U.S. FOOD AND DRUG ADMINISTRATION

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CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

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MEETING

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THURSDAY,
SEPTEMBER 20, 2007

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The meeting convened at 8:00 a.m. at the Hilton Washington, D.C.

North/Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, Clyde W. Yancy, M.D., Acting Chairperson, presiding.

PRESENT:

CLYDE W. YANCY, M.D., Acting Chairperson
RICHARD L. PAGE, M.D., Voting Member

JOHN C. SOMBERG, M.D., Voting Member
JUDAH WEINBERGER, M.D., Voting Member
EUGENE H. BLACKSTONE, M.D., Consultant
VALLUVAN JEEVANANDAM, M.D., Consultant
NORMAN S. KATO, M.D., Consultant
DAVID MILAN, M.D., Consultant
DOUGLAS MORRISON, M.D., Consultant

JAMES NEATON, Ph.D., Consultant
ROBERT PETERS, M.D., Consultant
MARK SCHOENFELD, M.D., Consultant
DAVID SLOTWINER, M.D., Consultant
CYNTHIA TRACY, M.D., Consultant
MARCIA S. YAROSS, Ph.D., Industry Representative

LINDA MOTTLE, M.S.M., R.N., C.C.R.P., Consumer Representative

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JAMES P. SWINK, Panel Executive Secretary
LILLY YUE, Ph.D., Chief, Cardiovascular and Opthalmic Device Branch
BRAM ZUCKERMAN, M.D., Director, Division of Cardiovascular Devices

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Adjourn

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P-R-O-C-E-E-D-I-N-G-S

8:06 a.m.

DR. YANCY: Good morning. My name is Clyde Yancy. I am medical director of the Baylor Heart and Vascular Institute at Baylor University Medical Center in Dallas, Texas, and I am chair of today's cardiovascular device panel. Welcome.

We would like to convene this meeting. If you haven't already done so, please sign the attendance sheets that are on the tables by the doors. If you wish to address this panel during one of the open sessions, please provide your name to Ms. Anne Marie Williams at the registration table.

If you are, indeed, presenting at one of these open public sessions today and have not previously provided an electronic copy of your presentation to FDA, it is important that you do so as soon as possible with Ms. Williams.

I note for the record that the

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voting members present constitute a quorum, as required by 21 CFR part 14.

I would like to also add that the panel participating in the meeting today has received training in FDA device law and regulations.

No one from the public or the press office is allowed into the panel area at any time during a break or during the conduct of the meeting, because there's proprietary information on the table that might compromise the work of others.

At this time I'd like to have the panel members introduce themselves so that we can all know who is in attendance.

We'll start with Dr. Zuckerman.

DR. ZUCKERMAN: Good morning. Bram Zuckerman, Director, FDA Division of Cardiovascular Devices.

DR. MORRISON: Good morning. Doug Morrison, interventional cardiologist from Yakima, Washington.

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DR. SLOTWINER: David Slotwiner, cardiac electrophysiologist at Long Island Jewish Medical Center and Albert Einstein College of Medicine.

DR. KATO: Norman Kato, private practice, cardiothoracic surgery, Los Angeles, California.

DR. WEINBERGER: Judah Weinberger, interventional cardiology, Columbia University.

DR. SOMBERG: John Somberg, professor of medicine and pharmacology, Rush University, Chicago, Illinois.

DR. PAGE: Richard Page, cardiologist, electrophysiologist, head of cardiology at the University of Washington in Seattle.

MR. SWINK: James Swink, executive secretary.

DR. NEATON: Jim Neaton, professor of biostatistics, from the University of Minnesota.

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DR. BLACKSTONE: Eugene Blackstone, head, clinical research, Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic.

DR. JEEVANANDAM: Valluvan Jeevanandam, chief of cardiothoracic surgery, University of Chicago.

DR. MILAN: David Milan, cardiac electrophysiologist, Massachusetts General Hospital.

DR. PETERS: Bob Peters, cardiologist, University of Maryland, chief of cardiology at the Baltimore Veterans Hospital.

DR. SCHOENFELD: Mark Schoenfeld, cardiac electrophysiologist, Hospital of St. Raphael, Yale University School of Medicine.

DR. YAROSS: Marcia Yaross, vice president, clinical quality, regulatory and health policy, Biosense Webster in Diamond Bar, California, and industry representative to the panel.

MS. MOTTLE: Linda Mottle,

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director of the Center for Health Care Innovation and Clinical Trials, ASU consumer rep.

DR. YANCY: Thank you. I appreciate your attention at this important meeting. I'd like to remind the attendees in the audience as well as the panel members to please place your communication devices on a silent or vibrate mode so as not to disrupt the proceedings of the meeting.

Mr. Swink is the executive secretary for the Circulatory Systems Devices Panel and will make certain important introductory remarks.

DR. ZUCKERMAN: Jim, before you start, just for the record, Dr. Tracy has also just joined. If she can introduce herself --

DR. TRACY: Cynthia Tracy, electrophysiologist, George Washington University Medical Center.

DR. YANCY: Good morning. Thank you for being here.

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MR. SWINK: I'll read the conflict of interest statement.

The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee of the Center for Devices and Radiological Health under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and consultants of the panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the panel's compliance with federal ethics and conflict of interest laws covered by but not limited to those found at 18 USC section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members

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and consultants of this panel are in compliance with federal ethics and conflict of interest laws.

Under 18 USC section 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it's determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to discussions of today's meeting, members and consultants of the panel who are SGEs have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their employer, spouse or minor child.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

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1 For today's agenda, the panel will
2 discuss and make recommendations regarding
3 clinical trial designs for cardiac ablation
4 devices designed to treat patients with
5 medical refractory atrial fibrillation.
6 Based on the agenda and all
7 financial interests reported by the panel,
8 members' and consultants' conflict of interest
9 waivers have been issued in accordance with 18
10 USC section 208 to Drs. David Milan, James
11 Neaton and Clyde Yancy.
12 The waivers allow these
13 individuals to participate fully in today's
14 deliberations. Copies of these waivers may be
15 obtained by visiting the agency Web site at
16 www.FDA.gov or by submitting a written request
17 to the agency's freedom of information office,
18 Room 630 of the Parklawn Building.
19 A copy of this statement will be
20 made available for review at the registration
21 table during this meeting and will be included
22 as part of the official transcripts.

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Marcia S. Yaross, Ph.D., is serving as the industry representative, acting on behalf of all related industry, and is employed by Biosense Webster, a Johnson & Johnson company.

We would like to remind members and consultants that if discussions involve any other products or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the panel of any financial relationships they may have with any firms at issue.

For this meeting on September 20th, 2007, I appoint Clyde W. Yancy, M.D. to act as a temporary chairperson for the duration of this meeting. This is signed by Dr. Daniel Schultz, September 18, 2007.

