FDA Circulatory System Devices Panel

General Issue: Clinical Trial Designs for Atrial Fibrillation Treatment Devices

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Goals

- Understand the current scientific and regulatory landscape for atrial fibrillation therapy.
- Design a clinical trial that will generate data to support a PMA application
  - Valid scientific evidence
  - Demonstrate reasonable assurance of:
    - Device **safety**
    - Device **effectiveness**
- Trial should:
  - Generate interpretable data
  - Be executable in a reasonable amount of time

FDA Review Team

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Agenda

- Atrial Fibrillation: Introduction to the topic
  - Lesley Ewing, M.D.
- Regulatory Perspective for AF Ablation Devices
  - Elias Mallis
- Clinical Issues Common to AF Ablation Trials
  - Randall Brockman, M.D.
- Medical Device Clinical Trial Design 101
  - Lilly Yue, Ph.D.
- Proposed Trial Designs for AF Ablation Devices
  - Felipe Aguel, Ph.D.

Atrial Fibrillation: Introduction to the Topic

Lesley Ewing, MD

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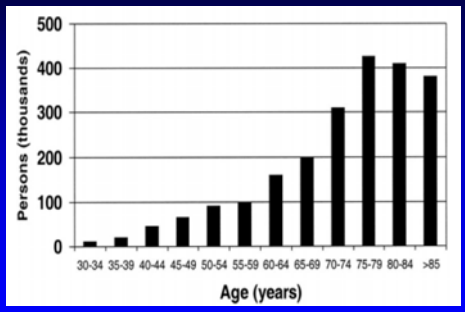
AF Prevalence



Fuster *et al.*
ACC/AHA/ESC Practice Guidelines

JACC Vol. 48, No. 4, 2006
August 15, 2006:e149–246

AF Background

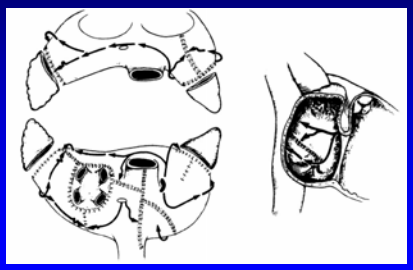
Classification of AF

- Paroxysmal – terminates spontaneously
- Persistent – sustained AF greater than 7 days
- Permanent – cardioversion failed or not attempted

- Treated to control ventricular rate/prevent HF, prevent thromboembolism, prevent symptoms
- Medical treatment is palliative and commonly not effective in maintaining sinus rhythm

Surgical Ablation Cox-Maze III

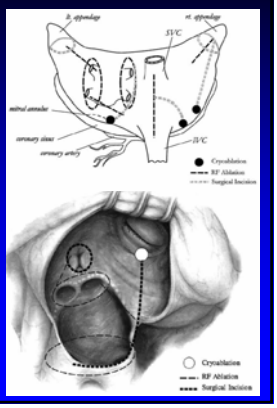
- Gold standard
- Long term freedom from AF of 70%-95%



Cox JL Cardiac Surgery in the Adult 2003

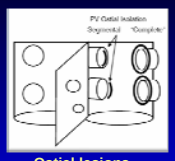
Modified RF Cox-Maze

- Most commonly performed concomitantly
- Many variations currently performed with a variety of devices
- Bi-atrial versus left atrial lesions
- Minimally invasive approach



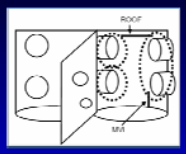
Mokadam et al
Ann Thorac Surg
2004;78:1665

