study subjects. This type of study design may be most appropriate for studies with subjective endpoints such as reduction in patient-reported symptoms, or when the risk level for the sham procedure is particularly low. FDA recognizes that it may be difficult for sponsors to develop a clinical study design with a sham control arm that both investigators and patients believe is ethical; for this reason, studies involving a sham control arm should be carefully designed with due consideration to risks versus benefits.

Potential advantages to randomized, controlled trial designs extend not only to evaluation of device effectiveness but also to evaluation of device safety. Adverse event rates may be affected by factors such as patient characteristics, device design, evolving procedural methods and operator experience and may be difficult to evaluate using historical control data rather than randomized control data. For example, multiple case series have suggested that catheter ablation to create pulmonary vein isolation for treatment of atrial fibrillation can be associated with severe adverse events.[2,3,4] In contrast, a recently reported, concurrently controlled but non-randomized study suggests that at least one catheter ablation procedure

used for pulmonary vein isolation may actually reduce the incidence of adverse events when compared to medical management.[5]

Whatever the concurrent control arm selected, FDA believes that several strategies could be employed to facilitate patient recruitment. These include, but are not limited to, 2:1 (or other) randomization schemes and crossover study designs that would allow medically managed control patients to receive ablation procedures after a pre-specified time (e.g., six months in a control arm). These considerations will allow study sponsors to develop reasonable study designs that facilitate assessment of safety and effectiveness by the FDA consistent with a least burdensome approach to device regulation.

Study End Points

Primary Effectiveness Endpoint

In the future, it may be feasible to demonstrate that ablation therapies for AF positively affect disease outcomes.[5] At the current time, it is probably most appropriate to evaluate ablation therapy for AF as a palliative therapy and to select endpoints that have the potential to clearly demonstrate a reduction in symptoms caused by AF.

Effectiveness endpoints should be clinically meaningful and amenable to robust evaluation during a clinical study. FDA believes that evaluation of reduction of AF burden (or reduction in the incidence of AF) is problematic as the primary endpoint for a study designed to evaluate therapy for paroxysmal AF. Measurement of this endpoint post-ablation could be strongly influenced by various, non-therapy-related factors. The potential for waning patient compliance with remote monitoring and recording procedures would be one concern. Because recording and reporting of symptomatic episodes is subjective, placebo effect could be an important concern during unmasked studies. As noted above, evaluation of AF recurrence can also be influenced by statistical concerns or issues related to disease natural history, e.g., the phenomenon of regression to the mean and the non-random recurrence pattern reported for paroxysmal AF.[2,3] Finally, evaluation of reduction in paroxysmal AF burden or recurrence may not be an optimal primary endpoint because it is difficult to determine or define the percent reduction that should be considered clinically significant.

For a primary effectiveness endpoint, FDA recommends the relatively unambiguous endpoint of freedom from symptomatic atrial fibrillation at one year. This outcome should be in the absence of antiarrhythmic drug therapy, or, alternatively, using an antiarrhythmic drug that was previously ineffective at a given dose. A one-year follow-up period both minimizes the confounding effects of the clustered, non-random AF

recurrence pattern that was previously discussed and provides sufficient time to evaluate adverse events, e.g., pulmonary vein stenosis, that may be manifest or progressive only at late time points in some patients.

Depending on the design of the device and the objectives of the study design, the following endpoints may also be appropriate:

- reduction of atrial fibrillation burden[ii]
- improvement in exercise tolerance
- improvement in quality of life
- improvement in symptom scores tracking dyspnea, dizziness, or palpitations.

We recommend that you explicitly define acute procedural and chronic procedural success, and scenarios indicating treatment failure. For example, persistence of symptoms at six months in a control arm might lead to patient crossover into an interventional arm, but should be counted as a treatment failure in the control arm. (Indications in labeling should reflect your definition of acute procedural success.)

