Investigational Device Exemption (IDE) Study Enrollment for Cardiac Ablation of Typical Atrial Flutter; Final Guidance for Industry and FDA Reviewers

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Center for Devices and Radiological Health

Cardiac Electrophysiology and Monitoring Devices Branch
Division of Cardiovascular and Respiratory Devices
Office of Device Evaluation

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. When submitting comments, please refer to the exact title of this guidance document. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Randall G. Brockman, M.D 301-796-6316 or email **randall.brockman@fda.hhs.gov (mailto:randall.brockman@fda.hhs.gov)**.

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to **CDRH-Guidance@fda.hhs.gov (mailto:CDRH-Guidance@fda.hhs.gov)** to receive a copy of the guidance. Please use the document number 1199 to identify the guidance you are requesting.

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This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Introduction

In the past few years, a great deal has been published in the medical literature that has increased the medical community's understanding of the etiology of typical atrial flutter (AFL), and how ablation is used to treat this disease. In addition, the Food and Drug Administration (FDA) is very much aware that past clinical study protocols may no longer be optimally designed to investigate typical AFL, and sponsors of Investigational Device Exemption (IDE) applications for cardiac ablation devices designed to treat typical AFL are having difficulty enrolling patients using these current study protocols. On April 26 and 27, 2000, FDA contacted 8 companies that sponsored past or current IDEs for typical AFL ablation, or had expressed interest to FDA in sponsoring a future IDE for typical AFL ablation. FDA asked these companies to consider participating in an initiative to identify possible changes to clinical study designs for typical AFL ablation that could improve enrollment rates.

FDA asked these sponsors to provide:

- Data on numbers of patients screened, enrolled, and excluded from the studies over time;
- Analysis of possible factors limiting enrollment;

- Suggestions for changes to the study design; and
- Discussions on how the proposed changes might impact the data analysis (e.g., poolability, introduction of confounding variables, changes to type of safety and effectiveness data collected, etc.).

In addition, FDA discussed this initiative with the clinical community at a May 20, 2000, session of the North American Society for Pacing and Electrophysiology (NASPE) annual meeting, and invited suggestions from those individuals in attendance.

FDA received many responses from both the industry and the clinical community, and would like to thank all those who participated in this endeavor for their thoughtful responses and excellent suggestions.

While there were no consensus suggestions from all of the respondents, several of the suggestions were recommended by many of those responding to this inquiry. The following section outlines FDA's current thinking on the various proposals that were made.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be approved/cleared for marketing. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the guidance and address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that information is being requested that is not relevant to the regulatory decision for your pending application or that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "**A Suggested Approach to Resolving Least Burdensome Issues (/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136685.htm)**" document.

Safety Endpoint

1. *FDA has had discussions with many sponsors on the most appropriate time-frame to collect safety data after an ablation procedure. Some sponsors have suggested that safety data need only be collected until the patient is released from the hospital.*

   Because the length of patient hospital stays after ablation seems to be decreasing (sometimes to only two or three days), FDA continues to believe it is important to collect major complication information for 7 days after the ablation occurs, regardless of whether the patient remains in the hospital this entire time. FDA believes that this 7 day time period will provide an

accurate assessment of the types and frequencies of safety problems that can occur after ablation, and is consistent with how safety is assessed for other types of cardiac ablation devices.

Effectiveness Endpoints

2. *Currently, FDA requests that the primary long-term effectiveness endpoint be defined as "No recurrences of typical AFL within 6 months of the ablation procedure." Several sponsors have proposed that this definition be modified to read "No recurrence of typical AFL with no addition of antiarrhythmic drugs (AADs) or no change in current AAD regimen from pre-ablation for 6 months following the ablation procedure."*

   FDA agrees that if patients with other more serious arrhythmias (see Issue #5) are included in the study, this associated revision to the definition of long-term effectiveness would be appropriate as some of these patients would not be expected to discontinue their AADs for the concomitant arrhythmia. If you chose to modify the long-term (6-month) effectiveness endpoint as described, your study protocol should address how the pre-ablation AAD regimen will be defined and how any changes to the regimen will be captured (i.e., through protocol and case report forms).

3. *Based on recommendations from the July 22, 1998 Circulatory System Devices Panel, FDA currently asks for acute and long-term (6-month) follow-up prior to submission of a PMA application. In addition, FDA has previously informed sponsors that 1 and 2-year telephone follow-up will be requested as a condition of approval, so current studies have been designed to incorporate case report forms for this type of follow-up. Sponsors proposed a reduction in the length of follow-up for both the primary long-term effectiveness endpoint as well as post-approval requirements.*

   FDA is willing to consider proposals for eliminating 1 and/or 2-year telephone follow-up, as well as shortening the length of follow-up necessary prior to submission of a PMA application. Some recommendations provided by respondents were for 3 month follow-up or "follow-up in line with clinical practice." If you would like to reduce or omit the telephone follow-up, or reduce the length of follow-up from 6 to 3 months or less, please provide a scientifically valid rationale to support your request. If you choose to use data from the literature to support such a request, please justify any differences between your investigational device and the devices used in the reported studies. In addition, when submitting literature data, it is important to describe when reported typical AFL recurrences were observed, and if available, the percent of patients included at each time point in the follow-up analysis. If you intend to propose the use of acute bi-directional conduction block as a surrogate endpoint for long-term (6-month) effectiveness, in addition to providing the scientific rationale described above, please address FDA's additional concern regarding the accuracy of the various methods used to ascertain bi-directional conduction block. At a minimum, the protocol should describe, in detail, acceptable

methods for establishing bi-directional conduction block. In addition, case report forms should include check-off boxes to indicate which method was used, and whether deviations to the method occurred, as well as a place for comments regarding the nature of any deviations.