Catheter Ablation Procedures

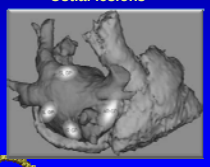


Ostial lesions

Pulmonary vein isolation



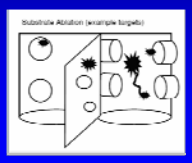
Circumferential lesions



Ablation of ganglionated plexi

Substrate modification

Autonomic ablation



Ablation of complex fractionated atrial electrograms

Published Catheter Ablation Effectiveness

- Effectiveness ranges from 28-100%
- Repeat procedures required in 20-40%
- Lower success rates reported for permanent AF
- No standard method of surveillance for AF recurrences
- No standard definition of clinical success
- No standard duration of follow-up

Complications of Catheter Ablation

- Inconsistently reported
- Unknown if all events were captured in retrospective reports
- Complications include:
  - Death (stroke, atrio-esophageal fistula)
  - Stroke
  - Tamponade
  - Pulmonary vein stenosis
  - Pericardial effusion
  - Iatrogenic atrial tachyarrhythmia
  - Phrenic nerve injury
  - Aortic root injury/fistula
  - Gastric dysfunction
  - Catheter entrapment with valve damage
  - Autonomic dysfunction

FDA Questions to Panel

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.)? How is bias accounted for if investigators or subjects are not blinded to their treatment as in the traditional trial design?

13

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?

14

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. Based upon the discussion of trial design for percutaneous catheters, please discuss your recommendations for trial designs to study surgical ablation in a sole-therapy situation.

15

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?

16

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?

17

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)?

18

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?

19

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.?

20

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?

21

Regulatory Perspective for AF Ablation Devices

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22

History of EP Catheters

- FDA's definition of "off-label" use:
  - Use of a device for an indication beyond what FDA approved (or cleared) to market
- Early 1990s: modified mapping catheters used off-label for ablation, tx of arrhythmias
- Mid 1990s: ablation catheters (4mm tip RF) approved for SVT
- Early 2000s: ablation catheters (8mm tip RF, irrigated, cryo) approved for atrial flutter

23

Status of AF Ablation

- Panel Meetings held in 1998 and 2000
- No device (surgical or percutaneous) currently approved for treatment of atrial fibrillation
- Ongoing investigational clinical studies
- Prevalent "off-label" use, as documented by:
  - Scientific publications documenting ablation studies for treatment of AF
  - Professional Society official policy positions which recognize heightened role of ablation in treatment of AF

24

FDA's Regulatory Role

- FDA evaluates medical device applications:
  - Submitted by sponsors (usually manufacturers)
  - For specific devices
  - For specific indications
- FDA assists sponsors to collect data that produce interpretable results to support market applications
- FDA evaluates valid scientific evidence (CFR 860.7)

25

FDA's Regulatory Role

FDA does not:

- Regulate practice of medicine, or how devices are used by physicians once legally marketed

27

Valid Scientific Evidence

- Usually consists of:
  - well-controlled studies
  - partially-controlled studies
  - studies without matched controls
  - well-documented case studies
  - other robust scientific evidence
- Does not usually consist of:
  - isolated case reports
  - random experience
  - reports lacking sufficient detail to permit scientific evaluation
  - unsubstantiated opinions

28

Safety and Effectiveness

- Safety: Probable benefits, with proper labeling, outweigh any probable risks.
- Effectiveness: Use of the device for its intended/conditions of use, with proper labeling, will provide clinically significant results.

29

Challenge of AF Studies

- Shared goal:
  - Medical device manufacturers to conduct and complete clinical studies
  - in a timely manner
  - and generate what FDA believes is valid scientific evidence
- FDA's proposed trial design options

30

Clinical Issues Common to AF Ablation Trials

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Topics

- Enrollment
- Monitoring
- Symptomatic vs. asymptomatic recurrence
- Special patient characteristics
- Anticoagulation
- Atrial transport function

Enrollment Issues

- AF classification
- Pre-enrollment AF documentation
  - Paroxysmal
  - Persistent
  - Permanent

HRS/EHRA/ECAS Consensus Recommendation

- "A minimum assessment of symptomatic AF and search for asymptomatic AF at six months intervals [after the blanking period] using one of the following:
  - 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
  - 24 to 72 hour Holter monitoring
  - Thirty-day auto triggered event monitoring or mobile cardiac outpatient telemetry"

