Guidance for Industry and for FDA Reviewers

Recommended Clinical Study Design for Ventricular Tachycardia Ablation

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U.S. Department Of Health And Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Pacing and Electrophysiology Devices Group
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 Jun Dong, M.D. 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 Jun Dong, M.D. 301-796-6317 or by email at jun.dong@fda.hhs.gov.

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Introduction

The use of cardiac ablation for the treatment of Ventricular Tachycardia raises many new questions of safety and effectiveness in comparison to the use of cardiac ablation for the treatment of Supraventricular Tachycardias. The following outline has been provided to aid sponsors in developing a protocol for the treatment of Ventricular Tachycardia. We have given you two study designs: non-randomized and randomized. *In no way is this outline intended to be all inclusive of the necessary components for a clinical study*. This outline was based on recommendations provided to the FDA by Circulatory System Devices Panel members and by comments offered by clinical investigators.

Note: *This guidance document represents the agency's current thinking on clinical study design for ventricular tachycardia ablation. It does not create or confer any rights of 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, regulation, or both.*

We have further qualified some of our recommendations in the form of italicized notes, such as this one, which explain the concern or reasoning behind our recommendation. If you choose not to follow our recommendations in designing your study, you should strive to address FDA's underlying concerns.

The remainder of this guidance document is in three parts:

I. Things to Consider in Designing Your Study
II. Non-Randomized Study Design Options
III. Randomized Study Design Options

I. Things to Consider in Designing Your Study

Designing a study to evaluate the safety and efficacy of an ablation system for the treatment of ventricular tachycardia poses unusual demands for many sponsors. The desire for steady and expeditious patient enrollment needs to be balanced against the claims the sponsor wishes to make for the device and the type of patients they wish to enroll. Choices made early on about inclusion criteria may impact which study design can be used or how long the study will take. Please consider the impact of the following inclusion criteria when designing your study:

Ischemic VT: For patients with ischemic VT, ablation may not be expected to cure the patient's VT. In that case, the goal of treatment could be to reduce the frequency of a patient's VT episodes, perhaps accompanied by an improvement in quality of life[1]. Therefore, your primary study endpoint of 6-month success should be a "reduction in VT episodes". These patients are suitable for either a randomized study (preferably with a marketed ablation system as the control arm) or a non-randomized study where each patient acts as his or her own control.

Idiopathic VT: For patients with VT in the presence of a structurally normal heart, it might be more realistic to attempt to rid the patient of VT symptoms for the duration of the follow-up period. In that case, your primary endpoint of 6-month success might be an "absence of VT" throughout the follow-up period. However, since the benefit of ablation is less well-established in these patients, a randomized study design is strongly encouraged. The benefit of choosing this type of study is that the follow-up period may be shortened since patients only need to be followed up to the point that they have their first VT episode.

Presence of ICD: If a non-randomized study is chosen and patients will act as their own control, considerable time will be saved if patients are enrolled already having an ICD. You can use ICD interrogation to establish the baseline frequency of VT episodes rather than requiring patients to go through an observation period prior to ablation. You may consider requiring that patients already have an ICD as part of your inclusion criteria.

