Clinical Study Designs for Surgical Ablation Devices for Treatment of Atrial Fibrillation

Guidance for Industry and Food and Drug Administration Staff

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Preface

Public Comment

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This guidance provides FDA's recommendations on clinical trial designs for surgical ablation devices intended for the treatment of atrial fibrillation (AF). The recommendations in this guidance address clinical studies for new surgical ablation devices intended for treatment of AF, as well as for legally marketed surgical ablation devices for which a new indication for treatment of AF is sought.

Atrial fibrillation is a complex arrhythmia and its precise mechanisms remain unclear. Current treatments span a spectrum of non-invasive to highly invasive options and include medical and surgical variants. The success of the MAZE procedure[1] and its successors has led to the development of surgical ablation devices designed to mark cardiac tissue in a manner similar to suture lines, thereby disrupting the path of the electrical impulses causing the patient's AF.

FDA believes that several important elements of appropriate clinical study design – such as inclusion and exclusion criteria and assessment of effectiveness – differ for subjects with longstanding persistent AF, persistent AF, and paroxysmal AF (defined in Section 3) as well as for stand-alone versus concomitant procedures. This guidance addresses those differences.

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

[1] Cox JL, Schuessler RB, d'Agostino Jr HJ et al; The surgical treatment of atrial fibrillation III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg* 1991;101:569-583.

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.

2. Scope

This guidance document addresses clinical study design issues associated with devices intended for surgical ablation, under direct visualization, for the treatment for AF as a rhythm disturbance. See the "Terminology" section below for a distinction between "AF as a rhythm disturbance" and "AF as a disease." The scope of this guidance includes:

Product code OCM - Surgical Cardiac Ablation Device, for Treatment of Atrial Fibrillation, Class III

The scope of this guidance document specifically excludes cardiac ablation devices not intended for use under direct visualization, as defined in Section 3.A, and cardiac ablation devices delivered intravascularly.

The following table outlines additional device types that are excluded from the scope of this guidance, unless a sponsor seeks to expand the indications of one of the listed devices to include "treatment of atrial fibrillation," in which case this guidance is applicable to that proposed indication. Although such devices may have a cleared indication of "ablation of cardiac tissue," FDA notes that these devices may not have been evaluated for treatment of AF as a rhythm disturbance.

Classification Regulation (21 CFR)	**Class**	**Product Code**	**Description**
878.4350	II	GEH	Cryosurgical unit and accessories
878.4400	II	GEI	Electrosurgical cutting and coagulation devices and accessories
		NEY	Microwave ablation system and accessories
		NTB	Ultrasound ablation system and accessories
		OAB	Low energy direct current thermal ablation system
		OCL	Surgical device for ablation of cardiac tissue
878.4810	II	GEX	Powered surgical laser instrument
none (post-Amendments)	III	LPB	Cardiac ablation percutaneous catheter
none (post-Amendments)	III	OAD	Cardiac ablation percutaneous catheter for treatment of atrial flutter
none (post-Amendments)	III	OAE	Percutaneous catheter intended for treatment of atrial fibrillation

FDA believes that the devices addressed by this guidance document are significant risk devices as defined in Title 21, Code of Federal Regulations (CFR) 812.3(m); for additional information, please refer to the Medical Device section of the Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors, which is available at http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm#risk. In addition to complying with the regulations governing institutional review boards (IRBs) (21 CFR part 56) and informed consent (21 CFR part 50), sponsors of such studies must obtain FDA and IRB approval of their application for an Investigational Device Exemption (IDE) before they may begin any study on an investigational device (see section 520(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 360j(g); 21 CFR 812.42).

3. Terminology

The following terms are defined as described for the purposes of this guidance document.

Term	**Definitions**
Failed electrical cardioversion	An electrical cardioversion is considered a failure if it is not able to restore sinus rhythm for 30 seconds or longer.
Paroxysmal AF	Recurrent AF (≥2 episodes) that terminates spontaneously within seven days. Episodes of AF of ≤ 48 hours' duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.
Persistent AF	AF which is sustained beyond seven days but no more than one year. Episodes of continuous AF in which a decision is made to electrically or pharmacologically cardiovert the patient after more than 48 hours, but prior to 7 days, should also be classified as persistent AF episodes.
Longstanding Persistent AF	Continuous AF of greater than one-year duration.
Permanent AF	The term permanent AF is not appropriate in the context of patients undergoing catheter or surgical ablation of AF, as it refers to a group of patients in continuous AF for which a decision has been made not to pursue restoration of sinus rhythm by any means.

Lone AF	AF in young individuals (under 60 years of age) without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension.
Continuous AF	Uninterrupted AF presented on all ECG monitoring performed during a defined period of time.