Heart Rhythm. 2007;4:816-861

FDA Recommended Monitoring

- Paroxysmal – frequent assessments over one year
- Permanent – assessment at 6 months
- Persistent – assessment as 9 months with available assessments if symptomatic

Recommended Monitoring and Follow-up

	HRS/EHRA/ECAS monitoring	HRS/EHRA/ECAS follow-up	FDA monitoring	FDA follow-up
Paroxysmal AF	Either 4 week TTM, or 24-72 hour Holter, or 30 day auto-triggered EM	12 months	Frequent Event Monitors (EM)	12 months
Persistent AF			7 day Holter + EM for Sxs	9 months
Permanent AF			Holter monitor	6 months

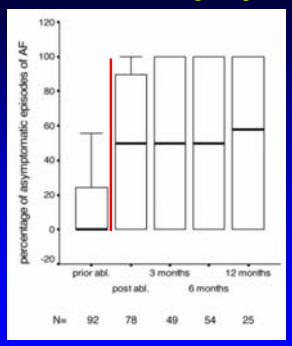
Conversion of Persistent or Permanent AF to Paroxysmal

- FDA has viewed a patient with pre-ablation permanent AF as having a binary result post-ablation
- Follow-up monitoring has been tailored to address that question
- We now have a question as whether or not that approach is appropriate

Symptomatic vs. Asymptomatic

- AF is associated with an increased long-term risk of stroke, heart failure and all-cause mortality
- The risks may not be substantially different for patients with symptomatic vs. asymptomatic AF
- AF ablation may change many episodes from symptomatic AF to asymptomatic AF

Conversion to Asymptomatic



Adapted from Hindricks, et al Circulation. 2005;112:307-313

Special Patient Groups

- AF frequently co-exists with important co-morbidities
- There may be interest in ablating AF in heart failure (HF) patients
- The presence of AF may be especially detrimental to patients with HF
- The risks and benefits of AF ablation may be different in patients with HF as opposed to patients without heart failure.

AF in Patients with HF

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)

ACC/AHA/ESC AF guidelines Circulation. 2006;114:700-752

Anticoagulation

- The ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation 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."

ACC/AHA/ESC AF guidelines Circulation. 2006;114:700-752

Anticoagulation (cont.)

- Study the need for anticoagulation, or
- The ablation should not impact the decision to treat with anticoagulation

43

Atrial Transport/Function

- Assessment of atrial pump function
- While FDA does not view this as a surrogate for stroke risk, it may provide useful information
- It may also provide additional safety information in terms of preservation of atrial mechanical function

44

Medical Device Clinical Trial Design 101

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Outline

- Choices of control groups
- Types of clinical studies
- Concluding Remarks

46

Choices of Control Groups

- Major purpose of control group
  - To see if the observed treatment effect is due to the investigational device, instead of, for example, progression of the disease, investigator or patient expectation, or other treatment.

47

Choices of Control Groups (cont.)

- Concurrent control group
  - Active control group
    - Approved device or optimal medical management
  - Sham (placebo) control
  - Baseline-control
    - Patient serves as his or her own control
    - Pre-treatment and post-treatment comparison
- Historical control group
  - A group of patients studied in previous clinical trial(s)
  - Patient level data are available in both clinical outcomes and baseline covariates.
- .....

48

Types of Clinical Studies

- Randomized controlled trials (RCT)
- Non-randomized comparative studies with
  - concurrent control
  - historical control
- One-arm study against an objective performance criterion "OPC" or a performance goal (PG)"
  - "OPC" or "PG": a number, a fixed target
  - **Its determination should be data-driven and through appropriate statistical modeling.**

49

Randomized Controlled Trial (RCT)

- All patients have a specified chance of receiving either treatment, avoiding both obvious and non-obvious clinical selection of patients for one treatment or the other.
- Expect that all patient covariates, measured or unmeasured, e.g., age, gender, duration of disease, …, are balanced between the two treatment groups.
- Expect the two treatment groups are comparable and observed treatment difference is an unbiased estimate of true treatment difference.
- But, the above advantages are not guaranteed for small, or poorly designed or poorly conducted randomized trials.

