Questions to Panel Members

The FDA has written and published a guidance document on trial designs for ablation catheter systems intended to treat AF. The FDA believes that RCT remains the gold standard for trial designs to evaluate new cardiac devices and new indications for devices currently on the market, but there are other trial designs that may be able to supply the required clinical data for market approval.

Please help the FDA and device manufacturers with discussion of the questions below. Both the FDA and device manufacturers desire to complete clinical trials that produce evaluable data.

1. What is an appropriate method to characterize effectiveness or clinical improvement?
    a. Absence of AF? Please define absence of AF – symptomatic only or all AF. Please define the manner in which it can be measured.
    b. Reduction of AF burden? Please define AF burden and how it can be measured both pre- and post-treatment.
    c. A composite functional endpoint (e.g. hospitalization, cardioversion, days of work missed, etc.)? Given that neither investigators nor subjects are blinded to their treatment, could bias be accounted for?
2. What trial designs are viable options to develop valid scientific evidence of the safety and effectiveness of a new ablation catheter system? Please consider the two example trial designs presented by FDA.
    a. What is the appropriate control for the study of the safety and effectiveness of ablation catheters for the indication of treatment of atrial fibrillation? Do the different types (i.e. PAF vs permanent AF) need different control groups?
    b. For what duration should safety of the ablation device be measured?
    c. For what duration should effectiveness of the ablation device be measured?
3. Given that catheter ablation is an invasive therapy, if the control group is noninvasive medical therapy, what should the comparisons be for safety and effectiveness?
4. If a performance goal derived from the medical literature is used for either safety or effectiveness comparisons, what should the values be and why?
5. Are your recommendations with respect to trial design for AF studies involving catheter ablation applicable to sole-therapy surgical ablation?

Questions common to all treatments for AF:

In addition to the general discussion of trial design issues above, FDA has questions about AF therapy as it pertains to some details of clinical trial protocols. FDA would like to ensure that trials are being performed consistent with current clinical practice. Please help the FDA and device manufacturers with the discussion of the questions below relating to the treatment of AF.

6. Please address the following issues with respect to anticoagulation:
    a. FDA agrees with the ACC guidelines which state “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.” Please comment.

    b. What data are needed to support instructions to discontinue anticoagulation after atrial fibrillation ablation?
7. If trial endpoints focus on symptomatic recurrence, how important is it to capture asymptomatic AF recurrences? What are the implications of asymptomatic AF recurrences in terms of the long-term risks of AF (e.g. tachycardia-mediated cardiomyopathy) and, for example, the need for anti-coagulation?
8. FDA currently classifies patients with AF into three groups: paroxysmal, persistent and permanent (according to criteria proposed in the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation).
    a. Do you believe that different types of AF should be studied separately?
    b. Should there be differences in the definitions of effectiveness for each patient group following ablation therapy, and should they be followed differently? If so, please provide recommendations (for example, with respect to duration, type of monitoring)?
9. What is the clinical implication of subjects undergoing ablation changing from permanent or persistent atrial fibrillation to paroxysmal atrial fibrillation? Should this impact the clinical trial design?
10. Should atrial fibrillation ablation trials specifically study high risk patients (such as those with heart failure)?
    a. If the panel does not feel that specific (potentially high risk) patient populations should be included in the clinical trials, can trial results using restricted enrollment criteria be applied to the general population?
    b. If yes, are there specific groups to which such results should not be applied (such as patients with advanced heart failure, severe left ventricular systolic dysfunction or “giant” left atria)? How should such patient groups be handled in terms of device indications, warnings/precautions, etc.?
11. Is it useful and/or important to collect information concerning atrial transport?
    a. If so, is there a specific method that should be used?
    b. What comparison should be used?