A. Surgery or Surgical Approach

We define surgery or the surgical approach as a clinical procedure carried out under direct visualization. This means that the clinician is able to see, either directly or by means of live video, the point or area of epicardial and/or endocardial contact between the ablating device and the cardiac tissue for all or some of the lesions. For example, included in this definition is open-chest surgery and minimally invasive surgery via thoracoscopy, as long as the clinician performs the majority of the ablation lesions under direct visualization. Specifically excluded from this definition are clinical procedures that are performed principally under indirect visualization, such as cardiac catheterization, or percutaneous approaches to the epicardium via pericardial access carried out under fluoroscopic or echocardiographic guidance. The guidance document entitled *Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation*, which is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072590.htm, addresses study design for catheter ablation as a therapy for AF.

B. Paroxysmal, Persistent, and Longstanding Persistent AF

The table above defines "paroxysmal AF," "persistent AF," "longstanding persistent AF," and "permanent AF" as used in this guidance. These terms are adopted from the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[2] with minimum modifications for the purposes of this guidance document. It is recognized that subjects may have paroxysmal and persistent AF. A patient's AF type should be defined as the most frequent type of AF experienced within six months of an ablation procedure.

Paroxysmal AF is by nature episodic and can occur in clusters with temporal gaps between recurrences. This makes the evaluation of therapy effectiveness for paroxysmal AF more difficult than for persistent and longstanding persistent AF. FDA believes that in addition to the above definition for longstanding persistent AF, subjects who have failed electrical cardioversion may also be considered to have longstanding persistent AF depending on the definition used for failed electrical cardioversion.

[2] Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. *Heart Rhythm* 2012;9(4):632-696.

C. AF as a Rhythm Disturbance versus AF as a Disease

AF as a rhythm disturbance should be distinguished from AF as a disease. AF as a rhythm disturbance refers solely to the presence of AF as diagnosed with appropriate electrocardiographic techniques. AF as a disease additionally refers to the functional impairments (e.g., congestive heart failure and thromboembolic stroke) caused by an AF rhythm. We refer to "elimination of AF" as an outcome of treating AF as a rhythm disturbance, and "cure of AF" as an outcome of treating AF as a disease. We note that the recommendations in this guidance only apply to those devices seeking an indication of treating AF as a rhythm disturbance but not those for cure of AF as a disease.

4. Study Design

FDA recognizes that there is no unique "best design" for clinical investigations of devices. However, the elements discussed in this document embody FDA's current thinking regarding appropriate study designs for these devices. The design, execution, and analysis of any clinical trial of a device should be appropriate to develop valid scientific evidence to substantiate the safety and effectiveness of the device for its intended use and patient population. (See 21 CFR 860.7.)

A. Randomized Controlled Trials

FDA believes that, in general, randomized controlled trials (RCTs) provide the least burdensome means of developing valid scientific evidence for surgical ablation devices intended for the treatment of AF. Potential advantages to RCT designs extend to evaluation of both device effectiveness and device safety. Randomization also provides a sound basis for statistical inference.

Assurance that subject populations are similar in test and control groups is best attained by randomly dividing a single sample population into groups that receive the test treatment (i.e., ablation using the study device) or control treatment (i.e., no ablation or ablation using an approved device for the indications being sought). This technique avoids systematic differences between groups with respect to known or unknown baseline variables that could affect safety and/or effectiveness outcomes. Variables that may affect the safety profile (adverse event rates) and/or effectiveness profile include patient characteristics, concomitant cardiopulmonary disease, pre-operative AF duration, left atrial size, ejection fraction, concomitant medications, device design, concomitant cardiac surgery, evolving procedural methods, and operator experience. Inability to eliminate systematic differences between treatment groups is a major problem of studies without a concurrent randomized control.

Based on these considerations, FDA recommends that the first choice to be considered in designing a study should be a RCT, where the control arm consists of treatment with an approved device or therapy for the indications that are being sought.

If you conduct a RCT, we recommend that you select an appropriate control therapy or control group. Whether a particular control is appropriate depends on:

- the specific indication for use under study;
- the intended target patient population;
- the availability of an approved device for the indications being sought;
- the device design;
- an assessment of potential confounding factors; and
- any concomitant cardiac surgeries.

B. Alternative Study Designs

Although we generally recommend RCTs, we will consider alternative study designs that are scientifically sound and adequate to answer relevant safety and effectiveness questions. To the extent that your alternative study design departs from the RCT design, we recommend you employ rigorous methodology designed to reduce potential sources of bias and other confounders. We also recommend that you thoroughly explain the scientific rationale supporting the design in your IDE submission. We note that if FDA finds that there is reason to believe that the risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, FDA may disapprove an IDE application. (See 21 CFR 812.30(b)(4).)

