Date: **August 15, 2007**
To: **Members of the Circulatory Support Devices Advisory Panel**
From: **Benjamin C. Eloff, Ph.D**

General Issue: Clinical trial designs for cardiac ablation devices designed to treat patients with medically refractory atrial fibrillation.

Executive Summary

Abstract

Atrial fibrillation (AF) is a disease that affects over two million Americans. Current standard-of-care medical therapies lead to AF recurrence in 50% of patients. Patients and physicians opt for device therapy over 50 thousand times per year to ablate the cardiac tissue thought to be responsible for the abnormal rhythm. The devices being used have been approved for other purposes such as treatment of atrial flutter, or supraventricular tachycardia, but have not been evaluated or approved for treatment of AF by FDA, and are being used off-label. Several manufacturers are sponsoring studies to provide a reasonable assurance of safety and effectiveness to support a premarket approval (PMA), with varying success. FDA has convened meetings of this advisory panel to discuss this issues twice previously in 1998 and 2000, but many of the same issues still exist. FDA is seeking the advice of the 2007 advisory panel to continue to discuss atrial fibrillation trial design issues.

Abbreviations used

FDA:	Food and Drug Administration	RF:	Radiofrequency
PMA:	Premarket Approval	RCT:	Randomized Controlled Trial
AF:	Atrial Fibrillation	PG:	Performance Goal
SAE:	Serious Adverse Event	HF:	Heart failure

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Introduction to Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia diagnosed and treated in clinical practice. Although not life threatening it has significant serious consequences to health and longevity for individuals afflicted. Because of this and its prevalence it is a major public health problem. There are multiple treatments available and many new therapies are being tested. Percutaneous catheter ablation is becoming much more common although no catheter ablation device is approved by the FDA for treatment of AF. It is this clinical environment that prompts the FDA to call an expert advisory committee for discussion of clinical trials that could be performed to best evaluate the safety and effectiveness of specific devices prior to approval for this indication.

It is estimated that over 2 million people in the US have either paroxysmal or persistent AF. [1] The prevalence of AF is estimated to be 0.4% to 1% in the general population and increases with age.

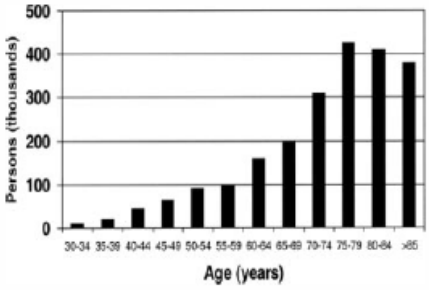

Figure 4. Estimated age-specific prevalence of atrial fibrillation (AF) based on 4 population-based surveys. Prevalence, age, distribution, and gender of patients with AF analysis and implications. Modified with permission from Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995;155:469–73.[19] Copyright © 1995, American Medical Association. All rights reserved.

AF can be characterized by the temporal recurrence of episodes. Based on the ACC/AHA/ESC guideline document[1] and the HRS consensus document[2] the classification used by the FDA is:

- Paroxysmal – recurrent AF that terminates spontaneously
- Persistent – recurrent AF sustained beyond 7 days or lasting less than 7 days but required pharmacologic or electrical cardioversion
    - Long standing persistent – continuous AF of greater than one year
- Permanent – cardioversion failed or not attempted

The HRS consensus document argues that the term permanent AF is not appropriate in the discussion of treatment of AF as that designation implies the decision to not treat has been made. The FDA would agree with this definition in the patient in whom the decision was made to not attempt cardioversion. Because of the lack of consistency of classification it has been difficult to compare or group treatment results reported in the literature from single center experience.

The duration of AF refers both to individual episodes and to how long the patient has been affected by the arrhythmia. Thus, a patient with paroxysmal AF may have episodes that last seconds to hours occurring repeatedly for years.

There are several theories on the etiology or mechanism of AF. Over the past decade or so it has become accepted that a subset of patients have focal AF with the trigger site being in the muscular sleeves of the pulmonary veins. The figure below is excerpted from the HRS consensus document. [2]

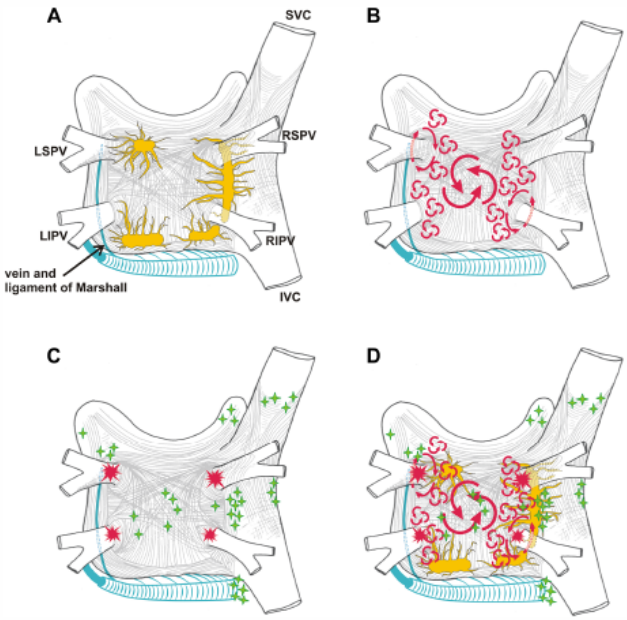

Figure 1 Structure and mechanisms of atrial fibrillation. **A:** Schematic drawing of the left and right atria as viewed from the posterior. The extension of muscular fibers onto the PVs can be appreciated. Shown in *yellow* are the four major LA autonomic ganglionic plexi and axons (superior left, inferior left, anterior right, and inferior right). Shown in *blue* is the coronary sinus which is enveloped by muscular fibers which have connections to the atria. Also shown in *blue* is the vein and ligament of Marshall which travels from the coronary sinus to the region between the left superior PV and the LA appendage. **B:** Large and small reentrant wavelets that play a role in initiating and sustaining AF. **C:** Common locations of PV *(red)* and also the common sites of origin of non PV triggers (shown in *green*). **D:** Composite of the anatomic and arrhythmic mechanisms of AF. (Adapted from Circulation,[13] Am J Cardiol,[336] and Tex Heart Inst J.[337])