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I have a few general announcements now. The transcripts of today's meeting will be available from Neal Gross & Company. He can be reached at 202-234-4433.

Information on purchasing videos of today's meeting can be found on the table outside of the meeting room.

And the presenters to the panel who have not already done so should provide FDA with a hard copy of remarks, including overheads.

The press contact for today's meeting is Karen Riley. Thank you.

DR. YANCY: Thank you, Mr. Swink.

The FDA will now give their presentation.

DR. ELOFF: Good morning. My name is Ben Eloff. I'd like to begin the FDA presentation by first thanking the members of the panel in advance for their careful consideration of this issue and their advice and guidance given during this meeting.

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I'd also like to thank the speakers we will hear during the open public hearings for their participation in this process.

FDA will be presenting on the topic of the general clinical trial designs for atrial fibrillation treatment devices.

FDA has two principal goals for this meeting: First, to understand the current scientific and regulatory landscape for atrial fibrillation therapy; second, to design a clinical trial that will generate data to support a PMA application that consists of valid scientific evidence and which demonstrates a reasonable assurance of device safety and device effectiveness.

This trial should also generate interpretable data and be executable in a reasonable amount of time.

At this time, I would also like to thank the members of the FDA team who've been instrumental in both the preparation of this

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meeting and the ongoing discussion and identification of issues relating to FDA's regulation of devices intended for the treatment of atrial fibrillation.

The agenda for our presentation is as follows: First, Dr. Lesley Ewing will present an introduction to the topic of atrial fibrillation. Next, Elias Mallis will provide the regulatory perspective for A.F. ablation devices.

Dr. Randall Brockman will follow with a discussion of the clinical issues common to A.F. ablation trials. Dr. Lilly Yue will provide the statistician's perspective on ideal clinical trial design.

And finally, Dr. Felipe Aguel will propose two trial designs for atrial fibrillation ablation devices.

I'd now like to introduce Dr. Lesley Ewing.

DR. EWING: Thank you, Dr. Eloff.

Good morning. Atrial fibrillation

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is an important public health problem, as the panel knows. There are millions of patients with atrial fibrillation across the world, and this is a broad spectrum of patients with a variety of comorbid conditions, and the prevalence increases with age.

These patients can be with or without heart disease. They can range from having no symptoms and be easily treated with rate control drugs to being highly symptomatic.

Atrial fibrillation can be classified by its temporal pattern and method of termination. Paroxysmal A.F. terminates spontaneously. Persistent A.F. is sustained A.F. lasting longer than a week and not terminating spontaneously, and a patient is classified as having permanent A.F. if cardioversion has failed or has not been attempted.

The goals of treatment are to control ventricular rate and prevent heart

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failure, prevent thromboembolic complications, and to prevent or control symptoms. Medical treatment is palliative and is commonly not effective in maintaining sinus rhythm.

The gold standard for surgical ablation is the Maze procedure. Long-term freedom from A.F. is reported to be from 70 to 95 percent. The surgery is complex, with many incisions in both atria, as you can see represented in the slide by the hashed lines.

To make the Maze procedure less complex, with fewer complications, modified procedures have been developed that use a number of different surgical ablation devices. This procedure is frequently performed, and usually is performed with another open-chest procedure such as mitral valve repair.

Some surgeons are doing ablation lesions only in the left atrium, although the literature suggests that the procedure has greater effectiveness with lesions performed in both atria. Minimally invasive sole-

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1 therapy surgical ablation is also being
2 developed.
3 There are many different
4 approaches to catheter ablation. Most
5 procedures include isolating the pulmonary
6 veins, with some approaches putting lesions
7 close to the ostia of the veins and some
8 widely encircling one or two pulmonary veins.
9 These lesion sets may also include connecting
10 lesions to the mitral valve or across the roof
11 of the left atrium.
12 Another approach involves ablating
13 fractionated atrial electrograms. And any of
14 these procedures may also include ablation of
15 ganglionated plexi.
16 There's a wide range of long-term
17 effectiveness reported in the literature.
18 Repeat procedures are reported to be required
19 in 20 to 40 percent. The reported success
20 rate is lower for patients with permanent A.F.
21 than paroxysmal.
22 There are many different methods

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reported for surveillance of A.F. recurrence, with lower success rates reported for the more vigorous monitoring. There are many different definitions of success across the many single-center clinical experience reports and no standard duration of follow-up.

The complications of catheter ablation are inconsistently reported. It's unknown if all events were captured in retrospective reports. The complications include death, stroke, tamponade, pulmonary vein stenosis, pericardial effusion, iatrogenic atrial tachycardia, phrenic nerve injury, aortic root injury or fistula, gastric dysfunction, catheter entrapment with valve damage, and autonomic dysfunction.

We would like the panel to consider these questions as you listen to the remainder of the presentations today. What is an appropriate method to characterize effectiveness or clinical improvement? Is it absence of A.F., reduction of A.F. burden, or

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1 composite functional end point?
2 We'd like for you all to consider
3 giving us definition of absence of A.F. Is it
4 symptomatic or all A.F.? And please discuss
5 and define the manner in which it can be
6 measured.
7 And we would like for a definition
8 of A.F. burden and how it can be measured both
9 pre- and post-treatment.
10 Is the composite and functional
11 end point -- could it be, for instance,
12 hospitalization, cardioversion, days of work
13 missed?
14 And how is bias accounted for if
15 investigators or subjects are not blinded to
16 their treatment as in the traditional trial
17 design?
18 What trial designs are viable
19 options to develop valid scientific evidence
20 of the safety and effectiveness of a new
21 catheter ablation system? And we will be
22 discussing various trial designs.

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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 -- that is, paroxysmal versus permanent A.F. -- do they need different control groups?

For what duration should safety of the ablation device be measured? For what duration should effectiveness of the ablation device be measured?

Given that catheter ablation is an invasive therapy, if the control group is non-invasive medical therapy, what should the comparisons be for safety and effectiveness?

If a performance goal derived from the medical literature is used for either safety or effectiveness comparisons, what should the values be and why?

Based on the discussion of trial design for percutaneous catheters, please discuss your recommendations for trial designs

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to study surgical ablation in a sole-therapy situation.

And we'd like for you to address the following issues with respect to anticoagulation. The 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.

What data are needed to support instructions to discontinue anticoagulation after atrial fibrillation ablation?

If trial end points focus on symptomatic recurrence, how important is it to capture asymptomatic A.F. recurrences? What are the implications of asymptomatic A.F. recurrences in terms of the long-term risks of A.F. and for the need for anticoagulation?