Non-Randomized Concurrent Controls

A non-randomized concurrent control design is one alternative to a RCT. Such a study would compare data from subjects receiving ablation treatment from the investigational device to data from subjects either receiving no ablation treatment or receiving an alternative treatment. (See 21 CFR 860.7(f)(1)(iv)(*a*), (*c*).) However, the comparability of the treatment and control groups may be reduced because the benefits of randomization are eliminated in such a study. Potential limitations on comparability include differences in patient care across investigational sites and factors that may introduce selection bias such as concomitant underlying disease and differences in AF disease. Thus, non-randomized studies should include rigorous steps to closely match subjects in the control group with subjects in the treatment group. Either covariate analysis or propensity score analysis can enhance the comparability of the treatment and control arms in such a study. We recommend that you prospectively describe in detail any methods of analysis in your clinical protocol.

Historical Controls

FDA will consider a study design implementing an historical control that compares data from a group of subjects receiving the test treatment with historical data from a group of comparable subjects external to the study who received no ablation treatment, but who followed an established effective regimen at an earlier time, or who received ablation from a device already approved for the indications being sought. (See 21 CFR 860.7(f)(1)(iv)(*d*).) FDA believes that if an historical control is employed, a thorough analysis of the relevant medical literature should be provided in support of your historical control choice. We recognize that, due to the heterogeneity of disease presentation and treatment in the target AF patient population and the variety of ablation, drug, and other

therapies that may be used for treatment of AF, the use of an historical control may complicate the collection and analysis of appropriate medical literature. Whenever possible, FDA recommends you use a control cohort for which patient-level data are available.

Performance Goals

If a RCT or a nonrandomized concurrent control design is not possible and if patient-level data are not available, FDA recommends that you propose a performance goal supported by a thorough analysis of the relevant medical literature. We anticipate significant challenges in arriving at an appropriate performance goal due to heterogeneity across published studies and rapid progress in the field of AF management.

C. Control Group Considerations

If your study utilizes a randomized or non-randomized concurrent control arm, appropriate potential concurrent control therapies may include:

- ablation therapy with one or more medical devices approved for the indications that are being sought;
- best medical therapy with antiarrhythmic drugs with or without electrical cardioversion.

Regardless of the concurrent control arm selected, several strategies may be appropriate to facilitate subject recruitment. Appropriate strategies may include use of 2:1 or other randomization allocation ratios, and selection of a control arm with therapy by best medical management instead of no therapy.

If you elect to use best medical therapy with antiarrhythmic drugs as the control therapy for evaluation of effectiveness, FDA recognizes that drug regimens are tailored to individual circumstances and that no unique optimal regimen exists. 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.

If your study design includes an historical control, we recommend you choose a control cohort with characteristics that will maximize the likelihood that your study outcomes will be interpretable, such as:

- patient level data is available for control group
- ablation lesion set for control group is known
- duration, method, and rigor of follow-up in study subjects is known
- surgical approach in control group is equivalent to that in study subjects
- AF disease and underlying heart disease in control group and study subjects is similar
- concomitant cardiac surgeries in control group and study subjects are the same.

D. Ablation Procedure Lesion Sets

We recognize that there may not be one set of ablation lesions or ablation lines that are generally accepted as being the most effective in treating AF. You should provide a valid justification for your lesion set if it deviates significantly from those widely accepted in the field. Also, we recommend that, to the extent possible, all enrolled subjects have the same set of ablation lesions performed. Any deviations from the protocol-specified lesion set should be clearly documented in the case report forms. In order to maximize consistency in terms of lesion sets, we recommend that the protocol include clear instructions regarding a pre-specified lesion set and the recommended device used to create each lesion. Failure to adhere to the pre-specified lesion set could make the data difficult to interpret.

AF ablation performed concomitantly with another surgical procedure has a different benefit/risk profile than surgery done solely for the purpose of performing AF ablation. When surgical AF ablation is an adjunctive procedure in a patient already indicated for cardiac surgery, the additional risk posed by the ablation procedure may be small compared to the risks of the primary surgical procedure. When the sole purpose of the surgery is to perform AF ablation, FDA intends to weigh the risk of the surgery and ablation procedure against the sole possible benefit of treatment of AF. In an IDE application for a trial where the only purpose of the surgical procedure is ablation for treatment of AF, you should provide a sound scientific rationale to support your hypothesis that the benefits of AF ablation outweigh the risks of the surgical procedure. (See 21 CFR 812.30(b)(4).) In this situation, the careful selection of the control population is particularly important to FDA's evaluation of your trial design and the study results.