Although diagnosis of AF is usually straightforward the treatment has remained challenging. Treatment goals are relief of symptoms if present, prevention of thromboembolic complications, preservation of cardiac function and improved longevity. First line treatment includes control of ventricular rate and anticoagulation if the patient is at risk for thromboembolism. The possibility of a curative treatment, as opposed to palliation with anti-arrhythmic medications, has led to a variety of ablative approaches and strategies. Treatment by ablation may work by protecting the left atrium from triggers in the pulmonary vein and/or changing the atrial substrate. Research is ongoing to determine the amount of improvement after ablation of autonomic ganglia.

In part drawing upon the work of Moe et al.[3], Cox et al., over the last 2 decades, have devised and refined a surgical procedure intended to treat atrial fibrillation[4-6]. Using a pattern of left- and right-atrial incisions/reapproximations and other techniques of tissue ablation (e.g., cryotherapy), the surgeon creates an atrial pathway down which the electrical impulse from sinoatrial node can preferentially travel; the location of the incision lines allow for activation of the entire atria while at the same time blocking the propagation of reentrant circuits presumed responsible for fibrillation. The current iteration of the procedure (the Cox-Maze III) is now generally considered to be the "gold-standard" for the surgical treatment of atrial fibrillation, with individual centers' series of results often reporting long-term rates of freedom from atrial fibrillation between 70% and 95%.(see figure below[7]) It is a fairly complex and lengthy operation, however, and many surgeons are thus reticent to perform it in either a stand-alone or concomitant fashion. Investigations by, among others, Haissaguerre et al.[8] and Sueda et al.[9] have stressed a greater contribution of the left atrium and pulmonary vein orifices (as compared to the right) in the genesis of some classifications of atrial fibrillation. Accordingly, there has been much interest in minimizing the necessary extent of the Maze procedure by limiting it to the left side only (e.g., pulmonary vein "isolation" only) and by utilizing discrete energy delivered by devices rather than the "cut-and-sew" approach. There is no generally accepted consensus to date on what constitutes either the type or extent of lesion sets necessary to best emulate the Cox-Maze III procedure.

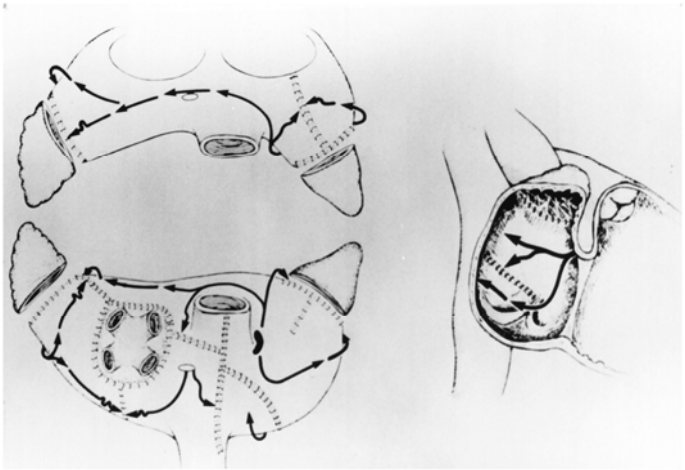

Figure 3: The Maze-III procedure. The lower left panel shows a posterior view of both atria. The left upper panel is drawn as if the atria had been cut in half with the front half flipped upwards. The right panel is a cut-away view of the right atrium.
The incisions are shown, and they create "dead-ends" for the macro-reentrant circuits that could otherwise result in atrial fibrillation. Heavy dark arrows represent the direction of propagation of a sinus beat following the procedure. Modified from: Cox JL. Surgical Treatment of Supraventricular Tachyarrhythmias. In: Cohn LH, Edmunds LH Jr, eds. Cardiac Surgery in the Adult. New York: McGraw-Hill, 2003[7].

The HRS consensus document states that catheter ablation in clinical practice is indicated in the patient with symptomatic AF refractory or intolerant to at least one Class 1 or 3 antiarrhythmic medication (AAD). The document also states that "in rare clinical situations, it may be appropriate to perform AF ablation as first line therapy".

There are many different techniques or approaches to percutaneous catheter ablation, with different success rates reported. These include segmental ostial pulmonary vein isolation, circumferential pulmonary vein isolation (continuous circular lesions) and ablation of complex fractionated atrial electrograms (CFAE). These approaches may include linear lesions in the posterior left atrium, linear lesions connecting the pulmonary vein isolation lesions to the mitral valve, isolation of the superior vena cava and/or ablation of non-pulmonary vein triggers. The Heart Rhythm Society consensus document on catheter ablation of AF states "Although much has been learned about the

mechanisms of AF, the mechanisms remain incompletely understood. Because of this, it is not possible to precisely tailor an ablation strategy to a particular AF mechanism."

Over the past decade there have been many single center reports of ablation results and there have been multiple consensus documents and guidelines recently published[1, 2, 10]. The single center reports have varied in terms of patient population treated and method of ablation. The method of determining acute ablation procedural success as well as chronic clinical success of the procedure has varied from center to center.