50

Risks of Non-Randomized Study with Concurrent Control

- Why non-randomized?
- RCT is sometimes not ethical or practical.
- In non-randomized studies, none of advantages provided by randomized trials is available.
- Major potential problems:
  - ***Selection bias***
  - ***Treatment group non-comparability***
- Two treatment groups were **not comparable before** the start of treatment, due to imbalanced baseline confounding covariates, for example,
  - One treatment group had much sicker patients.
  - Two treatment group patients had different physiological factors

51

Risks of Non-Randomized Study with Concurrent Control (cont.)

- Direct treatment comparisons would be **un-interpretable.**
- Are there any ways to adjust for the imbalanced baseline confounding covariates?
  - Yes. For example, traditional covariate adjustment methods or propensity score analysis.
- However, these statistical methods can only adjust for measured confounding covariates but not for un-measured.
- Suppose that all baseline confounding covariates were pre-specified and measured. But, if the covariate differences between the two group patients are extensive, the statistical methods may not work well.

52

Risks of Non-Randomized Study with Concurrent Control (cont.)

- Sometimes, it is difficult to know in advance whether some important baseline confounding covariates are left out and measured ones are appropriate.
- It may be impossible to predict in advance whether the patient population with the new treatment is comparable to the patient population with the control.
- The results of such a study may be more difficult to interpret and the study may be **more burdensome** than an RCT.

53

Risks of Non-Randomized Study with Historical Control

- Shares all the problems and risks associated with non-randomized study with concurrent controls.
- In addition, a major potential problem is **temporal bias** caused by evolution of medical practice and technology.
- Sponsor must have legal access to the historical data at the patient level and all the appropriate baseline covariates need to have been measured in both treated and historical groups.

54

One-arm Study with a Performance Goal

- OPC: objective performance criterion -- a fixed target.
- Used for prosthetic heart valves; obtained from historical data from multiple approved heart valve trials; by third-party experts.
- Study goal: e.g., assess
  6-month MACE rate < a parameter value (4%) + delta (3%)
- New name: PG, a fixed final target (here 7%),
  Ha: 6-month MACE rate < PG (here 7%)
- Study success decision: Upper bound of confidence interval (***NOT* a point estimate**) < PG (here 7%)

55

Major Problems and Risks with Performance Goal Approach

- Shares all the problems and risks associated with non-randomized study with historical controls.
- Only limited good historical data may be available for the development of a performance goal.
- Borrowing a performance goal developed for different indication or patient population is problematic.
- A PG obtained from literature review may be questionable
  - may be subject to publication bias.
  - difficult to appropriately assess the **pool-ability** of patients across different historical studies without patient level data.

56

Major Problems and Risks with Performance Goal Approach (cont.)

- Difficult to appropriately assess patient **comparability** between the current patient cohort and the historical patient cohort that was used to develop the PG.
- Who is responsible for developing a PG for a particular device?
- Who is responsible for checking if a PG developed is appropriate?
- Who is responsible for updating an existing PG?
- **It is Neither superiority Nor non-inferiority comparison!**
- Appropriate claim: pre-specified performance goal is met.

57

When may a PG be Used?

- The natural history of the disease or condition is well-understood.
- Targeted patient population is well-described and stable.
- Extensive clinical history and experience with the device have been obtained.
- No significant new questions of safety or effectiveness are expected.

58

How should a PG be Developed?