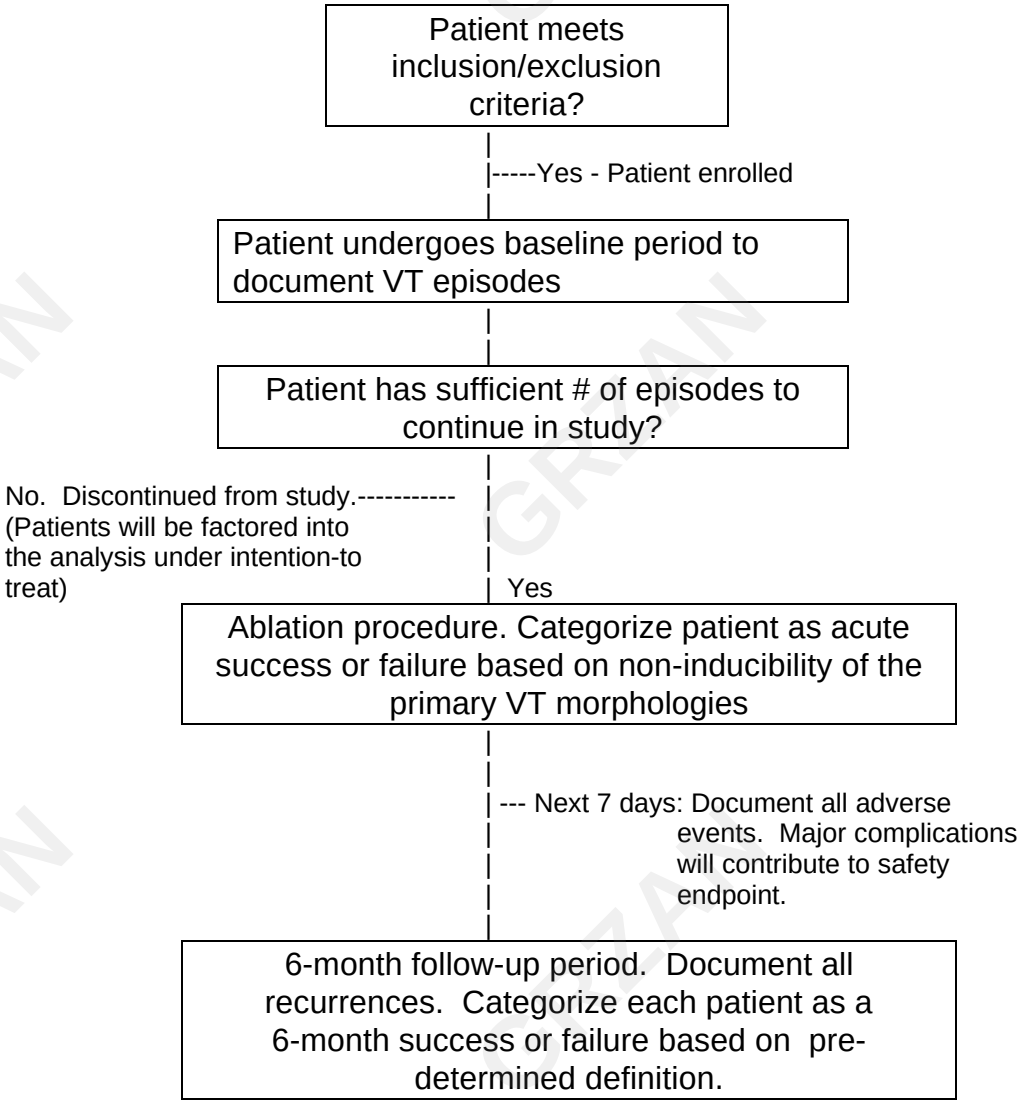
High-density VT's: If a non-randomized study is chosen and patients with low density VT's are included, both the baseline observation period and the follow-up period are extended in order to capture events. Therefore, you may consider requiring that patients have a relatively high density of VT's in order to be enrolled in the study.

1 Please consult FDA for advice on designing your clinical study if you intend to use Quality of Life as a primary endpoint, or if you intend to make labeling claims about Quality of Life.

II. Non-Randomized Study Design Options

A. Study Design

These studies are designed to be non-randomized, single arm studies where patients act as their own control. The figure below is a flow chart illustrating how patients would progress through the study.



B. Entry Criteria and Enrollment

An important point to remember is that patients are *enrolled,* and count toward your allotment, if they meet the entry criteria and sign the Informed Consent. Some patients may not receive ablation if they then go on to have too few episodes during the prospective baseline period to allow a statistical comparison between the baseline and the follow-up period. Patients should be notified of this possibility in the Informed Consent.

Special consideration should be given to the following inclusion/exclusion criteria:

1. Specify a frequency of VT episodes that sufficiently characterizes the patient prior to enrolling in the study.

2. Specify whether patients will be required to have an ICD prior to enrollment in the study.

3. Define the etiology of the patient's heart disease (i.e., ischemic VT).

4. Specify whether patients will be refractory to or intolerant of antiarrhythmic drug therapy.

C. Study Endpoints

Primary Endpoints

We recommend that you define the terms "acute success" and "6-month success" as they apply to individual patients. In addition, state hypotheses for the expected rates of acute success, 6-month success, and complications.

We recommend:

Acute Success Rate:
First, develop a definition of "success" that can be applied to each patient in the study. Typically, this would be defined as the acute non-inducibility of clinically relevant VT morphologies. Then, hypothesize an overall "acute success rate" for your study.

Note: *It is important that the clinician identify the clinically-relevant VT's prior to ablation therapy. These should include VT's which are responsible for the patient's symptoms and/or are greater than 20 seconds in duration.*

Note: *Because this study is intended to support the marketing claims for an ablation treatment system, "success" should only refer to successful ablation with the investigational system. If patients require additional*

treatments with non-investigational system components, they should be considered acute failures. An exception would be if you were trying to market your system as an "adjunctive treatment" to another (marketed) system.

6-month Success Rate:
First, categorize each patient as either a 6-month success or failure. Success can be defined as either a reduction in VT episodes or an absence of VT episodes at the end of the 6-month follow-up period. Then, hypothesize an overall "6-month success rate" for your study.