Effectiveness results range from 28[11] -30%[12] to 93%[13] -100%[14]. There is no standard definition for a successful acute or chronic ablation procedure. There also has not been any standard method of surveillance for AF recurrence. Most centers report a higher rate of success in patients with paroxysmal versus permanent AF. Many patients require more than one ablation procedure either to treat recurrence of AF or an iatrogenic arrhythmia such as left atrial flutter.

The figure below is excerpted from the Ablation for Paroxysmal Atrial Fibrillation or APAF trial reported in 2006[13].

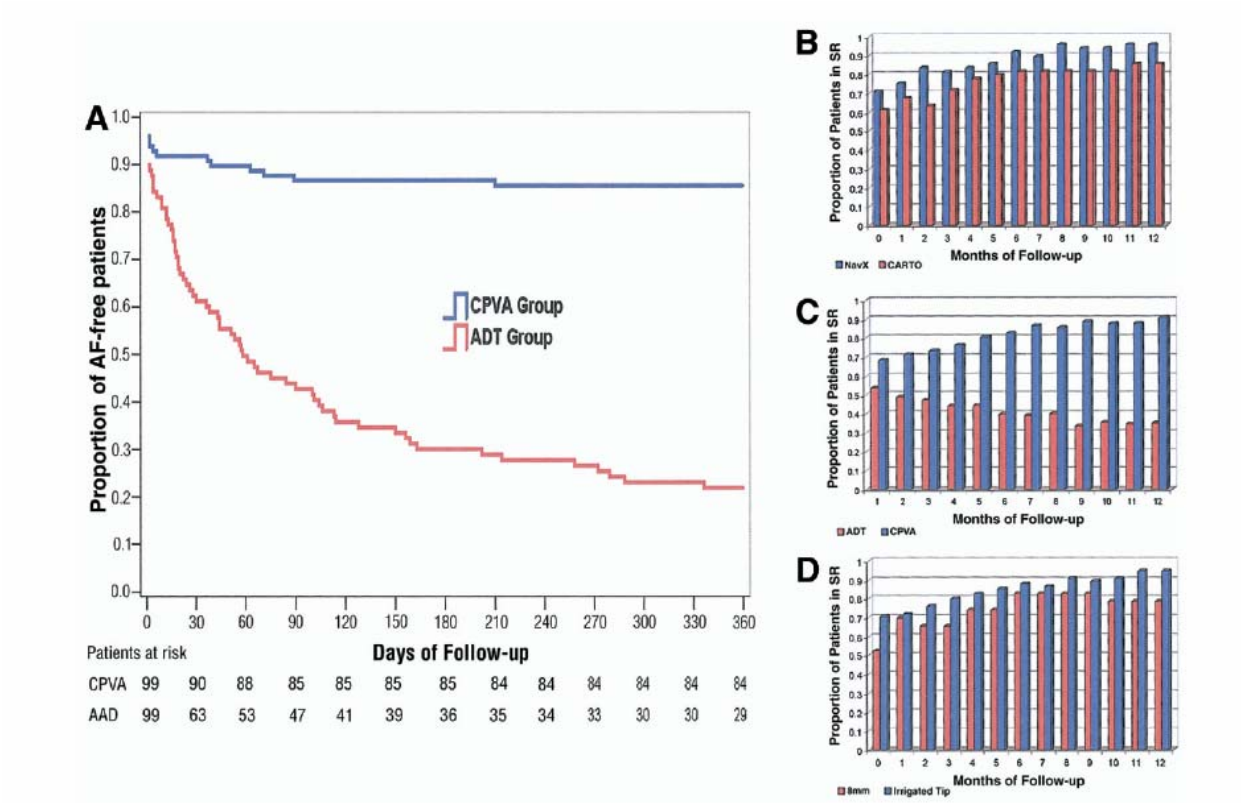

Figure 4. Outcomes in the APAF (Ablation for Paroxysmal Atrial Fibrillation) trial. **(A)** By Kaplan-Meier analysis, 86% of patients randomized to circumferential pulmonary vein ablation (CPVA) needed only a single procedure and were atrial tachyarrhythmia (AT)-free at the end of follow-up as compared with the 22% of patients randomized to antiarrhythmic drug therapy (ADT) ($p < 0.001$) who did not require a second ADT and were AT-free at the end of follow-up; time 0 started at the end of the 6-week blanking period for both groups. **(B and C)** Monthly rhythm analysis in the NavX versus CARTO subgroups (95% and 87% at 1 year, respectively, $p = 0.08$) and in the 8-mm versus irrigated tip catheter groups (95% and 78% at 1 year, respectively, $p = 0.03$). **(D)** By monthly rhythm analysis that also took into account the outcome of the second procedure and for patients controlled with combined therapy in ADT group, 93% of CPVA patients were free from ATs as compared with the 35% in the ADT group. SR = sinus rhythm.

The incidence of major complications in a survey by Cappato[15] in nearly 9,000 patients were reported to be 6% including death (0.05%), stroke (0.28%), cardiac tamponade

(1.2%), and PV stenosis(1.3%). However, safety has not been consistently addressed in the majority of the published literature. There are reports of rare catastrophic events, such as atrio-esophageal fistula.[16-18] the frequency of which need to be better characterized.

Perhaps of most significance for determining the effectiveness of the procedure is the type and duration of rhythm surveillance post ablation. A recent publication by Martinek et al[12] showed in a very small group of patients with implanted Medtronic AT500 pacemakers that the number of patients with long term freedom of AF off anti-arrhythmic medications was 29%.