5. Indications for Use

We recommend that your study design reflect the proposed intended use and indications for use of your ablation device. We believe that your proposed indications for use should identify factors that may affect the benefit/risk profile of your device, such as the type of AF treated, the surgical approach used, any concomitant procedures, and relevant patient characteristics. Specific aspects of the study design often limit the indications for use of a device upon approval. For example:

- if your study includes only subjects with longstanding persistent AF, the corresponding indications for use may be limited to the treatment of longstanding persistent AF;
- if your study design pertains only to ablation concomitant with mitral valve replacement or repair surgery, approval of your device may be limited to that specific indication; and
- if the only surgical procedure used in your study employs a minimally invasive surgical approach, your indications may be limited accordingly.

Other Indications

Surgical ablation devices have a range of potential indications beyond treatment of AF as a rhythm disturbance. These other indications include improvement in atrial transport function, improved ventricular function, reduced risk of stroke, reduced risk of heart failure and improved survival. However, FDA is not aware of any conclusive clinical evidence from

large randomized clinical trials that surgical AF ablation results in any of these patient benefits. Therefore, FDA does not consider elimination of AF to be an appropriate surrogate indicator for these benefits. As a result, we recommend that clinical studies directly measure and support any indications beyond treatment of AF as a rhythm disturbance. For example, a study that demonstrates restoration of atrial contraction, in addition to effective termination of AF, may support indications that include improved atrial transport function. Similarly, a study that demonstrates increased left ventricular ejection fraction and improvement in ventricular dimensions may support an indication for restoration or maintenance of ventricular function. If you would like to include a labeling claim regarding any of these other endpoints, the claim should be based on pre-specified statistical hypotheses. Additionally, if you aim to make claims regarding quality of life (QOL) or other subjective outcomes, the trial design should account for placebo effect. While the FDA suggests that you test clinically relevant secondary endpoints (e.g., improvement in QOL, exercise tolerance), please keep in mind that the claims allowed in the labeling may be limited by aspects of the study design (e.g., claims based on subjective endpoints will be problematic in an unblinded trial).

Indications that include reduction in the risk of stroke should be supported by a study designed to evaluate the risk of stroke either while continuing or following termination of anticoagulation therapy.

In summary, you should formulate the indications for use for which you plan to seek approval in concert with clinical trial hypotheses that will support the proposed indications for use.

6. Study Endpoints

Clinical studies involving subjects with paroxysmal AF and studies involving subjects with persistent forms of AF are likely to be different in terms of procedural complexity as well as ease of follow-up. Clinical studies involving these subjects may also differ in terms of appropriate effectiveness endpoints and in terms of appropriate inclusion and exclusion criteria. Where appropriate, the recommendations in this guidance address studies on treatment of paroxysmal AF, persistent AF, and longstanding persistent AF separately.

A. Primary Effectiveness Evaluation

General Recommendations and Considerations

We recommend that you demonstrate that the benefit to subjects from the therapy is both clinically meaningful and statistically significant relative to the increased risk associated with the use of the ablative device. We generally recommend you evaluate the primary effectiveness in the absence of antiarrhythmic drug (AAD) therapy. However, an outcome evaluated in the presence of an antiarrhythmic drug that was not effective in treating AF prior to study enrollment may serve as a primary or secondary effectiveness endpoint. In either case, you should justify your choice of effectiveness endpoint.

For the primary effectiveness endpoint, FDA recommends you evaluate freedom from AF through the minimum follow-up period recommended by relevant medical society guidelines, which currently is 12 months.[2] We believe that the primary effectiveness endpoint for a rhythm disturbance is AF elimination (without iatrogenic arrhythmias) and not necessarily the resumption of normal sinus rhythm. Freedom from AF should be defined as freedom from AF/atrial flutter (AFL)/atrial tachycardia (AT) episodes of 30 sec duration or longer on Holter or event recorder or for the full recording time on a standard 12-lead ECG and in the absence of Class I or III AADs.

FDA believes that reduction in AF burden is not an optimal primary effectiveness endpoint due to the absence of justification for an AF burden threshold that would be considered clinically significant and the technical challenges in precisely measuring AF burden without an implanted device. On the other hand, FDA recognizes that AF burden assessed at various points in time during follow-up may provide supplementary information concerning device effectiveness.

Arrhythmia monitoring plays an important role in the assessment of device effectiveness. Generally, we recommend periodic Holter monitoring as the preferred modality for assessing effectiveness, although other modalities, such as standard 12-lead ECG, trans-telephonic recordings, loop recorders, and event recorders may be adequate. FDA recommends an event recorder be made available following the ablation procedure for scheduled and symptom-driven recordings to capture symptomatic and asymptomatic atrial tachyarrhythmia recurrences. We believe that less direct evaluation modalities, such as reduction in perceived symptoms, are not able to demonstrate primary effectiveness due to the subjective nature of such modalities and the potential for placebo effect. Our recommendations for minimum arrhythmia monitoring in the follow-up after a surgical ablation procedure are included in section 8E of this guidance.