- The development of a PG should be data-driven.
- A sufficiently rich, recent, high-quality historical data should be available.
- Rigorous and scientifically valid statistical methodology should be used.
- Different performance goals should be appropriately developed for different patient populations and different indications for use.
- Validity assessment and appropriate updating should be performed.

59

General Hierarchy of Strength of Evidence in Well-Designed and Conducted Trials

- Randomized controlled trial
- Non-randomized study with concurrent control
- Non-randomized study with historical control
- One-arm study against an appropriately developed PG

60

Concluding Remarks

- Well-designed and conducted RCT provides the highest level of evidence for treatment comparison.
- Non-randomized comparative studies are not as definitive as RCT.
- Selection of a comparable control group is essential in a non-randomized comparative study.
- A PG should be determined by sufficient solid scientific evidence.

61

Proposed Trial Designs for AF Ablation Devices

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Topics

- Controls for AF ablation studies
- Trial with medical therapy control
- Hybrid trial with ablation device control

63

Comparators and Control Groups

- Attempt to control for as many factors as possible:
  - Condition to be treated
  - Patient demographics
  - Concomitant disease conditions
  - Concomitant therapy
- Control group may receive:
  - No intervention (sham)
  - A different intervention
  - Current standard therapy
- Control groups:
  - Randomized concurrent
  - Historical (patient level)
  - Patient as own control
- Other comparator
  - Performance goal

64

Randomized Concurrent Control

- Active control:
  - Optimal medical therapy
  - Ablation therapy with different device
- Strengths
  - Reduction in bias resulting from known and unknown confounding factors
- Limitations
  - Patients may not be willing to be randomized to optimal medical therapy because of the widespread off-label use of ablation catheters
  - Safety profile of optimal medical therapy is different from ablation
  - No ablative devices are currently approved to serve as control

65

Historical Control

- Previously collected patient-level data
  - Similar standard of care and patient population
  - Must have patient-level data on baseline covariates
- Strengths
  - Potentially easier to enroll patients
  - Potentially smaller sample size
- Limitations
  - FDA is not aware of any available & suitable patient-level data
  - Published results of catheter ablation for treatment of AF are widely variable and are therefore not suitable
  - Introduction of bias resulting from differences in patient population, medical management, and evolution of care

66

Patient as Own Control

- Comparison of the status of patients before and after treatment
  - A study success criterion is still needed
    - How much improvement is enough?
    - How to assess safety profile?
- Strengths
  - Potentially easier to enroll patients
  - Potentially smaller sample size
- Limitations
  - Difficult to ascertain the cause of changes in patient status
  - Difficult to develop a study success criterion
  - Heavily dependent on baseline status of patients

67

Performance Goal

- Prospectively defined and quantifiable metric derived from available data and clinical judgement
- Strengths
  - Potentially easier to enroll patients
  - Potentially smaller sample size
- Limitations
  - Difficult to define; unclear if suitable data are available
    - Published results of catheter ablation for treatment of AF are widely variable
    - Safety data seems to be under-reported in the published literature
    - There is likely a publishing bias

68

Two Trial Designs for Ablation of Paroxysmal AF

- **Traditional Trial Design**
  - Consistent with current FDA AF ablation guidance
  - Randomized controlled trial with optimal medical therapy as control
- **"Hybrid" Trial Design**
  - Based on most recent treatment guidelines
  - Randomized controlled trial with alternate ablation treatment control and performance goal

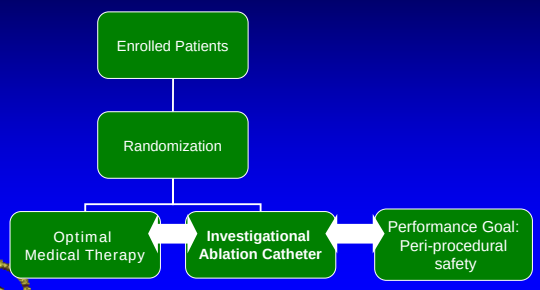
69

Design A: Traditional Trial Design Key Elements

- Multicenter, open-label, randomized, controlled
  - Comparator for effectiveness is **optimal medical therapy**
  - Comparators for safety are **optimal medical therapy & performance goal**
- Ablation as second-line therapy
  - Patients must have failed at least one anti-arrhythmic drug
  - At least two recent, documented AF episodes
- One year follow-up
  - Periodic Holter or trans-telephonic monitoring
  - Symptomatic episodes captured with event recorders
  - Clinically relevant asymptomatic episodes constitute effectiveness failure