There have been multiple reports that patients become less symptomatic or even asymptomatic after ablation even with continuation of AF episodes[19, 20]. There have been multiple unblinded studies of quality of life (QOL) in patients that have had catheter ablation to treat paroxysmal AF. One study showed that even without complete success of the procedure the QOL questionnaire results improved significantly[21].

Regulatory Status of Ablation Devices for Treatment of AF

In the early 1990s, there were no devices that were FDA-approved for the treatment of cardiac arrhythmias, such as supraventricular tachycardia (SVT), atrial flutter, or AF. However, there are several literature articles which discuss the use of electrophysiology mapping catheters being used off-label to treat cardiac arrhythmias. In this context, off-label applies to the use of devices for a purpose or indication other than the indication that FDA approved.

The off-label use of modified mapping catheters was problematic in that there were numerous reports of adverse events and device failures leading to patient injury. In an effort to regulate these Class III (the highest of the risk categories) devices, FDA called for clinical studies to support premarket applications (PMAs). The first generation of ablation catheters that FDA approved to market in the mid 1990s was the class of 4 mm tip, non-irrigated, radiofrequency (RF) catheters indicated for the treatment of SVT. (Note that FDA has since approved a cryoablation device for the treatment of AV node reentrant tachycardia).

After the first series of applications were approved for SVT, FDA formulated objective performance criteria (OPC) with the input of the Circulatory Systems Devices panel that were applied to the primary safety and effectiveness endpoints for these studies. Not surprisingly, once the initial class of ablation catheters was available for use to treat SVT, physicians began to use these catheters for another off-label indication, atrial flutter.

Similar to the original SVT paradigm, FDA worked with catheter manufacturers and the FDA Advisory Panel to develop clinical studies, performance goals, and endpoints for devices indicated for the treatment of atrial flutter. This next generation of device saw the expansion of ablation catheter technology to include 8-mm tip RF catheters and irrigated RF catheters. As a frame of reference, the first catheter for the treatment of atrial flutter was approved in 2002. A total of 6 ablation catheters for atrial flutter have been approved since that time.

As with the prior paradigm, the availability of more legally marketed ablation catheters meant that more catheters could be used off-label. With respect to treatment of AF, this was no exception. As explained elsewhere in this document, the off-label use of catheters for the treatment of AF has been prevalent for over 10 years, but its practice has increased significantly in line with the increased research and understanding of the etiology of AF. This fact is validated by the number of published papers on catheter ablation on the treatment of AF, as well as data from the Center for Medicare and Medicaid Services (CMS) which document the prevalent reimbursement of procedures for treatment of AF.

In turn, FDA has recognized the need for catheter manufacturers to develop clinical studies that generate valid scientific evidence, in order to scientifically evaluate the safety and effectiveness profile of devices intended for the treatment of AF.

FDA's Charge in Approving New Medical Devices

FDA approves a PMA if the application contains sufficient "valid scientific evidence" to assure that the device is reasonably safe and effective for the proposed intended use.

As defined 21 Code of Federal Regulations (CFR) §860.7, **valid scientific evidence** is evidence from:

- well-controlled investigations,;
- partially-controlled studies;
- studies and objective trials without matched controls;
- well-documented case histories conducted by qualified experts; and
- reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

The evidence required may vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, and the extent of experience with its use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety and effectiveness. Such information may be considered, however, in identifying a device the safety and effectiveness of which is questionable.

There is reasonable assurance that a device is **safe** when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device, when accompanied by adequate labeling (directions and warnings against unsafe use), outweigh any probable risks. Reasonable assurance of **effectiveness** is established when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate labeling, will provide clinically significant results.

In the review of a PMA for a Class III medical device, the scope and extent of FDA's charge, as directed by the FDA regulations, is to evaluate the exact device(s) and indications for use that are sought in the marketing application. What is important to clarify here is that different people may have differing objectives in what they intend to learn from the study of a novel device or a new intended use for that device. For example, a scientific researcher may be interested in exploring an answer to a provocative scientific question involving the device or patient population, either to serve as a platform for further research or for potential incorporation into clinical practice. In contrast, FDA does not run clinical studies, nor does the Agency identify the scientific question that a medical device manufacturer needs to address in a clinical study. Based on what the manufacturer proposes regarding the device and indication for use, FDA will provide guidance and direct the manufacturer to collect the safety and effectiveness information that is considered valid scientific evidence and which may provide reasonable assurance of safety and effectiveness to support a PMA application.

FDA is committed to the least burdensome principle throughout the regulatory process of medical devices. IDE regulations are written so as to not hinder investigations into novel uses of devices. FDA strives to help design trials that will produce interpretable data.

AF issues common to surgical and percutaneous therapies

FDA highlights important issues relating to the use of devices for the treatment of AF below. Each point below is reflected in one of the questions to the panel members to be discussed during the meeting. This section highlights important issues that are applicable to percutaneous catheter ablation and surgical ablation techniques.

Enrollment issues

FDA has felt that it is important to identify the type of AF in order to study patients with different patterns of AF separately, since we believe the safety and effectiveness profile of a device may be different depending on the type of AF being treated.

FDA has considered rhythm monitoring for recurrent AF to be important given the effectiveness endpoints that we have been considering. Those endpoints have focused on an electrocardiographic assessment of recurrent AF. Since recurrence of AF has been a focus of our attention, we have been concerned about the degree of documentation of AF prior to enrollment for purposes of study eligibility. For paroxysmal AF, we have asked that patients have a minimum of a 6-month history of AF with at least two (2) discrete episodes (documented by ECG) within the month prior to enrollment. For permanent AF, we have asked that patients have continuous AF for at least 3-6 months or have failed an attempt at cardioversion.