FDA believes that although single procedure success might not be the basis for the primary effectiveness endpoint, it should be reported in surgical AF ablation studies.

We also recommend that you explain the means by which your study design minimizes confounding factors, such as the placebo effect.

Acute Procedural Success

Your assessment of effectiveness of the device should include a measure of acute procedural success. We believe that a measure of acute procedural success includes completion of the protocol-defined ablation lesion set and achievement of conduction block across ablation lesions (e.g., PV entrance and/or exit block if PV encircling lesions are created, entrance and/or exit block from posterior LA segment if box lesion is used). Although we do not believe acute procedural success is a surrogate for the recommended primary effectiveness endpoint, the relationship between acute procedural success and primary effectiveness success should be reported and explored because it may provide important data for device labeling.

Longstanding Persistent and Persistent AF: Primary Effectiveness Endpoint

We generally recommend separate studies for different types of AF. However, if the sponsor decides to study persistent and longstanding persistent AF together, the sponsor should provide a clinically and scientifically valid justification for this approach. Additionally, the sponsor should pre-specify the minimum proportion of subjects to be enrolled as representative of each type of AF studied.

For both persistent and longstanding persistent AF, FDA recommends freedom from AF/AFL/AT for one year in the absence of Class I or III AADs as the primary effectiveness endpoint. The recommendations for minimum ECG monitoring during follow-up for persistent and longstanding persistent AF subjects are included in section 8E of this guidance.

Paroxysmal AF: Primary Effectiveness Endpoint

For paroxysmal AF, FDA recommends freedom from AF/AFL/AT for one year in the absence of Class I or III AADs as the primary effectiveness endpoint. We believe this follow-up period minimizes the confounding effects of a clustered, non-random AF recurrence pattern. Please refer to section 8E for the FDA recommendations for minimum ECG monitoring during follow-up for paroxysmal AF subjects.

Primary Effectiveness Failure

To facilitate determination of primary effectiveness, the FDA recommends that you pre-specify scenarios that are indicative of primary effectiveness failure. FDA believes the following are examples of scenarios indicative of primary effectiveness failure:

- Any electrocardiographically documented AF/AFL/AT episode of 30 sec duration or longer by Holter, event monitor or rhythm strip; or for the full 10 second recording of a standard 12-lead ECG, following any blanking period through the final follow-up visit;
- The use of Class I or III AADs (or an increased dose of a previously ineffective AAD if the sponsor only wants to claim benefit in the presence of a previously ineffective drug) following any blanking period through the final follow-up visit;
- DC cardioversion for AF/AFL/AT following any blanking period through the 12 months follow-up visit;
- Subsequent catheter ablation or surgical treatment for AF/AFL/AT following any blanking period through the final follow-up visit;
- Other scenarios indicative of treatment failure suggested by relevant medical societies.

B. Secondary Effectiveness Endpoints

Depending on the design of the device and its indications for use, appropriate secondary effectiveness endpoints may include:

- AF burden reduction
- improvement in symptom scores tracking dyspnea, dizziness, or palpitation
- improvement in QOL

- improvement in exercise tolerance
- improvement in ventricular ejection fraction
- improvement in atrial transport function
- atrial remodeling, assessed by decrease in atrial size.

If you intend to present comparisons between groups for a secondary effectiveness endpoint in your labeling, your protocol should include a pre-specified hypothesis for each and an adjustment for multiplicity, as appropriate. Your sample size estimation should take these secondary endpoint hypotheses into account. For secondary endpoints subject to placebo effect, including exercise tolerance, QOL, and symptom scores, we recommend that you design your study to minimize the placebo effect.

Atrial Transport Function

Assessment of the return of atrial transport function following AF ablation has been reported in the literature, and restoration of atrial transport function has been cited as a benefit of the surgical MAZE procedure[3] as well as surgical ablation for isolation of the pulmonary veins for treatment of AF.[4] To date, however, clinical trials have focused almost exclusively on elimination of AF as a rhythm disturbance. FDA believes that recovery of atrial transport function may have a positive impact on QOL and on reduction of the morbidities associated with AF such as stroke and heart failure. If you intend to assess atrial transport function as part of the study, you should consider coupling this assessment with evaluation of morbidity reduction and improvement in QOL. For example, see the scoring method for evaluating and reporting the restoration of atrial transport function proposed by Melo et al.[5]

Ventricular Function

Termination of the AF rhythm disturbance and the associated erratic and elevated ventricular rates may result in improvement in ventricular function. If you plan to assess ventricular function, your study design should include some means for evaluating ventricular function and ventricular dimensions, both pre- and post-procedure. This may include echocardiographic or other imaging evaluations of ventricular dimensions and ejection fraction coincident with assessment of rhythm state at the effectiveness evaluation.