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1 FDA currently classifies patients
2 with A.F. into three groups -- paroxysmal,
3 persistent and permanent. Do you all believe
4 that the different types of A.F. should be
5 studied separately? Should there be
6 differences in the definitions of
7 effectiveness for each patient group following
8 ablation therapy? And should they be followed
9 differently?
10 And what is the clinical
11 implication of subjects undergoing ablation
12 changing from permanent or persistent A.F. to
13 paroxysmal A.F.? Should this impact the
14 clinical trial design?
15 Should atrial fibrillation
16 ablation trials specifically study high-risk
17 patients such as those with heart failure? If
18 the panel does not feel that specific
19 potentially high-risk patient populations
20 should be included in the clinical trials, can
21 trial results using restricted enrollment
22 criteria be applied to the general population?

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If yes, that the trial should study high-risk patients, are there specific groups to which such results should not be applied? And how should such patient groups be handled in terms of device indications, warnings, precautions, et cetera?

And finally, is it useful and/or important to collect information concerning atrial transport? If so, is there a specific method that should be used? And what comparisons should be used?

And now Mr. Elias Mallis will give a presentation on regulatory perspectives.

MR. MALLIS: Thank you, Dr. Ewing, for providing the background on the disease of atrial fibrillation as well as the questions, we look forward to a rich discussion today during the course of the panel meeting.

I'd like to take a few minutes now and turn our attention to the regulatory perspective of ablation devices intended for the treatment of A.F.

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I'll first present a brief history of FDA's regulation of electrophysiology catheters as it relates to off-label use of ablation catheters, a problem which has been identified as a barrier to enrollment of A.F. ablation studies.

In this context, the term "off-label" refers to legally marketed devices -- that is, devices that FDA has approved or cleared to market -- and which are used in actual clinical practice for a purpose or indication beyond what FDA approved to market.

The interventional cardiologists in this room may well appreciate the well-documented example of off-label use of biliary stents. Although FDA has cleared a number of biliary stents to market, it is well reported that these devices have primarily been used for cardiovascular applications.

Since the onset of FDA's medical device amendments of 1976, there is a longstanding history of electrophysiology

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mapping catheters gaining entry to the market as Class II medical devices through the pre-market identification or 510(k) process.

By the early 1990s, electrophysiologists discovered the utility to treat arrhythmias by means of percutaneous catheter ablation. Unfortunately, there were no legally marketed ablation catheters with which to perform this procedure.

As a result, the function of mapping catheters was altered to permit them to deliver energy sufficient to ablate the target tissue within the heart.

FDA became aware of this practice in part due to reports of serious adverse events involving these modified mapping catheters. FDA then worked with E.P. manufacturers so that they could develop the clinical data necessary to support approval of ablation catheters which are regulated as Class III devices requiring pre-market, or PMA, approval.

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As a result of this effort, the first generation of ablation catheters was approved by FDA in the mid 1990s. These catheters featured four-millimeter-tip electrodes that employed R.F. energy and were indicated for the treatment of supraventricular tachycardia, or SVT.

In this context, FDA defined the treatment of SVT as the treatment of AVNRT and AVRT and the creation of heart block in patients with A.F. with an uncontrolled ventricular response.

As of now, of this approval, the potential for off-label use with ablation catheters now was in place, as physicians could now choose to treat their patients for arrhythmias other than SVT.

By the late 1990s, E.P. manufacturers began to pursue the indication of atrial flutter. This period primarily saw an evolution of catheter technology to now include longer ablation tip electrodes up to

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1 eight millimeters as well as different energy
2 modalities, such as open-lumen irrigated R.F.
3 and cryo.
4 By the early 2000s, this next
5 generation of catheters was approved to
6 market, which meant that more devices were
7 available for potential off-label use.
8 Some of our panelists and members
9 of this audience are aware that FDA held panel
10 meetings in 1998 and 2000 on the topic of
11 trial designs for A.F. ablation. However, as
12 we can all likely appreciate, the scientific
13 perspectives on A.F. trial design have evolved
14 as the knowledge and investigation of the
15 treatment of this disease has taken off since
16 the last panel meeting in 2000.
17 As of now, in 2007, no device,
18 either surgical or percutaneous catheter, is
19 approved by FDA for the treatment of atrial
20 fibrillation. As we'll hear later today, a
21 number of manufacturers are actively
22 conducting clinical studies to collect the

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data that may support approval of their devices for the indication of treatment of A.F.

Unfortunately, these manufacturers face several challenges, most notably of which is the prevalent off-label use of ablation catheters, which hinders their ability to recruit patients into their studies.

The prevalent off-label use is well-documented in scientific publications which report ablation studies for the treatment of A.F. using unapproved catheters, presentations at leading scientific meetings by physicians explaining their research on A.F. ablation, and by the fact that professional societies have recently taken official policy positions, recognizing the heightened role of ablation in the treatment of A.F.

So to put this background into a regulatory context for you, FDA's role is to evaluate medical device applications that are

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submitted by an applicant. This applicant is usually a medical device manufacturer who submits an application for a specific device and for a specific indication.

FDA also provides guidance, advice and, in general, assists sponsors to design clinical studies that collect data and which produce interpretable results. It is important that the collected data are considered valid scientific evidence. I'll explain how FDA defines this term in a few minutes.

Ultimately, this leads to FDA's overall regulatory role and mission to establish reasonable assurance of the safety and effectiveness of medical devices marketed in the United States.

Within the regulatory framework, FDA does not regulate the practice of medicine or how physicians choose to use these devices once they are legally marketed.

FDA's regulations provide a

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definition of valid scientific evidence in terms of what it usually does and does not consist of. Valid scientific evidence may include well-controlled studies, partially controlled studies, studies without match controls, well-documented case studies and other robust scientific evidence.

In contrast, isolated case reports, random experience, reports that lack sufficient detail to permit a scientific evaluation, and unsubstantiated opinions are not considered valid scientific evidence.

In a few minutes, Dr. Lilly Yue will review with you the statistical implications of these options and where they may or may not apply in general terms.

And later, Dr. Felipe Aguel will present for your consideration two proposed trial designs that reflect what FDA believes to be studies whose data may potentially be considered valid scientific evidence in the specific context of A.F. ablation.