Since by definition, different types of AF have different recurrence patterns, FDA has taken the approach that different types of AF should be studied separately. We have taken this approach since we feel that the duration of follow-up and the burden of follow-up monitoring/documentation may be different.

For paroxysmal AF, we have felt that a minimum of 1 y follow-up with frequent surveillance monitoring (for recurrent AF, focusing on symptomatic AF) is important. For permanent AF, we have felt that a minimum of 6 months follow-up, with an assessment of rhythm at 6 months (either by 12-lead ECG or a 24 hour Holter Monitor) was adequate based on the following assumption: If AF is not identified at 6 months, then a patient with pre-ablation permanent AF is unlikely to have been in AF during the preceding 6 months (blanking period aside). For persistent AF, we have taken an intermediate approach, requesting 9 months of follow-up, asking for a 7 day Holter Monitor at 9 months and the availability of an Event Recorder if symptoms of recurrent AF are reported. As an alternative, the 2007 HRS consensus document offers the following approach to monitoring for industry-sponsored device approval studies:

A minimum assessment of symptomatic AF and search for asymptomatic AF at six months intervals thereafter using one of the following:

i) Trans-telephonic monitoring for four weeks around the follow-up interval for symptom-triggered recording with a minimum of weekly transmissions to detect asymptomatic events
ii) 24 to 72 hour Holter monitoring
iii) Thirty-day auto triggered event monitoring or mobile cardiac outpatient telemetry[2]

FDA has also been concerned that AF ablation might result in conversion of one type of AF to another. For example, a patient with pre-ablation permanent AF may experience post-ablation paroxysmal AF. The 2007 HRS consensus document does not

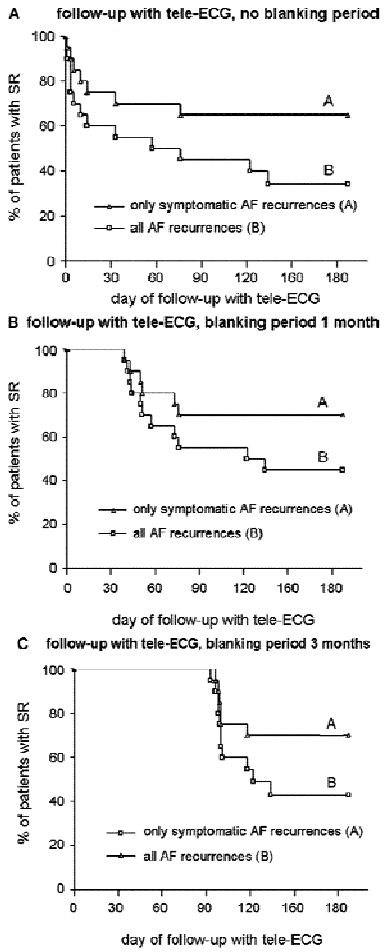

Figure 2. *Diagram showing the postinterventional follow-up after AF ablation using transtelephonic ECG transmissions every 2 days. The time to the first AF relapse is illustrated on a Kaplan-Meier survival analysis. Plot B represents the analysis including all documented AF recurrences. Plot A represents the analysis including only symptomatic AF recurrences and thereby simulating a symptom-only-based follow-up. Figure 2a shows the analysis without any blanking period. In Figure 2b, a blanking period of 1 month was introduced. AF recurrences during that month were ignored and not considered as therapeutical failures. In Figure 2c, the blanking period was extended to 3 months. The long-term outcome did not change compared to the 1-month blanking, suggesting that all patients with AF recurrences after the first postinterventional month continued to have AF recurrences. From Piorkowski et al. J Cardiovasc Electrophysiol. 2005*[21]

differentiate between the classifications of AF for the purpose of post-ablation monitoring.[2]

FDA recognizes that this approach is predicated on an assessment of recurrence of AF as the primary effectiveness endpoint. However, FDA has recently received feedback from the Circulatory System Devices panel that recurrence of a clinically insignificant arrhythmia of short duration by itself may not be an appropriate method to characterize effectiveness. FDA is open to alternative definitions of effectiveness; however, the sponsor is responsible for presenting accurate quantitative data to support their measurement of effectiveness. For example, if the proposed definition for effectiveness is a "clinically significant" recurrence, the sponsor would need to account for investigator and patient bias, and a means to quantify the endpoint.

Symptomatic and asymptomatic recurrence

AF is associated with an increased long-term risk of stroke, heart failure and all-cause mortality [22, 23]. This may not be substantially different for patients with symptomatic vs. asymptomatic AF[24]. There is published literature to suggest that AF ablation may convert some patients from symptomatic AF to asymptomatic AF[19].

The figure to the left from Piorkowski et al[20] demonstrates the rates of symptomatic and asymptomatic recurrence of AF post-ablation, with different blanking periods. Interestingly, the duration of the blanking period has no effect on the rates of recurrence in these patients. The following quote from Arya et al[25] is instructive for the detection of asymptomatic AF: "The rate of asymptomatic AF varies among the different studies and this difference largely arises from the *intensity* of the follow up."

AF in heart failure

Heart failure is a public health problem and frequently co-exists with AF. The following table is reproduced from the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation[1]:

TABLE 2. Prevalence of AF in Patients With Heart Failure as Reflected in Several Heart Failure Trials

Predominant NYHA Class	Prevalence of AF (%)	Study
I	4	SOLVD–Prevention (1992)(14a)
II-III	10 to 26	SOLVD–Treatment (1991) (14b) CHF-STAT (1995) (14c) MERIT-HF (1999) (14d) DIAMOND-CHF (1999) (501)
II-IV	12 to 27	CHARM (2003) Val-HeFT (2003) (848)
III-IV	20 to 29	Middlekauff (1991) (14e) Stevenson (1996) GESICA (1994) (14f)
IV	50	CONSENSUS (1987) (14g)

Additionally, SCD-HeFT [26] reported ~ 15% of enrolled patients (NYHA class II/III) had AF (or atrial flutter).