Published results indicate that current catheter ablation therapies used to treat AF may commonly require two or more ablation procedures in order to achieve treatment success in a substantial subset of treated patients.[6] When you design your study, FDA recommends that your study design not define early repeat ablation (e.g., no more than two months post-ablation) as a treatment failure. Conversely, we recommend that you do not count any patient who requires more than three ablation procedures as a treatment success. The number of ablation procedures performed on each patient should be recorded and reported. Each repeat ablation should restart the recommended twelve-month follow-up period.

Primary Safety Endpoints

In considering primary safety endpoints, FDA acknowledges that an ablation intervention arm and a drug intervention arm may have different safety criteria.

[ii] Experience suggests that technical, clinical, and patient compliance considerations may make it difficult to complete a valid determination of change in atrial fibrillation burden using external arrhythmia event recorders. Automatically-triggered, implantable event recorders with a high sensitivity and specificity for detection of AF (or similar AF detection capabilities incorporated within implantable cardiac pacemakers or implantable cardioverter-defibrillators) can provide a valid means to evaluate this parameter.[2,3]

Ablation Procedure Safety Endpoint

For an ablation procedure safety endpoint, FDA recommends for the devices addressed in this guidance document, a composite serious adverse event endpoint that includes, but need not be limited to, the following:

- transient ischemic attack
- cerebrovascular accident
- major bleeding
- cardiac tamponade
- pulmonary vein stenosis
- pericarditis
- myocardial infarction
- diaphragmatic paralysis
- death.

There may be other safety endpoints specific to a particular device design or energy source. The risk analysis that you perform for your device should provide information that will drive the development of these device-specific safety endpoints, and you should include them in the study design. Note that if the ablation procedure involves placement of left atrial ablation lesions, FDA recommends assessing pulmonary vein stenosis using a baseline imaging evaluation (CT or MRI), with assessment at least at, but not limited to, three months and one year for stenosis progression. In addition, FDA recommends yearly imaging for five years for long-term follow-up, given the current incomplete understanding of the presentation and progression of pulmonary vein stenosis.

Composite Serious Adverse Event Endpoint

For a drug intervention arm, FDA recommends a composite serious adverse event endpoint, which includes, but need not be limited to, the following:

- life-threatening arrhythmia
- transient ischemic attack
- cerebrovascular accident
- anaphylactic reaction
- pulmonary hypertension (if amiodarone therapy)
- death.

For either type of composite safety endpoint (ablation or drug), FDA recommends that you incorporate hierarchical or other weighting schemes, as appropriate, for each combination of adverse events.

Data Collection Forms

FDA recommends that sponsors design the case report forms to optimize collection of information relevant to the primary safety and efficacy endpoints, minimizing the accumulation of data that may be peripheral or irrelevant to the clinical study. Experience has shown that this approach can reduce the total number of data point errors and thereby diminish the amount of time and effort needed for the data clean-up process.

Study Groups

FDA recommends that sponsors design their studies to include patient populations in which the proposed therapy is most likely to show benefit. Study design parameters such as inclusion and exclusion criteria and measures of success and failure will likely depend on whether the device is intended to treat paroxysmal and/or persistent AF, or permanent AF. For paroxysmal or persistent AF, FDA recommends that the study inclusion criteria include patients who are highly symptomatic and who have failed treatment with at least one antiarrhythmic drug. Permanent AF patients are less likely to be highly symptomatic but will have been in AF for at least six months and failed at least one antiarrhythmic drug.

You should explicitly delineate your inclusion and exclusion criteria. We recommend that you use inclusion and exclusion criteria to precisely define the treated patient population and to carefully select a patient population likely to benefit from the proposed therapy. Evolution in device design, procedural methods, and operator experience all may change our understanding of which patients are likely to benefit from a proposed procedure completed with a specific ablation device. Examples of inclusion and exclusion criteria that may be appropriate for pulmonary vein isolation studies designed to treat paroxysmal AF are listed below.