70

Design A: Traditional Trial Design Randomization Scheme



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Design A: Traditional Trial Design Comparisons

- Primary Effectiveness
  - Investigational device vs. medical therapy
  - Superiority testing
- Primary Safety
  - Investigational device vs. performance goal derived from similar invasive procedures
  - Procedure-related events
- Secondary Safety
  - Investigational device vs. medical therapy
  - Shared events
  - Noninferiority testing

72

Design A: Traditional Trial Design Pros & Cons

- Strengths
  - **Randomized controlled trial**
  - Eliminates some sources bias
- Limitations
  - Unwillingness of patients to randomize because of widespread off-label ablation
  - Lack of investigator equipoise
  - Placebo effect may be greater for interventional therapy
  - Different expected adverse events

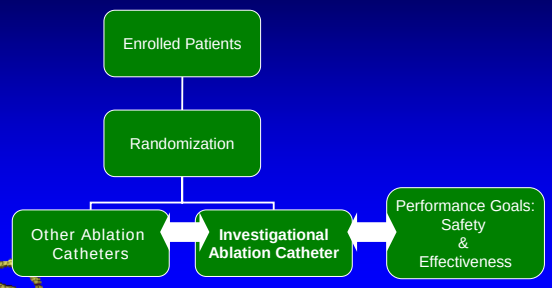
73

Design B: Hybrid Trial Design Key Elements

- Multicenter, patient-blinded, randomized, controlled
  - Comparators for effectiveness are **active ablation control & performance goal**
  - Comparators for safety are **active ablation control & performance goal**
- Ablation as second-line therapy
  - Patients must have failed at least one anti-arrhythmic drug
  - At least two recent, documented AF episodes
- One year follow-up
  - Periodic Holter or trans-telephonic monitoring
  - Symptomatic episodes captured with event recorders
  - Clinically relevant asymptomatic episodes constitute effectiveness failure

74

Design B: Hybrid Trial Design Randomization Scheme



75

Design B: Hybrid Trial Design Comparisons

- Primary Effectiveness
  - Investigational device vs. performance goal derived from published literature
- Secondary Effectiveness
  - Investigational device vs. ablative treatment with other marketed catheters
  - Non-inferiority testing
- Primary Safety
  - Investigational device vs. performance goal derived from similar invasive procedures
- Secondary Safety
  - Investigational device vs. ablative treatment with other marketed catheters
  - Non-inferiority testing

76

Design B: Hybrid Trial Design Pros & Cons

- Strengths
  - **Randomized control** for key secondary endpoints
  - All patients receive similar intervention
    - Potentially easier enrollment
    - Blinding eliminates patient reporting bias
    - Investigator equipoise more likely
- Limitations
  - Unknown safety or effectiveness profile of control catheters
  - Use of multiple catheters makes it difficult to standardize procedure and pool results

77

Discussion of Two Trial Designs

- Common to both trials:
  - Multicenter, randomized, controlled
  - Ablation as second-line therapy
  - One year follow-up for marketing application
  - Up to five year post-approval study
- **Traditional Trial**
  - In accordance with FDA guidance document
  - Randomized control and performance goal for safety
  - Optimal medical therapy as control for effectiveness
- **Hybrid Trial**
  - Based on recent AF treatment guidelines
  - Hybrid between randomized control and performance goal
  - Ablation catheters as control

78