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COMMENTS ON CLINICAL TRIAL DESIGNS FOR CARDIAC ABLATION DEVICES

Food and Drug Administration

Circulatory System Devices Panel of the Medical Devices Advisory Committee

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AdvaMed, the Advanced Medical Technology Association, is the world's largest association representing manufacturers of medical devices, diagnostic products, and medical information systems. Our members produce nearly 90 per cent of the health care technology purchased annually in the United States and more than 50 per cent purchased annually around the world. Our members range from the largest to the smallest medical technology innovators and companies.

Thank you for the opportunity to comment on clinical trial designs for cardiac ablation devices designed to treat patients with atrial fibrillation. AdvaMed recognizes the importance of providing safe and effective medical devices to the American public in a timely manner. AdvaMed commends the FDA for providing an opportunity for stakeholders including recognized experts in the field of atrial fibrillation to provide input on clinical trial designs.

Current clinical trial designs have been influenced by the FDA guidance document on clinical trial designs for atrial fibrillation devices published in 2004. Although the Guidance, consistent with 21 CFR Part 820.7, recognizes a variety of potential trial designs that provide valid scientific evidence, medical device companies have been encouraged by the FDA to conduct randomized, controlled trials comparing catheter ablation to anti-arrhythmic drugs. This has been unduly burdensome for patients, clinical investigators, and industry. Patients for whom drugs have been unsuccessful may be randomized to drug therapy; investigator time is consumed with fruitless screening activities; and sponsors are burdened with the high costs of conducting a lengthy trial that may jeopardize the viability of their companies.



Since the issuance of the FDA Guidance in 2004, the American Heart Association and European Society Cardiology Association have issued "Guidelines for the Management of Patients with Atrial Fibrillation" and the Heart Rhythm Society, European Heart Rhythm Association, and European Heart Rhythm Society have issued an Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation. These publications reflect the current standard of care for treating atrial fibrillation patients and describe advances in atrial fibrillation treatment strategies. These documents recognize catheter ablation as the second line of therapy, following attempted medication therapy.

Since the issuance of the Guidance in 2004, the routine performance of atrial fibrillation ablation procedures with catheters has expanded significantly in the clinical community. This expansion was acknowledged by FDA at the January 2007 Boston Atrial Fibrillation Symposium with Dr. Randall Brockman's reference to "standard of care ablation catheters". However, no ablation catheters have been approved for the treatment of atrial fibrillation. This fact is a reflection of the difficulty industry is experiencing in conducting clinical trials in a timely fashion. It is not a reflection of industry's lack of interest in developing treatment devices that ultimately receive FDA approval based on sound clinical data.

Currently, there are two major challenges when conducting atrial fibrillation ablation clinical trials:

- Because there is no appropriate "alternate therapy" for studies using a randomized control design, patients are reluctant to participate in the current studies that require randomization to medication. They have been reticent to participate in randomized trials when the control arm is anti-arrhythmic drugs because the majority of patients referred for ablation have not been successfully treated by medications or the side effects of medications have proven to be intolerable. Patients do not want to delay potentially effective treatment by participating in a clinical trial that could require them to continue drug treatment that has been unsuccessful for them in the past when they can receive the standard of care with the off-label use of an ablation catheter today. This has resulted in very slow enrollment rates and therefore, very long clinical trials. The enrollment problem is exacerbated by the limited numbers of qualified ablation centers to serve as study sites and who are willing to conduct studies with randomization to drugs. As a result of the long enrollment times, the investigators at these expert centers may be conducting two or more trials simultaneously and distributing patients among the trials. Enrollment statistics from three ongoing trials show that approximately 14,000 patients must be screened to yield 250 study subjects. In other words, less than 2% of screened patients are successfully enrolled. Clinical study sites report that patient refusal is a key reason for screen failures in these studies. After enrollment is complete, a one-year

follow-up is typically followed by at least another year during which data is analyzed and a regulatory submission is prepared and reviewed. Based on current enrollment rates, more than six years can elapse between the time a company completes its feasibility clinical study and the time the new device is available to American patients. This is a significant burden on industry and unduly impedes the evaluation of an important therapeutic device.

- The second challenge is the nature of atrial fibrillation itself. As a disease and as an arrhythmia to be ablated, atrial fibrillation is highly variable compared to other supraventricular tachycardias. Therefore, the establishment of objective performance criteria as an alternative clinical trial design has historically been difficult. It is important to note however, that with the publication of the Heart Rhythm Society Expert Consensus Statement, we believe clinical studies can be conducted with sufficient consistency in design and evaluation criteria to allow for alternate study designs to be established for demonstrating safety and effectiveness. Furthermore, we believe that well designed and executed approaches such as objective performance criteria or “patient as own control” would be more clinically meaningful than a comparison of an ablation procedure outcome to a medication therapy outcome in a patient population that is medication resistant.

AdvaMed recognizes that the field of atrial fibrillation ablation is dynamic and that treatment strategies will continue to evolve. We also acknowledge that a revised FDA guidance may have an effect on currently approved pivotal IDE studies. With this in mind, AdvaMed proposes the following:

1. For pivotal IDE trials currently underway, allow the trials to continue as approved or allow sponsors to amend their protocols to improve enrollment conditions. FDA should be open to the use of hybrid and/or Bayesian statistical analysis that allow pooling of already enrolled subject data with the new study design data without inflicting a sample size penalty or weighting one data set more than the other.
2. For trial designs proposed prior to FDA approval of the first ablation catheter for the treatment of atrial fibrillation, allow sponsors to follow the principles of the Heart Rhythm Society Expert Consensus Statement. These studies should include any of the following options:
 - a. randomization to “standard of care” catheter ablation;
 - b. single-arm study utilizing safety and efficacy endpoints and objective performance criteria (OPCs) based on expert clinical opinion as supported by the literature;
 - c. patients used as their own controls.

After a revised guidance is issued, we recommend allowing IDE approved studies to continue as approved or allow protocols to be amended to be consistent with the FDA revised guidance.

3. For trial designs proposed after one or more ablation catheters have been FDA approved for marketing for the treatment of atrial fibrillation, allow all the options previously mentioned with the marketed devices included as “standard of care” ablation catheters.

In addition to its general support for the Heart Rhythm Society Expert Consensus Statement, AdvaMed makes the following additional recommendations for AF clinical trial designs:

1. If standard of care medical management is used as the control arm, expand the drugs that are allowed to include those routinely used, but not specifically indicated for, the treatment of atrial fibrillation (e.g., Amiodarone).
2. Ensure consistency of definitions and terminology by adopting the Heart Rhythm Society definitions for paroxysmal, persistent, and long-standing persistent atrial fibrillation.
3. To facilitate enrollment, allow patient consent at the referring site.
4. Allow six-month safety and efficacy endpoints with post-approval follow-up and reporting for twelve-month efficacy.

AdvaMed thanks FDA for the opportunity to provide comments on this important health issue. AdvaMed appreciates FDA’s recognition of the potential public health impact of untreated or sub-optimally treated atrial fibrillation and acknowledgement that today there are no ablation devices specifically approved for its treatment. While we understand that FDA regulates medical devices and not the practice of medicine or the off-label use of medical devices by clinicians, we appreciate FDA’s willingness to innovate potential alternative study designs. Industry recognizes the challenges in balancing the need to reflect advances in clinical treatment of atrial fibrillation since the issuance of the 2004 FDA guidance, the disciplined evaluation of innovative catheter technologies, and sound clinical trial design.