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1 As mentioned before, FDA considers
2 the valid scientific evidence collected in
3 terms of the safety and effectiveness of a
4 device. A device is considered safe if the
5 probable benefits with proper labeling
6 outweigh any probable risks of the device.
7 Reasonable assurance of
8 effectiveness is established when it can be
9 determined, based on valid scientific
10 evidence, that the use of the device for its
11 intended use and conditions of use, when
12 accompanied with proper labeling, provide
13 clinically significant results.
14 The barriers to study enrollment
15 that you will hear about today are significant
16 in nature. That is one of the reasons why FDA
17 is holding this public meeting among key
18 stakeholders on this topic.
19 The goal for us on this issue is,
20 indeed, a shared one. That is, for a medical
21 device manufacturer to overcome the barriers
22 to study enrollment and to complete clinical

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1 studies in a timely manner that generate valid
2 scientific evidence that permit FDA to
3 evaluate the approvability of these devices.
4 In looking ahead, one possible
5 outcome is that the currently approved
6 clinical studies that some sponsors have in
7 place will lead to device approval. However,
8 in the case where these existing studies do
9 not lead to device approval, the agency would
10 continue to be faced with the off-label use
11 problem.
12 Keep these scenarios in mind as
13 you deliberate and discuss the specific trial
14 designs that Dr. Aguel will share with you.
15 I do thank you for your
16 participation at this meeting, and we'll now
17 next hear from Dr. Randy Brockman on some
18 specific clinical issues pertaining to A.F.
19 ablation.
20 DR. BROCKMAN: Good morning. I'm
21 Randy Brockman. I'm an electrophysiologist
22 with FDA. And I'm going to discuss some

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clinical issues we deal with with the A.F. ablation trials.

I'm going to briefly discuss enrollment and monitoring, symptomatic versus asymptomatic recurrence, some special patient characteristics, the issue of anticoagulation, and then atrial transport function.

Well, in terms of enrollment issues, FDA has felt that it's important to identify the type of atrial fibrillation in order to study patients with different patterns of A.F. separately, since we believe the safety and effectiveness of profile of a device may be different depending on the type of A.F. being treated.

FDA has considered rhythm monitoring for recurrent A.F. to be important, given the effectiveness end points that we've been considering. Those end points have focused on an assessment -- on an electrocardiographic assessment of recurrent A.F.

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1 Since recurrence of A.F. has been
2 a focus of our attention, we've been concerned
3 about the degree of documentation of A.F.
4 prior to enrollment for the purposes of study
5 eligibility.
6 As examples, for paroxysmal A.F.,
7 we've asked that patients have a minimum of a
8 six-month history with at least two discrete,
9 documented episodes, documented by any rhythm
10 recording. For permanent A.F., we've asked
11 that patients have continuous A.F. for at
12 least three to six months or have failed a
13 cardioversion.
14 For monitoring, the 2007 HRS
15 consensus document offers the following
16 approach for industry-sponsored device
17 approval studies: A minimum assessment of
18 symptomatic A.F. and search for asymptomatic
19 A.F. at six-month intervals after the blanking
20 period, using one of the following:
21 transtelephonic monitoring for four weeks
22 around the follow-up interval for symptom-

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1 triggered recording with a minimum of weekly
2 transmissions to detect asymptomatic events,
3 24 to 72-hour Holter monitoring, or 30-day
4 auto-triggered event monitoring or mobile
5 cardiac outpatient telemetry.
6 But since different types of A.F.
7 have different recurrence patterns, we've
8 taken the approach that different types of
9 A.F. should be studied separately, again.
10 We've taken this approach in part since we
11 feel that the duration of follow-up and the
12 burden of follow-up monitoring and
13 documentation may be different.
14 In order to evaluate the safety
15 and effectiveness of devices, FDA has
16 recommended the following. For paroxysmal
17 A.F., we felt that a minimum of one year of
18 follow-up with frequent surveillance
19 monitoring focusing on symptomatic A.F. is
20 important.
21 For permanent A.F., we felt that a
22 minimum of six months follow-up with an

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assessment of rhythm at six months was adequate based on the following assumption: If A.F. is not identified at six months, then a patient with pre-ablation permanent A.F. is unlikely to have been in A.F. during the preceding six months, the blanking period notwithstanding.

For persistent A.F., we've taken an intermediate approach, requesting nine months of follow-up, asking for a seven-day Holter monitor at nine months and the availability of an event recorder if symptoms of recurrent A.F. are reported. And we're interested in your thoughts on our approach.

Sorry, this gets a little bit small, but this is a summary slide of the different recommendations for monitoring and duration of follow-up with the consensus document recommendations towards the left and FDA's towards the right.

The consensus document doesn't really differentiate recommendations based on

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1 the type of A.F. except for paroxysmal A.F. it
2 does elaborate as follows, and I'm quoting,
3 "If the A.F. was paroxysmal, optimally
4 multiple 24-hour Holter monitors and/or four
5 weeks of monitoring, preferably with an auto-
6 trigger event monitor or by mobile outpatient
7 cardiac telemetry, is recommended to optimize
8 identification of asymptomatic episodes."
9 And again, your thoughts about the
10 appropriate type and duration of monitoring
11 will be very helpful to us.
12 The possibility of conversion from
13 one form of A.F. to another has come up. FDA
14 has viewed a patient with pre-ablation
15 permanent A.F. as having a binary result post-
16 ablation, meaning after the ablation we've
17 thought the rhythm would be either permanent
18 A.F. or a non-A.F. rhythm. Follow-up
19 monitoring has been tailored to address that
20 question.
21 But we now have a question as to
22 whether or not that approach is appropriate.

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And so just as an example, a patient with pre-ablation permanent A.F. may experience post-ablation paroxysmal A.F. And at the moment, we've only asked for a focused rhythm assessment at six months, and our question is is that an issue that should be addressed in the study design.

We also have questions about the significance of symptomatic versus asymptomatic A.F. A.F. 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 versus asymptomatic A.F. And A.F. ablation may change many episodes from symptomatic A.F. to asymptomatic A.F.

In support of this last bullet is the graphic on this slide. This is out of circulation, an article by Hindricks. This is a box-and-whisker plot showing the percentage of asymptomatic A.F. episodes among patients

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with documented A.F. recurrences with before and after A.F. ablation.

You see medians, quartiles and the highest values are shown, and you can see a substantial increase in the proportion of asymptomatic episodes from pre-ablation, which is to the left of the red line, to post-ablation, to the right of the red line.

And it's unknown how much of this difference represents a physiologic change versus a placebo effect, but nevertheless, with this in mind, what are the implications for success in an ablation trial as well as the need for anticoagulation?

We have questions about special patient groups. A.F. frequently coexists with important comorbidities, a number of which might deserve special consideration. One example might be a patient with a giant left atrium, but I'm going to focus on patients with heart failure.

There may be interest in ablating

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A.F. in heart failure patients. The presence of A.F. may be especially detrimental to patients with heart failure.

And the risks and benefits of A.F. ablation may be different in patients with heart failure as opposed to those without heart failure, since patients with heart failure may have enlarged left atria, left ventricular systolic dysfunction, and may not tolerate invasive procedures as well as patients without heart failure.

Patients with A.F. and heart failure have been reported to be from four to 50 percent, with the proportion of patients with A.F. increasing as the New York Heart Class worsens.

While I've focused on heart failure, there may be other patient groups you think should be specifically addressed as well.