C. Primary Safety Evaluation

For primary safety evaluation, FDA recommends a composite safety endpoint consisting of serious adverse events including, but not limited to:

[3] Yuda S, Nakatani S, Kosakai Y, et al. Long-term follow-up of atrial contraction after the maze procedure in patients with mitral valve disease. *J Am Coll Cardiol* 2001;37(6):1622-7.

[4] Thomas L, Boyd A, Thomas SP, et al. Atrial structural remodeling and restoration of atrial contraction after linear ablation for atrial fibrillation. *Eur Heart J* 2003;24(21):1942-51.

[5] Melo JQ, Neves J, Adragao P et al. When and how to report results of surgery on atrial fibrillation. *Eur J Cardiothorac Surg*. 1997;12(5):739-44.

- all-cause death
- stroke and transient ischemic attack (TIA)
- myocardial infarction (MI)
- thromboembolic events (pulmonary embolism and peripheral embolism)
- excessive bleeding
- deep sternal wound infection/mediastinitis
- damage to the specialized conduction system requiring permanent pacemaker
- damage to peripheral structures, such as the esophagus and phrenic nerve
- pulmonary vein (PV) stenosis.

Depending on the specifics of the surgical approach and the device/safety, there may be other appropriate serious adverse events to include.

In terms of safety and evaluation of adverse events, the investigational plan must include a description and analysis of all increased risks to which subjects will be exposed by the investigation. (See 21 CFR 812.25(c).) The sponsor must immediately conduct an evaluation of any unanticipated adverse device effect (UADE) (21 CFR 812.46(b)), and ensure that any reviewing IRB and FDA are promptly informed of significant new information about an investigation (21 CFR 812.40). If the sponsor determines that a UADE presents an unreasonable risk to subjects, the sponsor must terminate all investigations presenting such risk as soon as possible, and not later than five working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the UADE (21 CFR 812.46(b)(2)).

FDA believes that a one year follow-up for safety evaluation provides sufficient time to evaluate adverse events such as PV stenosis that may be manifested or progressive only at late time points in some subjects. A shorter follow-up period, e.g., less than one year, may be appropriate if using your device under direct visualization does not pose a risk of PV stenosis. If you believe this is the case, you should provide a sound rationale for follow-up duration of less than one year.

Pulmonary Vein Stenosis

When PV stenosis is identified as a risk associated with your device, we recommend that you evaluate PV stenosis using a baseline imaging study (CT or MRI), followed by an assessment using the same method within 3 to 6 months of the ablation procedure to screen for PV stenosis. If subjects show evidence of PV stenosis, we recommend additional follow-up imaging at twelve months post-procedure to evaluate stenosis progression.

Consistent with the recommendation from the 2012 HRS/EHRA/ECAS Expert Consensus Statement in Surgical and Catheter Ablation of AF,[2] FDA recommends that PV stenosis be categorized as mild < 50%, moderate 50-70% and severe ≥ 70% reduction in the diameter of a PV or PV branch; a severe PV stenosis should be considered a major complication and thus contribute to the primary safety endpoint. We also recommend that an independent, masked observer in a central core laboratory perform all evaluations of the imaging studies done to evaluate PV stenosis.

Case report forms should include a means for determining whether subjects are experiencing symptoms suggestive of PV stenosis.

We believe subjects in a control arm who are not undergoing ablation are unlikely to experience PV stenosis and therefore need not be evaluated by imaging. A study using a surgical ablation procedure that involves direct visualization of the ablation device when used in the vicinity of the pulmonary veins need not include assessment of PV stenosis. If you determine that the risk of PV stenosis is minimal and therefore reason that PV assessment is not warranted in your study, we recommend that you describe how you made this determination and provide a scientific rationale in support of your reasoning.