Inclusion/Exclusion Criteria

4. *Currently, FDA requests that only patients with "2 or more symptomatic episodes of typical AFL within 12 months of enrollment, where at least one episode has been documented within 6 months of enrollment" be included in the study. Sponsors proposed that enrollment be expanded to include "patients with only 1 documented symptomatic episode within 12 months of enrollment."*

   FDA's July 22, 1998, advisory panel indicated that they want to ensure that a patient is indeed in typical AFL, and that the patient reported symptoms do not reflect some other disease state. FDA agrees that it is appropriate to include a patient after a single documented symptomatic episode since the current standard of care for patients with typical AFL is to treat following one documented episode. However, it is unclear to FDA why sponsors have requested inclusion of patients whose documented typical AFL episodes occurred more than 6 months before enrollment. The screening data provided by sponsors indicates that only a very small percentage of patients would be influenced by this change. If you would like to incorporate these changes to your inclusion criteria, please provide a scientifically valid rationale to address FDA's concerns and to support such a request.

5. *Currently, FDA requests that only patients with clean typical AFL (i.e., no concomitant arrhythmias requiring active treatment within three months prior to enrollment, or expected to need treatment during follow-up) be included in the study. Sponsors proposed that enrollment be expanded to include "patients with typical (clockwise or counterclockwise) AFL, as well as those taking class IA, IC, and III oral antiarrhythmic drugs (AADs) for concomitant atrial fibrillation (AFib) where the AADs fail to prevent typical AFL occurrence."*

   Based on our current understanding that typical AFL and AFib are indeed linked disease processes, this approach is acceptable to FDA. FDA also realizes that patients with typical AFL often have arrhythmias other than AFib. FDA believes that patients who receive active treatment or who change their AAD regimen during follow-up, regardless of the reason, should be considered typical AFL ablation failures for the long-term effectiveness endpoint. In addition, it is unclear to FDA whether the current objective performance criteria (OPC) for safety will be appropriate if the study population now includes significantly sicker patients (those with additional AFib). If you would like to expand your study to include patients with AFib, please explain how you plan to address the effect that treatment for this arrhythmia will have on the typical AFL long-term effectiveness endpoint(s), and also how the safety OPC will be affected, if at all.

6. *Currently, FDA requests that patients be excluded from the study design if they cannot be taken off their AADs or are expected to need AAD's (for any concomitant arrhythmias). Sponsors proposed that enrollment be expanded to exclude only those patients "who cannot be taken off of their AAD's for their AFL, SVT or VT."*

   As discussed in Issue #5 above, FDA is concerned that any treatment with AAD's for any concomitant arrhythmia (including SVT or VT) during ablation follow-up will affect the ability to assess the effectiveness of the typical AFL ablation procedure. If you would like to expand your study to include patients who may need AAD's for their non-AFib concomitant arrhythmias, please explain how you plan to address the effect that new or increased treatment with AADs will have on the typical AFL long-term effectiveness endpoint(s).

7. *Previously, FDA asked that patients be excluded if they have a history of failed ablation. Sponsors proposed to expand enrollment to include patients with previous ablations.*

   FDA believes that patients with previously failed ablations may be more difficult to treat, and enrollment of these patients could confound the effectiveness results. In addition, FDA is concerned that if a previous ablation has not been completely resolved, then tissue remodeling could affect the final line of block laid down during the typical AFL ablation procedure. If you would like to expand your study to include patients with previous failed ablations, please describe how you will address the issues identified above to support your request.

8. *Currently, FDA requests that patients be excluded if they have permanent leads in or through the right atrium. Sponsors proposed to expand enrollment to include patients with permanent leads in or through the right atrium.*

   FDA believes that this change could increase the number of adverse events due to entanglement with leads. In addition, the screening data provided in response to this enrollment initiative indicates that only a very small percentage of patients would be influenced by this change. At this time, FDA continues to believe that patients with permanent leads in or through the right atrium should be excluded because of the increased safety risks for these patients.

9. *Currently, FDA requests that studies exclude patients with unstable angina. Sponsors proposed to expand enrollment to include patients with unstable angina if these patients are not amenable to revascularization.*

   FDA believes that patients with unstable angina are also electrophysiologically unstable. In these patients, the mechanical and electrical stimulation that occurs during electrophysiology studies and cardiac ablation are likely to increase the risk of arrhythmic adverse events (e.g., VT episodes). At this time, FDA continues to believe that these studies should exclude patients with unstable angina because of the increased safety risks for these patients.

Number of Investigational Sites

10. *Sponsors proposed an increase in the number of investigational sites.*

While FDA is willing to consider protocols with increased numbers of investigational sites, please be aware that this could adversely affect your ability to statistically assess the poolability of data from various investigational sites. If you would like to incorporate more sites into your study design, please provide a rationale for the number of sites requested.

More in Guidance Documents (Medical Devices and Radiation-Emitting Products) (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm)

Cross-Center Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081752.htm)

Office of Compliance Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070269.htm)

Office of the Center Director Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110228.htm)

Office of Communication and Education Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070271.htm)

Office of Device Evaluation Final Guidance 2010 - 2016 (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm198577.htm)

Office of Device Evaluation Final Guidance 1998 - 2009 (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070272.htm)

Office of Device Evaluation Final Guidance 1976 - 1997 (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080283.htm)

Office of In Vitro Diagnostics and Radiological Health Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070274.htm)

Office of Surveillance and Biometrics Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070275.htm)

Office of Science and Engineering Laboratories Final Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070277.htm)

Draft Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm407274.htm)

Radiation-Emitting Products Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm283507.htm)

Withdrawn Guidance (/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm425025.htm)