In terms of anticoagulation, you've seen this, but I'm going to read it

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again. 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.

FDA's impression is that one of the reasons patients and, perhaps, clinicians are interested in A.F. ablation is the thought that warfarin may be stopped if the ablation is considered to be successful. FDA is unaware of conclusive data that supports the routine discontinuation of anticoagulation following catheter ablation of A.F.

We feel that either the need for anticoagulation should be studied -- in other words, the trial should be large enough to detect a difference in thromboembolic stroke between those receiving anticoagulation and

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1 those not receiving anticoagulation -- and we
2 recognize that this would be a very large
3 sample size; we have not asked any single
4 device manufacturer to do that -- or the
5 ablation shouldn't impact the decision as to
6 whether or not anticoagulation should be
7 prescribed.
8 In other words, a patient's stroke
9 risk should be used to determine the need for
10 anticoagulation according to the guidelines
11 rather than specifying an arbitrary time point
12 after the ablation at which point the protocol
13 states anticoagulation may be discontinued.
14 We're certainly interested in your thoughts on
15 this subject.
16 And finally, FDA has asked for
17 studies to include an assessment of atrial
18 pump function. While we don't view this as a
19 surrogate for stroke risk, it may provide
20 useful information. It may also provide
21 additional safety information in terms of
22 preservation of atrial mechanical function.

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We're interested in whether or not you think this information is likely to be helpful and, if so, what the best method for characterization is.

And now I'd like to introduce Dr. Lilly Yue, who will discuss statistical issues. Thank you.

DR. YUE: Thank you, Dr. Brockman.

Good morning. I'd like to give our now statistical panel members a little tutorial, Medical Device Clinical Trial Design 101.

In this talk, I will revisit the choices of control groups, types of clinical studies, and then conclude with remarks.

Choices of control groups. First of all, why do we need a control group? Well, we need a control group to see if the observed treatment effect is due to the experimental device instead of such as progression of the disease, investigator or patient expectation, or other treatment.

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1 Choices of control groups include
2 concurrent control groups and historical
3 control groups. In concurrent control groups,
4 we have active control group with approved
5 device or optimal medical therapy. We could
6 have a sham control. Also we could have a
7 baseline control.
8 Now, here, patient serves as his
9 or her own control, with a pre-mark, pre-
10 treatment and post-treatment comparison.
11 Historical control group is a
12 group of patients studied in previous clinical
13 trials. Here, patient-level data are
14 available in both clinical outcomes and
15 baseline covariates.
16 Types of clinical studies,
17 randomized controlled trials, RCT, now
18 randomized the comparative study with a
19 concurrent control or historical control.
20 One-arm study against the objective
21 performance criterion, OPC, or performance
22 goal, P.G.

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Now, here, OPC or P.G. is a number, a face target. Its determination should be data-driven and through the appropriate statistical modeling.

As we all know, in a well-designed and conducted RCT, all patients have a specified chance of receiving either treatment, avoiding both obvious and non-obvious clinical selection of a patient for one treatment or the other. It's expected that all patient covariates measured or unmeasured -- for example, gender -- the original disease are balanced between the two treatment groups.

In expectation, two treatment groups are comparable, and observed treatment difference is unbiased estimate of true treatment difference. However, the above advantages are not guaranteed for small or poorly designed or poorly conducted RCT.

Risks of non-randomized study with a concurrent control -- why non-randomized?

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Because sometimes RCT is not ethical or practical. But unfortunately, in non-randomized studies advantages provided by RCT are no longer available.

Major potential problems include selection bias caused by such as treatment assignment based on physician clinical judgment or patient preference and treatment group non-comparability. That means two treatment groups who are not comparable before the start of treatment due to imbalanced baseline confounding covariates.

For instance, one treatment group had much sicker patients, or two treatment groups of patients had different physiological factors. Therefore, direct treatment comparisons would be non-interpretable.

A question to ask is are there any ways to adjust for the imbalance of baseline confounding covariates. As we know, the answer is yes.

However, these statistical methods

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can only adjust for measured confounding covariates but not for unmeasured ones. That means we can only adjust for what we have, and we cannot adjust for what we do not have.

Let's suppose all baseline confounding covariates were pre-specified and measured, but if the covariates, the differences between the two treatment groups are extensive, the statistical method may not work well.

In reality, sometime it's hard to know ahead of time whether some important baseline confounding factors are left out or even measured ones are appropriate ones. It may be impossible to predict in advance whether the patient population with a new treatment is comparable to the patient population with the control.

Consequently, the results of such study may be more difficult to interpret and that study may be more burdensome than RCT.

Risks of non-randomized study with

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a historical control. Such study shares all the problems and the risks associated with non-randomized study with a concurrent control.

Additionally, a major potential problem is a temporal bias caused by evolution of medical practice and technology. With such study, sponsor must have legal access to the historical data at a patient level, and all the appropriate baseline covariates need to have been measured in both treated and historical groups.

One-arm study with a performance goal. Objective performance criterion, OPC, is a fixed target. It has been used for heart valves. It was a big turn from historical data of multiple approved heart valves by third-party experts. Some people call four percent OPC. Some others call seven percent OPC.

To avoid the confusion, we have a new name now, performance goal, which is a

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fixed final target, here, seven percent.

So we are testing whether six-month MACE rate is less than the performance goal -- here, seven percent.

Please note that with such study, the study's success, considering criterion is upper limit of confidence interval, not upon estimate is less than the performance goal -- here, seven percent.

Major problems and risks with the performance goal approach. This kind of study shares all the problems and the risks associated with a non-randomized study with historical controls.

Additionally, we may have only limited good historical patient-level data available for the development of a performance goal. Now, what we can we do? One suggestion could be borrowing. However, borrowing a performance goal developed for a different indication or patient population is problematic.

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1 How about you get one from later
2 research or review. Well, a performance goal
3 obtained from later research and review may be
4 questionable also. It may be subject to
5 publication bias. It may be harder to
6 appropriately assess the pool-ability of a
7 patient across different historical studies in
8 literature without patient-level data.
9 Furthermore, it may be hard to
10 appropriately assess patient comparability
11 between the current patient cohort and the
12 historical patient cohort that was used to
13 develop the performance goal.
14 Also, there are some logistic
15 issues. For example, who is responsible for
16 developing a performance goal for a particular
17 device and a particular patient population?
18 Who's responsible for checking if a
19 performance goal developed is appropriate?
20 Who is responsible for updating existing
21 performance goal?
22 With such a study, it's neither

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superiority nor non-inferiority comparison. Appropriate claim is pre-specified performance goal is met.

When may a performance goal be used? It can be used when the natural history of the disease or condition is well understood, targeted population is well described and stable, extensive clinical history and experience with the device have been obtained. No significant new questions of safety and effectiveness are expected.