The presence of AF may be detrimental to patients with heart failure in the following ways (ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult—Summary Article [27]).

1. the loss of atrial enhancement of ventricular filling may compromise cardiac output;
2. the rapid heart rate may increase demand and decrease coronary perfusion (by shortening ventricular filling time);
3. the rapidity of ventricular response may diminish both cardiac contraction (by aggravating abnormalities of the force-frequency relation) and cardiac relaxation; and
4. the stasis of blood in the fibrillating atria may predispose patients to pulmonary or systemic emboli.

Consequently, there may be interest in attempting to ablate AF in heart failure patients in an attempt to prevent AF recurrence.

Patients with heart failure may have left ventricular systolic dysfunction, enlarged left atria, and may not tolerate invasive procedures as well as patients without heart failure. Therefore, the risks and benefits of AF ablation may be different in patients with heart failure as opposed to patients without heart failure.

Anticoagulation

FDA's impression is that one of the reasons patients (and perhaps clinicians) are interested in AF ablation is the thought that warfarin may be stopped if the ablation is considered to be successful. FDA is unaware of conclusive data that supports the routine discontinuation of anti-coagulation following catheter ablation of AF. Additionally, the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation[1] states **"Drugs and ablation are effective for both rate and rhythm control, and in special circumstances surgery may be the preferred option. Regardless of the approach, the need for anticoagulation is based on stroke risk and not on whether sinus rhythm is maintained."**

Consequently, FDA has two issues regarding anti-coagulation after ablation for AF.

First, for the purpose of the clinical trial, FDA feels that either the need for anti-coagulation should be studied (i.e. the trial should be powered to detect a difference in thromboembolism between those receiving anti-coagulation and those not receiving anti-coagulation), or the ablation should not impact the decision as to whether or not anti-coagulation should be prescribed (i.e. a patient that is an appropriate candidate for anti-coagulation prior to the ablation should remain an appropriate candidate for anti-coagulation after the ablation).

Second, once a device is legally-marketed, any labeling suggesting cessation of anticoagulation after the AF ablation should be substantiated by the clinical trial data; the supporting analyses should be pre-specified in the clinical trial protocol. This type of labeling change would require the submission of another marketing application.

Atrial Function

The goal of AF ablation has generally been in terms of reducing/eliminating AF. However, AF is associated with an increased long-term risk of stroke.[28] There are mixed reports in the literature concerning the effect of left atrial ablation on left atrial transport[29, 30] In the absence of clinical trials of AF ablation powered to look for a reduction in stroke, FDA has felt that some assessment of left atrial transport might provide useful information. This could be in terms of comparing pre-ablation assessments to post-ablation assessments (for patients in SR prior to ablation), comparing post-ablation assessments in successes vs. failures, or it could be in terms of comparing post-ablation assessments in successes to a control group without AF.

The following represents a partial list of the methods that have been described to assess left atrial function:

- Presence or absence of an A wave[31]
- Peak A-wave velocity[29]
- Atrial emptying fraction[29]
- LAA peak emptying velocity[30]
- PV flow systolic wave[29, 30]
- PV flow a-reversal (peak AR)[30]

Trial Design Issues

Below, FDA highlights important points of consideration to issues relating to current and proposed trials designed to support PMAs for catheters intended to treat AF. This discussion is provided as background information to panelists and is intended to relate directly to the questions to be discussed during the meeting.

Discussion of prior AF panel meetings.

The Circulation System Devices Advisory panel met to discuss questions about premarket trials to support the indication of AF treatment by catheter ablation in 1998 and again in 2000. The transcripts for those panel meetings are in the references/appendix to this panel pack.

In 1998 the panel agreed that there was insufficient data in the medical literature to support objective performance criteria or performance goals (PG) for AF catheter ablation clinical trials. They stated that there was no standard for comparison to catheter ablation, "there is no therapy equivalent and *[sic]* should be used as a control". They agreed that the best trial design would be a single arm trial comparing pre-ablation status to post-ablation status. There was no discussion of what absolute value for a chronic performance goal might be adequate with this pre- post-ablation trial design.

The 1998 panel also agreed that patients should have failed one or two antiarrhythmic medications prior to being treated with ablation. There was no consensus about what the acute procedural effectiveness performance goal should be but they did agree that there should be a measurable procedural goal. Chronic effectiveness was discussed as a percent decrease of number of episodes when compared to a monitored baseline period. Several panel members stated that that decrease should be at least 75% of episodes. The risk of stroke and measurement of atrial transport were discussed and the panel agreed that patients should continue to be anti-coagulated until there was data showing that catheter ablation changed the risk for thromboembolism. There was no consensus on what type or duration of arrhythmia monitoring should be employed in these trials.

At the 2000 panel meeting the panel suggested that it might be difficult to enroll patients into a randomized trial and were concerned that the control group would essentially be randomized to an ineffective medical treatment. The methods for measuring the acute procedural success of the ablation lesions were discussed. The meeting ended with a discussion of pulmonary vein stenosis and pulmonary hypertension.

As there have been significant advances in the field of catheter ablation of AF the FDA has additional questions for the advisory panel that can build on these prior discussions.