Neurological assessment

Available literature suggests that clinically evident neurological injury as well as asymptomatic cerebral embolism may occur in ablation subjects periprocedurally. The pathophysiology and clinical significance of asymptomatic cerebral emboli remain unclear, but there may be some emboli that are not completely asymptomatic and thus are more appropriately categorized as stroke or TIA when adequately investigated. Therefore, subjects undergoing surgical ablation should undergo standardized neurological evaluation before and after the ablation procedure. Moreover, the agency recommends that at least a subset of study subjects undergo more specialized neurologic evaluations. The following points should be considered when designing the neurological assessment for the subset of patients:

- The number (percentage) of patients in the subset should depend on the type of device, the type of trial, and existing pre-clinical and clinical data;
- The neurological assessments should occur at baseline, prior to discharge, 1 month post procedure, and after any neurological event;
- Clinical tests should include a standardized complete neurological physical examination. Standarized scales for assessment of neurologic deficit (such as the NIH Stroke Scale (NIHSS)) and of stroke disability (such as the Modified Rankin Score (MRS)) should be considered for those diagnosed with neurological events at the time of the event and at 90 days post-event. Cognitive testing should be considered when assessment of global neurologic function is appropriate;
- The neurological physical examination should be performed by a neurologist. Personnel performing other tests should be certified (external certification for NIHSS, either internal or external certification for MRS). The assessors should be independent from the study;
- The use of specialized neuroimaging techniques should be considered when a goal is detection of asymptomatic vascular injury;

7. Study Groups

FDA recommends that your study include patient populations in which the proposed therapy is most likely to show benefit. Selection of study subjects should carefully balance inclusion of subjects with characteristics needed to support a broad indication with exclusion of subjects to control for potential confounding factors. We recommend that your protocol list inclusion and

exclusion criteria to define precisely the patient population likely to benefit from the proposed therapy. Additionally, your study design should account for prior complications and previous treatments of AF.

The selected inclusion and exclusion criteria should ensure that subjects have a type of AF (i.e., paroxysmal, persistent, or longstanding persistent) that is consistent with the device's proposed indication for use. For all types of AF we expect the subjects to have a documented history of AF-associated symptoms. Moreover, we recommend that your protocol specify the minimum AF documentation requirement for the type(s) of AF you intend to study. In this regard, we believe you should follow the relevant recommendations from the 2012 HRS/EHRA/ECAS Expert Consensus Statement in Surgical and Catheter Ablation of AF.[2]

Consistent with ACC/AHA/ESC 2006 Guidelines for the Management of Patients with AF[6] and HRS/EHRA/ECAS Expert Consensus Statement,[2] we recommend that AF ablation trials primarily include subjects who have failed or are intolerant to at least one Vaughan-Williams[7] class I or class III AAD. Depending on the study design, it may also be possible to include subjects who have failed only rate control medical therapy. We also believe that for the purpose of interpreting study results, subjects with confounding characteristics should be excluded from your study. For example, subjects with a previous left atrial ablation procedure should be excluded from your study, unless that patient population is consistent with the indications you are seeking.

8. Other Study Design Recommendations

A. Anti-Arrhythmic Drug Therapy

We recommend that you evaluate the long-term effectiveness of the ablation procedure in the absence of AAD therapy. That is, if you reinitiate AAD therapy after the procedure, all study subjects that receive ablation treatment should discontinue AAD use prior to the end of any blanking period. Alternatively, either as a primary or secondary effectiveness endpoint, it may be appropriate to evaluate the effectiveness of ablative therapy in the presence of a previously ineffective AAD therapy, as explained above. FDA considers AAD therapy to include primarily Vaughan-Williams[7] Class I and Class III agents but not to include rate control medical therapy. FDA does not consider rate control medical therapy to be likely to affect AF recurrence and it would be appropriate to continue to administer these agents to study subjects consistent with widely accepted medical practice.

[6] Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation. *Circulation* 2006;114:e257-e354.

[7] Vaughan Williams EM. Classification of anti-arrhythmic drugs. *Symposium on Cardiac Arrhythmias.* 1970;449-472.

B. Anticoagulation

We recommend that you describe in detail your post-procedure anticoagulation protocols. You may elect to design your study with a pre-specified period that requires anticoagulation following the ablation procedure. Beyond such a defined period of required anticoagulation, we recommend that your protocol follow the published practice ACC/AHA/ESC 2006 Guidelines for managing patients with AF. These guidelines advise treatment with anticoagulation therapy according to the patient's stroke risk rather than according to the presence or type of AF, as advised by the HRS/EHRA/ECAS Expert Consensus Statement.[2] The protocol should clearly specify appropriate monitoring and documentation of anticoagulation status during the follow-up phase.

C. Non-Inferiority Versus Superiority

If the control group consists of subjects treated with a legally marketed surgical ablation device, the study may be designed to demonstrate non-inferiority or superiority. If your study hypothesis is intended to test non-inferiority, we recommend you provide an appropriate clinical justification for the non-inferiority margin that you choose. If your study hypothesis is intended to test superiority, we recommend you demonstrate a statistically meaningful benefit/risk profile showing improved benefit, reduced risk, or both. For non-inferiority studies, in addition to the non-inferiority margins used to test your study hypotheses, we recommend you establish a minimum acceptable performance floor to prevent the potential non-inferiority creep after several iterations of trials.