How should a performance goal be developed? The development of a performance goal should be data-driven. 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 checking and appropriate updating should be performed.

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Among well-designed and conducted trials, general hierarchy of strength of evidence is as follows: RCT, non-randomized study with a concurrent control, non-randomized study with a historical control, and one-arm study against appropriately developed performance goal.

In concluding, 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 and the performance goal should be determined by sufficient, solid, scientific evidence.

Next speaker is Dr. Aguel, talking about proposed trial designs for A.F. ablation devices. Thank you.

DR. AGUEL: Thank you, Dr. Yue.

I will describe the control groups

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that FDA believes may be used in A.F. ablation clinical studies. Then I will describe two trial designs FDA believes are likely to generate valid and interpretable data for purposes of assessing the safety and effectiveness profile of ablation catheter devices intended for the treatment of atrial fibrillation.

An appropriate control group should be chosen to account for as many confounding factors as possible, such as the condition being treated, patient demographics, disease conditions other than that being treated, and other therapy administered that is not the focus of the clinical trial.

A control group in a clinical trial may receive either no intervention, sham procedure, a different intervention than that being studied, or the current standard therapy.

Some possible control groups for an A.F. ablation trial are a randomized active

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control, a historical control, and using patients as his or her own control. In addition, it may be possible to use a success criterion for the trial based on a performance goal without the use of a control.

A randomized concurrent control is the gold standard for clinical trials and what is recommended in the percutaneous A.F. ablation guidance document. FDA believes this is the least burdensome approach in terms of producing interpretable clinical data.

Some examples of an active control include optimal medical therapy and ablation therapy with a different device than that being investigated. The reason a randomized active control is considered the gold standard is the fact that randomization will reduce bias resulting from known as well as unknown key patient covariates.

One important limitation is that if optimal medical therapy is used as the control, patients may not be willing to be

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1 randomized because of the widespread use of
2 off-label ablation catheters.
3 Furthermore, the safety profile of
4 an invasive ablation procedure is expected to
5 be different from that of a non-invasive
6 management with medical therapy.
7 Currently there are no devices
8 approved for treatment of A.F. This raises a
9 limitation in using an ablative therapy as a
10 control treatment. As I will discuss later in
11 my presentation, this is a limitation that FDA
12 believes can be overcome.
13 A historical control consists of
14 previously collected clinical data. For
15 historical control to be a good comparator, it
16 is important that the data have been collected
17 rigorously, using a similar standard of care
18 and a similar patient population as that in
19 the clinical trial.
20 Because of this, it is important
21 that patient-level data, including baseline
22 covariates such as patient age, gender,

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severity of A.F., and concomitant cardiovascular disease be available in order to analyze the trials appropriately.

There are two principal strengths of using historical control instead of a randomized control. The first is that it may be potentially easier to enroll patients because all patients enrolled will be ablated.

The second is a potentially smaller sample size compared to the randomized concurrent control because the control group data will have already been collected.

The principal limitation of using historical control is the availability of suitable patient-level data complete with patient baseline covariates. Specifically for A.F. ablation trials, published results are widely variable. The variable reported outcomes, combined with a lack of patient-level data, makes it difficult to use these data as a historical control.

In addition, the lack of

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randomization will allow introduction of bias resulting from differences in patient population and medical management as well as evolution of patient care.

Using a patient as his or her own control was recommended in the 1998 and 2000 panel meetings regarding A.F. trial design issues. Despite the previous panels' recommendations, FDA believes it is difficult to implement this trial design for the reasons I will mention shortly.

Using a patient as own control consists of comparing the status of patients before and after the investigational treatment. It is important to note that using patients as own control is insufficient for making a decision regarding the outcome of the clinical trial.

A study success criterion is still needed for the trial. Important parameters that are difficult to define but should be pre-specified include how much improvement is

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enough to call a patient a successfully treated patient. Perhaps more importantly, what proportions of patients demonstrating improvement is good enough to consider the treatment effective?

Furthermore, it is important to assess the safety of the device being studied and patients as own control will not serve as a control group for assessing the safety profile of the device.

The strengths of using patients as own control are similar to those of using a historical control. It is potentially easier to enroll patients and the sample size may be potentially smaller compared to a randomized concurrent control.

The principal limitation is that it may be difficult to ascertain the cause of changes in patient status, particularly for paroxysmal A.F. It is also difficult to derive a clinically meaningful success criterion for the trial.

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In the absence of a good or feasible control, a performance goal can also be used as a comparator. Ideally, a performance goal should be derived from a large collection of patient-level data, but FDA recognizes that leveraging published literature reports may be a least-burdensome alternative.

Thus, a performance goal is prospectively defined in quantifiable metric derived from available data as well as clinical judgment and experience. The strengths are those of a single group clinical trial. It may be easier to enroll patients, and it may potentially result in a smaller sample size.

The principal limitation of using a performance goal in lieu of a control group is that a clinically meaningful performance goal is difficult to define. At this point, it is unclear if suitable data are available for deriving a safety or an effectiveness

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performance goal.

Published effectiveness results are widely variable, and published results seldom provide details regarding safety data. It seems that adverse events are under-reported in the published literature. There may also be a publication bias whereby only the most successful studies and experiences are published.

I will now describe two trial designs FDA has considered for gathering valid scientific evidence supporting the safety and effectiveness of percutaneous ablation catheters indicated for treatment of paroxysmal atrial fibrillation.

The first trial design is consistent with the current FDA guidance document on the topic. It is a randomized controlled trial where the control is optimal medical therapy.

The second trial is based on recent treatment guidelines. It is a hybrid

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1 trial with a randomized active ablation
2 control as well as a performance goal for both
3 safety and effectiveness.
4 The first trial design is a multi-
5 center, open-label, randomized controlled
6 trial. The comparator for effectiveness is
7 optimal medical therapy. The comparators for
8 safety are optimal medical therapy, control,
9 and the performance goal.
10 Key inclusion criteria are that
11 patients have failed at least one anti-
12 arrhythmic drug and that at least two recent
13 episodes of A.F. be documented.
14 For purposes of submitting a
15 marketing application, a one-year follow-up is
16 adequate. A.F. monitoring consists of a
17 periodic Holter and transtelephonic
18 monitoring. Symptomatic episodes are captured
19 with event recorders made available to
20 patients.
21 Asymptomatic episodes that are
22 clinically relevant -- that is, those that