Development of current guidance document

The agency developed and published a quidance document in 2004[32] discussing the different types of trial designs for pre-market clinical trials meant to support the safety and effectiveness of new devices indicated for the percutaneous ablation of atrial fibrillation. In that guidance document the randomized controlled trial is discussed as being the least burdensome but other trial designs are also discussed. At that point in time, supported by prior panel discussions, the agency felt that there was insufficient literature data available to determine either performance goals or a historical control. In

multiple discussions with different device manufacturers the option of using the effectiveness results reported in the literature was discussed. Manufacturers at that time agreed that a randomized trial against medical therapy was more feasible than comparing their new device effectiveness against single center reported effectiveness results. In addition the medical literature at that time did not contain sufficient information about the safety of the percutaneous ablation procedures.

Trial Design

Device manufacturers and FDA are tasked with designing a trial that can be executed and that will develop clear and interpretable safety and effectiveness data to support a marketing application for ablation devices with an AF indication. While FDA believes that a randomized controlled trial (RCT) is least burdensome in terms of developing clear and interpretable data, there are clearly precedents for use of non-randomized clinical studies that support a marketing application. When nonrandomized designs are employed, issues related to bias and confounding must be adequately addressed so that FDA can confidently conclude that favorable safety and effectiveness results are truly due to the device treatment employed.

However, several factors currently may make it difficult to recruit and enroll patients in an RCT. The healthcare facilities with extensive AF ablation experience are tertiary care centers. By the time patients are referred to the investigators in tertiary care centers, they may have been referred specifically for ablative treatment. Furthermore, in many cases patients are referred specifically for ablative treatment as a first line therapy, despite the recommendations in the most current guidelines for treatment of AF. [1, 2] As a result, patients are unwilling to be randomized in a trial where they may or may not receive the treatment they have been told they should receive to treat their AF.

FDA recognizes that the increasingly widespread use of ablation devices without an AF indication will likely make it increasingly difficult to recruit patients for a randomized trial where the control arm is not ablative treatment. After one or more devices are legally marketed with an AF indication, FDA expects that manufacturers seeking an AF indication for new devices will conduct randomized controlled noninferiority trials where the legally marketed device(s) will serve as an active control.

FDA believes that placebo effect associated with new device use, the patient population actually enrolled, and the rigor of follow-up are key factors to consider when discussing appropriate trial design.

The new device placebo effect is a particularly important consideration when specifying the control group, the study endpoints, and the monitoring modality that will be used to evaluate the effectiveness of ablation catheters. Self-reported AF symptoms have been shown to correlate poorly with AF episodes.[19, 20] Furthermore, FDA is not aware of a feasible means of quantifying the placebo effect in patients who have received ablative treatment for AF. For these reasons FDA believes endpoints should not depend solely on self-reported outcomes or symptoms in trials where patients and investigators are not blinded to the treatment received.

Heterogeneity of the treatment effect is an important consideration when designing the inclusion and exclusion criteria for the AF study. FDA believes it is likely that ablation catheters will have a different risk/benefit profile when used to treat patients with both AF and HF than patients with lone AF. FDA is not aware of any data suggesting that results from a lone AF patient population can be pooled with results from a patient population with AF and concomitant HF.

When designing a clinical trial a balance needs to be struck between protocol standardization and studying devices the way they will be used in clinical practice which may vary from institution to institution. In general, FDA believes that in order to generate evaluable data that will support a marketing application, the ablation procedure, the anti-arrhythmic drug regimen, and post-treatment monitoring should be standardized to the extent possible. FDA may analyze different treatment strategies separately at the time of a PMA application, with the knowledge that these subgroup analyses have limitations.

The confidential briefing package in the attached yellow folder contains summaries of trial designs currently in the pivotal phase provided by the sponsors currently pursuing pivotal trials all of whom have been invited to participate in this panel meeting. In addition, brief summaries of two proposed randomized trial designs are provided in tab 2 of the panel pack binder which will respectively be referred to as Trials A and B.

Trial A, the first design, is similar to the design most device manufacturers are currently pursuing and what is recommended in the guidance document titled "Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation - Guidance for Industry and FDA Staff".[32] It is a multicenter, open label, randomized controlled trial designed to compare ablation treatment to best medical therapy. The primary effectiveness endpoint is a direct comparison of the proportion of patients free from symptomatic AF recurrence through 1 year of follow-up. Because the adverse events expected to occur in the device ablation group is expected to be different from those in the anti-arrhythmic drug group, the primary safety endpoint, the rate of periprocedural serious adverse events (SAEs), is compared to a performance goal.

Trial A: RCT of novel device to medical therapy

- Multicenter, open-label, randomized
- Primary Effectiveness: novel device vs. medical therapy
- Primary Safety: novel device vs. performance goal derived from similar invasive procedures.
- Secondary Safety: novel device vs. medical therapy

Trial B has recently been considered based on the ACC/AHA/ESC guidelines[1] which identify cardiac ablation as second line treatment for patients who have already failed medical management. With these guidelines, FDA believes cardiac ablation can be considered the standard of care for some patients. FDA believes that widely accepted care should be used in the control group for RCTs. Market approval of medical products is a separate but important issue. Therefore, FDA is proposing the following alternative trial design.

Trial B is like the first trial design, a multicenter open label trial. However, it contains three arms so that it is a hybrid between a randomized controlled trial and a trial with a

performance goal control. As a means of reducing bias, patients are randomized between ablative treatment with the investigational device and ablative treatment with another ablation catheter. The third arm is the performance goal. The primary effectiveness and safety endpoints are a comparison to performance goals. However, critical secondary safety and effectiveness endpoints are evaluated based on the comparison of the performance of the investigational device with that of other ablation catheters – not necessarily approved for AF indications.