Sample Size

We recommend that you provide a statistical justification for any sample size calculation. FDA recommends that you take into account all endpoints, primary and secondary, when calculating the sample size, especially in the circumstance where you intend to present comparisons between groups in your labeling for any secondary effectiveness endpoints. This will help to provide statistical robustness for your study endpoints. We believe that, due to low event rates, the primary safety endpoint will likely drive the sample size in most studies.

D. Follow-Up of Study Subjects

We recommend that you develop standardized protocols for outpatient follow-up visits to be conducted at 30 days, three months, six months, nine months, and twelve months regardless of the AF type being studied (i.e. paroxysmal, persistent, or longstanding persistent AF). Follow-up visits should typically include documentation of symptoms and assessment of cardiac rhythm with 12-lead ECG, Holter monitoring, or other equivalent cardiac rhythm measurements. For paroxysmal AF indications, the minimum following-up screening for atrial tachyarrhythmia recurrences should include a 12-lead ECG at each follow-up visit, scheduled and symptom-driven event recording from the end of the blanking period to the end of follow-up, and a Holter at the end of the follow-up period. For persistent and longstanding persistent AF indications, the minimum follow-up screening should include a

12-lead ECG at each follow-up visit, a Holter every 6 months, and symptom-driven even monitoring. For evaluation of PV stenosis, the follow-up visits should include CT or MR imaging, as appropriate.

In addition to the premarket follow-up considerations discussed above, extended, long-term post-approval studies may be appropriate for class III (premarket approval) devices to assess the stability of the treatment effect and any specific long-term safety and effectiveness concerns that arise during the premarket study. For devices for which post-approval studies are anticipated or a possibility, we recommend your study continue to follow subjects every six months beyond marketing approval. In the event that FDA requires a post-approval study as a condition of the PMA approval (see 21 CFR 814.82(a)(2)), incorporating this extended follow-up in the original pivotal study will allow you to easily convert the premarket study into a post-approval study. This may free you from having to obtain new informed consent from study subjects for additional follow-up and having to recruit new subjects. In such an approach, you would obtain subject consent for up to five years of follow-up, but specify a one-year follow-up time period for purposes of gathering premarket safety and effectiveness data. Upon approval of your device, subjects who were treated with your device during the clinical investigation could be followed for a total of up to five years post-ablation as part of a post-market study without the need to seek a new informed consent for the additional follow-up period.

The importance of adequate and appropriate follow-up of study subjects cannot be overemphasized. Complete results obtained from effective follow-up contribute significantly to our ability to evaluate your marketing application; therefore, we recommend you make every effort to ensure that subjects participate in all scheduled post-procedure testing specified in your study protocol. Since missing data may be an issue at the time of data analysis, FDA recommends that the investigational protocol pre-specify one or more methods for handling missing data.

E. Blanking Period

A blanking period is a time interval following treatment during which success criteria are not counted for purposes of evaluating study endpoints. Since cardio-thoracic surgery in and of itself can provoke transient episodes of AF, and it is believed that these early recurrences are not indicative of longer-term success, we recommend that you employ a blanking period of three months during which the effectiveness of the device is not evaluated by arrhythmia monitoring. During the blanking period, you should monitor subjects for AF recurrence and you should record and document any AF events, but you should not consider recurrence of AF during this period as treatment failures.

F. Investigator Selection and Training

Sponsors must select investigators who are qualified by training and experience to investigate the device that is the subject of the study (21 CFR 812.43(a)). If the primary investigator does not have experience with electrophysiological techniques, we recommend that an investigator who has such expertise participate in the investigational procedure to assist with

verification of conduction block. If an investigator or other site staff lack a thorough knowledge of the clinical procedures used in your study, we recommend that you provide training on the procedures. It may be appropriate to include a small number of subjects per site that will not be included in the endpoint evaluation (sometimes termed "roll-in" subjects) in order to avoid a learning curve bias. The inclusion of a subject as a "roll-in" subject should be specified prior to treating the subject and prior to subject randomization (if applicable).

G. Study Monitoring

Sponsors must ensure proper monitoring of the investigation (21 CFR 812.40), and the investigational plan must include the sponsor's written procedures for monitoring the investigation and the name and address of any monitor. (See 21 CFR 812.25(e).) We recommend that you select experienced monitors and ensure that investigators adhere to the investigational plan. A sponsor who discovers that an investigator is not complying with the investigational plan must promptly either secure compliance or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation (21 CFR 812.46(a)). We recommend you establish an independent Clinical Events Committee comprised of practicing physician of appropriate expertise to adjudicate reported adverse events. In addition, please see the FDA's guidance entitled Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring, which is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf for recommended approaches to monitoring clinical investigations involving FDA-regulated products.