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1 require cardioversion or a non-scheduled
2 hospital or doctor's visit -- constitute an
3 effectiveness failure.
4 After the device is legally
5 marketed, patients in the original trial are
6 followed for up to five years. This follow-up
7 may consist of a yearly call or doctor's visit
8 to ascertain whether the patient is alive,
9 whether the patient has been cardioverted,
10 reablated, whether anti-arrhythmic or
11 anticoagulation regimen has been changed, and
12 whether the patient has suffered a stroke.
13 Enrolled patients in this trial
14 design are randomized to receive either
15 ablation treatment or optimal medical therapy.
16 The results in each study group are compared
17 for both safety and effectiveness. In
18 addition, the rate of peri-procedural adverse
19 events in the investigational ablation
20 catheter group are compared to a pre-specified
21 performance goal.
22 The primary effectiveness end

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1 point is a superiority comparison of the
2 proportion of patients free from symptomatic
3 A.F. through one year in the investigational
4 device group to that of the control group.
5 The primary safety end point
6 evaluation is complicated by the fact that
7 patients in the investigational group undergo
8 an invasive procedure and patients in the
9 control group do not. Therefore, a safety end
10 point is split into events specific to the
11 ablation procedure and events that are common
12 to both study groups.
13 The proportion of patients
14 experiencing at least one adverse event
15 specific to the procedure -- such as
16 tamponade, phrenic nerve paralysis, esophageal
17 damage, and pulmonary vein stenosis -- is
18 compared to a performance goal.
19 The proportion of patients
20 experiencing at least one event that is not
21 necessarily procedure-related, such as stroke
22 and death, is directly compared between the

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1 investigational group and medical therapy
2 group as a secondary end point using a non-
3 inferiority success criterion.
4 The most important advantage of
5 this design are all the advantages of a
6 randomized control. This is a key point,
7 because known as well as unknown key
8 covariates will be balanced by the
9 randomization.
10 Hence, we do not need to worry
11 about the unknown covariates producing
12 significant confounding and leading to a lack
13 of clear interpretability of results.
14 The limitations include
15 willingness of patients to be randomized
16 because of the widespread availability of
17 ablative treatment with devices used off-
18 label, lack of investigator equipoise,
19 differences in the placebo effect between
20 patients who receive ablation treatment versus
21 those that receive medical therapy, and the
22 difference in the expected safety profiles

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mentioned earlier.

In an attempt to maintain the randomized controlled trial design while minimizing its drawbacks, FDA has proposed a hybrid or three-arm trial design consistent with the most recent A.F. treatment guidelines. This trial is a multi-center, patient-blinded, randomized controlled trial.

Patients randomized to the active ablation control group are treated with an ablation catheter that is legally marketed with indications other than treatment of atrial fibrillation. Until a device is approved with A.F. indications, multiple ablation catheters should be included in the control group.

Because the safety and effectiveness profile of the devices used in the control group patients has not been rigorously studied and is therefore unknown, a performance goal comparator should also be used in the trial.

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The inclusion criteria, pre-market follow-up duration, and monitoring modality and scope of a post-market study are the same as that for the traditional trial design I mentioned earlier.

The key point in this design is that all patients enrolled in the study will receive ablative treatment. Patients are randomized to receive ablative treatment with either the investigational catheter or one of several catheters legally marketed with indications other than atrial fibrillation.

Comparisons to both safety and effectiveness performance goals are needed because the safety and effectiveness profiles of the catheters used in the control group are unknown.

The primary safety and effectiveness end points consist of a comparison between the effectiveness and adverse event rates of the investigational device and a performance goal. The confidence

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bounds of the observed effectiveness and adverse event freedom rates should be greater than the pre-specified performance goal.

If and only if the primary end points are met are the key secondary end points evaluated. These secondary end points consist of a comparison between the effectiveness and adverse event rates observed in the investigational and control groups.

These comparisons should be based on a non-inferiority hypothesis, although a sponsor could conduct a superiority comparison as long as such an analysis is pre-specified. These secondary end points are considered essential end points for study success.

The advantages of this trial design are that a randomized control is used while reducing the problems associated with an optimal medical therapy control. Patients' reluctance to be randomized should be reduced because they know they will receive ablative treatment once enrolled in the trial.

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1 Patients can be blinded to the
2 treatment received, thus reducing the placebo
3 effect. Lack of investigator equipoise should
4 no longer be an obstacle recruiting sites and
5 enrolling patients.
6 New challenges that emerge in this
7 trial design are that the catheters used in
8 the control group have unknown safety and
9 effectiveness profiles, and the use of
10 multiple catheters in the control arm may
11 raise pool-ability questions since the
12 procedure may be difficult to standardize in
13 the study.
14 In summary, FDA believes that
15 conducting a randomized controlled trial is
16 the least burdensome means to obtain
17 scientifically valid and interpretable data
18 for purposes of a marketing application. Both
19 trial designs described are multi-center
20 randomized controlled trials. Both use
21 ablation as second-line therapy and use the
22 same follow-up modalities and duration.

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The traditional randomized control design is consistent with FDA's current guidance document on trial designs for percutaneous A.F. studies. The hybrid or three-arm trial design uses an active ablation control.

Because currently there are no catheters that are approved with indications of treatment of atrial fibrillation, a performance goal is also used as a comparator.

FDA hopes to get the panel's opinion regarding the merits and challenges of the two trial designs described as well as any others the panel may deem more appropriate.

In addition, and equally important, FDA hopes to get the panel's recommendation of a value for the performance goals used in assessing the safety and effectiveness of percutaneous ablation devices intended for treatment of A.F. Thank you.

DR. YANCY: I'd like to thank the FDA and its members for really providing a

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very scholarly review of the issues and giving us the substance from which we need to construct our deliberations.

Let me remind panel that our charge here is to discuss atrial fibrillation trial issues.

In that context, then, the things that I heard FDA tell us, in addition to the natural history of atrial fibrillation and the fact that there have been two past panels to address this, has been that there is significant off-label use; that there are important patient cohorts that have to be considered, especially those with atrial fibrillation and heart failure; that the issues around performance goals are very important, and we need to be very deliberative in our thought process in the construction of those; that, importantly, there are at least two template trial designs that have been suggested to us today -- trial A, a traditional design, and trial B, one that is

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a hybrid design.

Importantly, the concept of investigator equipoise was raised, and it is evident that we need to consider these issues in our deliberations.

We have 15 minutes now to discuss our questions with the FDA based on their presentations, and perhaps we can focus on these trial design issues, but anything else you heard is appropriate for questions and answers.

So that having been said, I'd like to open this up for panel members to begin to query the FDA. I'd like to start with just one brief question, and it regards actually trial A design -- that is, a traditional design.