Note: *Patients should demonstrate a clinically meaningful decrease in VT episodes at six months to be categorized as a "6-month success". You may have different definitions of "success" and "failure" for different categories of patients (for example, requiring an absence of episodes in patients with a low density of episodes during the baseline).*

Note: *Patients should be categorized as 6-month successes or failures regardless of whether they were acute successes. We suggest you stratify the VT recurrence rates for both the acute successes and the acute failures.*

Complication Rate:	The percentage of patients undergoing an ablation procedure who sustained at least one major complication.

Note: *While FDA does not distinguish between "procedure-related" and "device-related" complications, we do suggest that you stratify all the reported complications according to whether they occurred acutely (within the first week following the ablation procedure) or later. Please refer to the Appendix for suggestions on how to distinguish major complications from minor complications.*

D. Study Protocol

VT Episode Documentation

If you define 6-month success as a decrease or absence of VT episodes, you should also prospectively specify the method of counting the number of VT episodes. This may include one or more of the following:

1) ICD interrogation;
2) Event monitoring; and
3) ECG from hospital visit.

Note: *To avoid discrepancies in accuracy of VT counting methods, we recommend that you use the same data collection methods both pre- and post-ablation.*

Note: *Use of ICD interrogation may overcount minor VT episodes. If an ICD is used, only count those VT episodes that were greater than 20 seconds in duration, or of sufficient duration to result in delivery of therapy.*

Note: *We recommend that you carefully consider ways to reduce the potential for VT episode reporting bias. For example, we do not recommend retrospectively assessing the frequency of VT. Instead, we believe that baseline data collection should begin only after a patient has enrolled in the study. Also, we do not recommend using patient self-report as a method for counting VT episodes.*

Pre-Ablation Procedures

1) Baseline data collection - quantify the number of VT episodes for six months prior to ablation.
2) Echocardiogram for assessment of ventricular ejection fraction and presence of intraventricular thrombus.
3) Neurologic examination by a neurologist.

Post-Ablation and Follow-up Recommendations

1) Attempt reinduction of primary VT substrates.
2) Echocardiogram for assessment of ventricular ejection fraction and presence of intraventricular thrombus.
3) Neurologic examination by a neurologist.
4) Count VT episodes for six months post-ablation.
4) Perform routine follow-up evaluations (physical exam, ECG) out to at least six months. Continue with follow-up phone contact to 12 months.

Repeat Ablations

While it may be desirable to allow patients the opportunity for repeat ablations, it is important to do so while maintaining the integrity of the study design. In general, this means that patients can receive additional repeat ablations once they are categorized as 6-month failures. Specifically:

- If your definition of 6-month success is “absence of VT episodes”, then a patient may receive a second ablation once they experience their first VT episode, provided you have allowed sufficient follow-up to capture acute adverse events (7 days).
- If your definition of 6-month success is “reduction in VT episodes”, then a patient may receive a second ablation once they experience a sufficient number of episodes to classify them as a 6-month failure.

NOTE: *Because this information will appear in your labeling, you should strive for consistency in offering repeat ablations. Each investigator should be encouraged to apply the same criteria in deciding whether patients should receive a second ablation.*

E. Statistical Analysis

Recommended Statistics

Use descriptive statistics to present demographic data, success rates, complication rates, and pre- and post-ablation counts of VT episodes. For success rates and complication rates, specify the 95% confidence limits for those proportions. For pre- and post-ablation counts of VT episodes, specify the medians (or the mean, if you are able to show that the data are normally distributed).

To compare your observed success rates to your hypothesized success rates, use a test of a single proportion.

Stratifying 6-month Efficacy by Success vs. Partial Success

As a secondary analysis, you may want to stratify your long-term efficacy results into two groups: patients who were clearly asymptomatic at follow-up, and patients whose targeted VT’s were eliminated, but who developed new VT morphologies that resulted in symptomatic episodes during the follow-up period.

III. Randomized Study Design Options

A. Study Design: Two Options

These studies are designed to be randomized with a concurrent-control where patients are randomly assigned to receive ablation or a control treatment. The control treatment is preferably ablation with a market-approved ablation system. However, it *could* be drugs if you are trying to establish your system as a first-line treatment for VT (and provided patients are not drug refractory). There are two choices for comparing the 6-month outcomes of the two groups:

OPTION 1: Classify each patient as a 6-month "success" or "failure" and compare the proportion of successes between the two groups. If this option is chosen, patients in both treatment arms will proceed through the study as if they were their own control, and the relative proportions of successes will be compared. Please follow the recommendations outlined in the previous section, "Non-Randomized Study Design Options" for all patients. You can skip the rest of the recommendations that follow, however please read the sections on "Crossovers" and "Statistical Analysis", below.