Trial B: RCT of novel device to "standard of care" ablation therapy and PG

- Multicenter, open-label, randomized
- Primary Effectiveness: novel device vs. PG based upon literature reports
- Secondary Effectiveness: novel device vs. "standard of care" ablation therapy
- Primary Safety: novel device vs. PG based upon literature reports
- Secondary Safety: novel device vs. "standard of care" ablation therapy.

Both trial designs have several elements in common, including follow-up monitoring modality, pre- and post-approval follow-up duration, and inclusion and exclusion criteria. Both trial designs also include at least one endpoint involving a comparison of device performance to a PG derived from historical data. With these two general trial designs in mind, FDA would like the panel to discuss what is an adequate control group and what is an adequate value for the PG's in each trial.

For the purposes of the present discussion, please note that FDA is open to suggestions of other trial designs that, in the opinion of the panel, can be performed in the present medical climate and would result in a reasonable assurance of safety and effectiveness for the device when used in accordance with its labeling. Please note that the prior panel meetings on this subject resulted in recommendations for single-armed trials without a firm recommendation of a value for a PG. If a PG is recommended, please discuss the derivation of a value to be implemented.

Randomized Controlled Trials and Performance Goals

A control group serves as the standard comparison for some intervention. It is typically a group of patients with essentially the same condition, demographics, and prognostic values as those in the treatment group, except that they do not receive the intervention under investigation. The control group may receive no intervention, a different intervention, or the current standard therapy regimen. By attempting to control for as many factors as possible during the study, then any differences observed between treatment and control groups on selected patient outcome measures are presumed to be due to the introduction of the intervention during the clinical trial.

There are different types of control groups that may be employed in device clinical trials. The concurrent randomized control group is considered the gold standard for clinical trials. This type of control can effectively minimize bias in allocating patients to the control or experimental group, effectively balances the two groups with respect to critical demographic and study variables, and support the assumptions associated with standard statistical hypothesis testing[33, 34].

As previously noted a randomized controlled trial design is applicable to AF ablation catheter evaluation when effectiveness is being evaluated. However, the comparison between device and drug management with respect to safety may be difficult due to the

fact that device and drug management could have completely different safety profiles; i.e. sets of serious adverse events are different among treatment arms. Hence, a PG may be needed in order to evaluate some aspects of the safety profile of the catheter regardless of the RCT design.

The essence of a PG is that it is designed to be used as a fixed target(s), a value that should be an objective and meaningful standard to provide a comparison when evaluating the safety and effectiveness of a medical device. It is typically expressed as a rate[35, 36]. Thus, the PG is used as a replacement for traditional concurrent control groups. A PG serves as a benchmark, a minimally acceptable value used in a pass/fail approach in determining if a particular device application is ultimately approvable for marketing. By definition then, a PG is not a control group, but a comparison standard in lieu of a traditional control group.

The PG may be derived from historical trials[37]. Ideally, historical trials should provide patient level data including the clinical outcomes and baseline covariates. However, in order to deem historical trials data acceptable for derivation of a performance goal, several criteria should be met. First, the study groups must be well understood. Second, the patient population must be the same in the historical study as in the proposed treatment group. Third, medical management should be similar for the two study groups. Finally, the time difference between the historical and treatment assessments cannot be too wide. Even if these criteria are met, there is still a chance of confounding factors being completely responsible for an observed treatment effect.

Pocock lists five requirements for valid historically controlled studies:[37, 38]

1. Control group received the precisely defined treatment in a recent study.
2. Criteria for eligibility, workup and evaluations must be the same.
3. Prognostic factors are completely known and same in both groups.
4. No unexplained indications lead one to expect different results.
5. If differences in prognostic factors, not sufficient to explain any observed difference in outcomes.

FDA has put PG's to limited use in the device approval process[39]. Some examples include cardiac ablation catheters, replacement heart valves, ophthalmic criteria for certain refractive procedures, and there has been significant preliminary work done in an effort to establish PG's for hip replacement systems.[40]

O'Malley et al., and others provide descriptions of the history and rationale for the use of PG's in the device approval process[35, 41-44]. Others have discussed the fact that under certain conditions, valid and useful data may be obtained when using non-experimental designs in the design, conduct, and analysis of clinical trials[33, 45-47]. In clinical trial design, there are situations where a great deal may be known about the natural history of the disease, the underlying patient population is well described and relatively stable, there is extensive clinical history and experience, a stable and well known standard of care, and the appropriate technology is relatively stable.[48]

FDA has established precedents based upon the above scientific reasoning for the use of PG's in the medical device approval process. PG's should only be considered when there is extensive history, knowledge, and clinical experience including, but not

necessarily limited to: (a) the underlying disease process associated with a device, (b) the intended patient population for the device, (c) the design and operational characteristics of the device, (d) all relevant safety and effectiveness parameters for the device, (e) current standard of care for the disease condition and patients associated with the device are all very well known and are not subject to any significant debate within the appropriate medical device, clinical, academic, industry, and patient communities, and (f) there should be an expectation of a significantly positive treatment effect. These criteria should be considered as a minimum standard prior to any serious consideration of employing PG's in the medical device approval process.

Rigorous and scientifically valid methodologies have been developed and employed in the derivation of any PG for use in the medical device approval process. While there is clearly room for appropriate clinical input, as well as other relevant evidence in the discussion of PG development, the fundamental derivation of a PG should be data driven. This implies that a PG must be derived from recognized and generally complete historical datasets, and be the product of appropriate statistical modeling and analytical techniques. In addition, the pivotal trial that will be conducted to collect patient data for comparison with the selected PG must incorporate an appropriately sized and powered sample size. Further, there should be a designated provision for periodically evaluating, and updating the PG based on more recent experience and data[43, 49, 50].

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