Examples of Inclusion Criteria (Paroxysmal Population)

- Highly symptomatic patients, i.e., $\geq$2 discrete atrial fibrillation episodes per month for 2 months preceding trial entry and $\geq$6 discrete atrial fibrillation episodes in the 6-12 months preceding trial entry

- Absence of structural heart disease as demonstrated by transthoracic echocardiogram of all four chambers of the heart
- Failure or intolerance of ≥1 antiarrhythmic drug

Examples of Exclusion Criteria (Paroxysmal Population)

- Left atrial size ≥50 mm
- LV ejection fraction <40%
- Current use of amiodarone, or use of amiodarone in the preceding 6 months[iii]
- Known cerebrovascular disease, including history of stroke or transient ischemic attack (TIA)
- Previous left heart ablation procedure, either by surgery or by percutaneous catheter, for atrial fibrillation

Appropriate inclusion and exclusion criteria for studies involving patients with persistent AF might be similar to those suggested above, with the possible exception of the suggested frequency of AF recurrence that is specified as an inclusion criterion. An appropriate recurrence rate for patients with frequent persistent AF could be substituted.

Inclusion and exclusion criteria for studies involving patients with permanent AF will also likely be similar with the exception of symptoms, left atrial size and, possibly, ejection fraction. You may have additional inclusion and exclusion criteria depending on your study design, and your device's indications, design features, and performance characteristics.

Sample Size

We recommend that you provide a statistical justification for any sample size calculation. FDA recommends that sponsors perform both safety endpoint and effectiveness endpoint calculations. We believe that the safety endpoints will drive sample sizes in the majority of cases.

[iii] Because a prolonged time (months) is required to clear amiodarone from cardiac tissue, it can be difficult or impossible to effectively withdraw a patient from amiodarone therapy within the setting of a clinical study. Additionally, because of potentially severe side effects associated with prolonged amiodarone therapy, we believe it may be inappropriate to define arrhythmia suppression achieved by previously effective amiodarone therapy plus ablation as a clinical success.

Patient Follow Up

We recommend that you develop standardized monitoring protocols and include outpatient follow up visits at, but not limited to, one, three, six and twelve months. These visits should typically include documentation of symptoms and assessment of cardiac rhythm with 12-lead electrocardiogram (ECG), Holter monitoring, or other equivalent cardiac rhythm measurements.

For any ablation procedures that involve lesions in the left atrium, we recommend that imaging studies to assess pulmonary vein stenosis be completed at baseline and at three months in all patients. If an individual patient demonstrates pulmonary vein narrowing at three months or has symptoms potentially related to pulmonary vein stenosis (pulmonary hypertension) at six or twelve months, we recommend that pulmonary vein imaging studies be completed for that patient at six and twelve months. Your study should specify the extent or percentage of narrowing that constitutes stenosis.

The importance of adequate and appropriate follow-up of study subjects cannot be overemphasized. Our experience is that many clinical investigators omit or perform incomplete post-procedure testing and evaluations once the procedure has been completed. Results obtained from effective follow-up contribute significantly to the review and approval process; therefore, the study protocol should be followed as written without omission of post-procedure testing.

Blanking Period

A blanking period is a time interval during which success criteria are not evaluated. Reports in the literature suggest that current left atrial ablation procedures that are used to treat AF may not decrease the incidence of AF until four to six weeks following ablation. You may wish to include in the study design a blanking period of at least four weeks during which device efficacy by patient monitoring is not assessed as part of the study record. If a blanking period is used, it should restart after any repeat ablation procedure is performed.

Anticoagulation

We recommend that you explicitly define and explain post-procedure anticoagulation protocols, as currently there is no evidence-based consensus guideline for anticoagulation following percutaneous catheter based AF ablation.

Study Monitoring

In designing your studies with catheter ablation devices intended for the treatment of AF, we recommend that you develop a comprehensive monitoring plan for these studies. Please note that sponsors are required to include written monitoring procedures in applications for investigational device exemptions (21 CFR 812.25(e)). Experience has shown that if sponsors make adequate provisions for monitoring studies, quality of the studies and data will follow. Therefore, we recommend:

- selecting qualified monitors
- ensuring investigator adherence to the investigational plan and other requirements
- ensuring investigator compliance in regard to recordkeeping and reporting.

References

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