OPTION 2: Count the number of recurrent episodes during the six-month follow-up period and compare these values between the two groups. If this option is chosen, you will not need a baseline period as patients will not act as their own controls. Instead, you will combine the data from patients in each group and compare the average (or median) recurrence rates. In this case, all patients must complete the entire 6-month follow-up period.

If Option 2 is chosen, the rest of this section applies to your study design:

B. Entry Criteria

Special consideration should be given to the following inclusion/exclusion criteria:

1) Specify whether patients will be required to have an ICD.
2) Define the etiology of the patient's heart disease (i.e., ischemic VT).

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C. Study Endpoints

Primary Endpoints

We recommend that you prospectively define endpoints for comparing acute success, 6-month success, and complication rate across the two treatment groups. Keep in mind that if you wish to make claims of superiority of your device compared to the control device, your hypotheses and sample size calculations should reflect this.

Acute Success Rate Comparison:
We recommend that success be defined as the acute non-inducibility of clinically relevant VT morphologies. Hypothesize a clinically-relevant difference between the treatment group and the control group in terms of acute success. Perform a sample size calculation on this endpoint.

Note: *It is important that the clinician identify the clinically relevant VT's prior to ablation therapy. These should include VT's which are responsible for the patient's symptoms and/or are greater than 20 seconds in duration.*

Note: *Because this study is intended to support the marketing claims for an ablation treatment system, "success" should only refer to successful ablation with the investigational system. If patients require additional treatments with non-investigational system components, they should be considered acute failures. An exception would be if you are trying to market your system as an "adjunctive treatment" to another (marketed) system.*

6-month Recurrence Rate Comparison:
Hypothesize a clinically-relevant difference between the treatment group and the control group in terms of the average number of recurrences in the 6-month follow-up period. Perform a sample size calculation on this endpoint.

Note: *We recommend that you prospectively specify the method of counting the number of VT episodes during the six-month follow-up period.*

Complication Rate Comparison:
Hypothesize a clinically-relevant difference between the treatment group and the control group in terms of the complication rate. Perform a sample size calculation on this endpoint. As with the Non-Randomized Study Design, you complication rate will be based on the percentage of patients with major complications (see Appendix A).

D. Study Procedure

VT Episode Documentation

Prospectively specify the methods for counting VT episodes, which may include one or more of the following:

1) ICD interrogation;
2) Event monitoring; and
3) ECG from hospital visit.

Note: *If an ICD is used, only count those VT episodes of at least 20 seconds duration, or of sufficient duration to result in delivery of therapy.*

Pre- and Post-Ablation Procedures

Refer to the Non-Randomized Study design for recommendations on procedures for patients in the ablation arm of the study.

Follow-up Recommendations

Document the number of VT episodes in the six-month period following delivery of therapy for patients in either arm of the study.

Crossovers and Repeat Ablations

Allowing patients to cross over to the other treatment arm and/or allowing repeat ablations are options that raise similar issues of study integrity. In both cases, there is the potential for losing information about the 6-month efficacy endpoint. As with the Non-Randomized Study Design, there are ways to minimize this problem:

For Option 1: Crossovers – Patients randomized to either arm of the study may cross over to the other arm once they are categorized as 6-month failures, but no sooner than one week after the initiation of treatment. If you choose to incorporate crossovers into your study, you will minimize further bias by offering this option to patients in either arm. Repeat ablations – follow the rules developed in the Non-Randomized Study (page 7).

For Option 2: Crossovers – Patients may only cross over to the other treatment arm once they have completed the full 6-month follow-up period. Similarly, repeat ablations should only occur after the patient has completed the 6-month follow-up period.

E. Statistical Analysis

Analysis of Efficacy

For Option 1: compare the 6-month success rates of the two treatment modalities using a test for the difference between two proportions.

For Option 2: compare the two treatment modalities in terms of their overall impact on VT recurrence. Compare the number of VT episodes in the six-month follow-up period for patients in both groups, assuming crossovers were not allowed prior to the six-month follow-up period.

Analysis of Safety

For Option 1 or 2: Compare the complication rates of the two arms of the study using a test for the difference between two proportions.

Appendix A
Definition of Major Complication Rate

Major complication rate: The percentage of patients treated with the investigational device who experience any adverse event which occurs within the first week following the investigational procedure; AND:

- is life-threatening; or
- results in permanent impairment of a body function or permanent damage to a body structure; or
- necessitates significant intervention, such as major surgery, to prevent permanent impairment of a body function or permanent damage to a body structure; or
- requires hospitalization or an extended hospital stay; or
- results in moderate transient impairment of a body function or transient damage to a body structure; or
- requires intervention such as medication or cardioversion to prevent permanent impairment of a body function or damage to a body structure.

A "minor" complication would be any event that results in *minimal transient impairment* of a body function or damage to a body structure, or which *does not require any intervention other than monitoring*.