I'm somewhat troubled with the description of optimal medical therapy, because the criterion to go forward with an ablative procedure is, in fact, recurrent or refractive disease that ostensibly has failed

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1 medical therapy, so the definition of optimal
2 medical therapy appears to be a disconnect.
3 And I wonder if what is really
4 implied is background medical therapy with
5 novel new therapy. And so if you have any
6 context about what you'd accept as optimal
7 medical therapy, I'd like to hear that.
8 DR. BROCKMAN: I think in my mind
9 it's very much what you just said. There's
10 important background therapy. Obviously, I'm
11 -- I think anticoagulation is very important.
12 Certainly, we have not, to any
13 large degree, accepted studies where A.F.
14 ablation is used first line. So in my mind,
15 it's failure of one anti-arrhythmic drug, and
16 we generally define that as Class I or Class
17 III.
18 There have been arguments put
19 forward that by doing that, we actually select
20 a group of patients into a control arm that
21 are resistant to drug therapy. I think that
22 is one of the limitations of that trial

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1 design, but that is the design that we have,
2 up till now, been using.
3 DR. YANCY: Questions from the
4 panel?
5 Dr. Page, please?
6 DR. PAGE: Thank you very much
7 for, really, a very nice comprehensive review
8 of AFib and options.
9 In terms of the potential trials
10 that are put forward and having read the
11 briefing materials, it looks to me like
12 protocol A is untenable based on the fact that
13 randomized trials thus far have been
14 unsuccessful in recruitment, and that, as is
15 mentioned, generally patients, once they've
16 already failed one drug, the option of going
17 to another drug trial, as opposed to ablation,
18 really is unacceptable to most of the patients
19 I'm seeing these days.
20 So I wonder whether you -- as
21 putting forward A and B, whether you're saying
22 A more is kind of a straw man and whether this

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is more about designing B, or whether we ought to be also considering the idea of a one-arm study with performance goal.

DR. BROCKMAN: I think any feedback you have for us will be appreciated. I think before we close the door on trial design A, just hold that thought and wait for the sponsor's presentations.

DR. PAGE: Thanks.

DR. YANCY: Dr. Morrison?

DR. MORRISON: I'd like to ask about this -- the definition of this term "failure." Patients who are said to have failed multiple medical therapies. If I -- I mean, certainly, there are people who live in atrial fibrillation quite successfully, and we now have the affirmed data that suggests that as a strategy, rate control may provide a good alternative, with stroke prevention, to trying to get them out of it.

So if the issue of failure is symptoms, it also seems to me that we have

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lots of historical precedent of issues where patients have symptoms and have a problem, and the relationship between the two is not very well demonstrated. I see that as an interventional cardiologist every day of the week, where we have tight lesions, symptoms, and no evidence of ischemia in the territory subserved by that tight lesion.

So it seems to me critically important to separate the emotional concept of failure and the very predictable effect of telling a patient you've failed from what exactly is failure of medical therapy.

DR. BROCKMAN: Not all symptoms are associated with AFib, and AFib can be -- can occur without symptoms. I agree with you completely. It's one of the reasons that we have been -- have pushed to a degree to have episodes of A.F. documented by rhythm monitoring and not simply based on symptoms.

It's also one of the reasons that we have tried to focus on symptomatic A.F.

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1 This is not one of the things we discussed,
2 but in my own mind the benefit of A.F. --
3 treatment of A.F. is one of two things:
4 Either make the patient feel better or reduce
5 the long-term consequences of A.F.
6 DR. MORRISON: Again, not to push
7 this to an obnoxious extreme, but it seems to
8 me, having lived through the era when we were
9 sure that treating PVCs prevented sudden
10 death, lots of us spent lots of time
11 documenting the PVC burden, and assuming not
12 only that we were making patients live longer
13 but they were less symptomatic.
14 And when we took the time to
15 compare the documents that they provided with
16 their Holter monitors, in many patients --
17 maybe most patients -- it was almost random
18 whether their symptoms related to the times
19 when they had bigeminy or frequent PVCs or
20 what have you.
21 And it seems to me that's a daily
22 issue with atrial fibrillation. Lots of

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1 people have palpitations and dyspnea and chest
2 pain and all sorts of things.
3 Demonstrating that that has any
4 relationship whatsoever to paroxysm of atrial
5 fibrillation is a lot more tricky an issue.
6 And it seems quite relevant, if we're
7 declaring that people are failures.
8 DR. YANCY: Certainly, if I may
9 interject, your questions about patient
10 selection and the ideal candidate for these
11 procedures are appropriate, but recognize that
12 our charge is to really review industry-
13 sponsored AFib trials using catheter
14 technologies -- and as we all know, there's a
15 whole other repository of clinical trial work
16 being done by other sponsoring entities,
17 especially government, to move forward with
18 better description of natural history and
19 those kinds of things.
20 DR. MORRISON: I appreciate that,
21 Dr. Yancy, but it seems to me, number one, my
22 colleague Dr. Page is suggesting we dismiss a

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randomized trial option based on the fact that these patients have failed therapy out of the box.

And number two, industry is here because they're saying we can't randomize because equipoise doesn't exist, and having lived through this with trying to randomize patients between CABG and PCI or trying to randomize patients to a revascularization strategy before vascular surgery, it seems to me that the perception of equipoise and the fact of equipoise are not the same thing.

And I'm driving at that right out of the blocks because I don't agree that model A should be dismissed here.

DR. YANCY: The point's well made.

Can we continue, please?

We actually have a question from our industry representative, Dr. Yaross.

DR. YAROSS: Thank you.

And I do appreciate the -- all the efforts of FDA and panel to really address

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this issue, which has been very challenging for industry.

I have two questions. One was just a follow-up on what we were just discussing. In the design A, it talks about follow-up including clinically relevant asymptomatic episodes constituting an effectiveness failure.

And, Dr. Brockman, you were talking a minute ago about the goal perhaps being addressing symptomatic A.F., and there seems -- maybe you could elaborate on -- if the goal is to address symptomatic A.F., why you would consider an asymptomatic episode to be a failure.

DR. BROCKMAN: I was speaking about what we have done thus far.

DR. YAROSS: Okay, thank you. And then my second question comes from Dr. Aguel's presentation in terms of the patient as own control design.

I believe you mentioned that that

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trial design does not yield a safety profile, and I'm not clear why that wouldn't -- why that wouldn't be the case, so maybe you could elaborate.

DR. AGUEL: Well, we wouldn't have a control against which to compare the rate of adverse events. It would be difficult to capture the adverse events prior to ablative treatment versus those after ablative treatment, just because the same problems we have with the -- with trial design A, where there's a -- an invasive procedure being done, you would expect the adverse event rate to be higher post-procedure just because of the intervention.

DR. YAROSS: Okay. I would agree that you don't have a safety comparator, but you would have a risk profile and a benefit profile, benefit comparatively, and then the risks associated with that.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: Thank you.

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1 The first protocol is obviously,
2 compared to the second, an ideal protocol.
3 The second is -- as I think many of us feel,
4 is a response to problems.
5 But I was trying to get at what
6 FDA is hoping to accomplish. I didn't
7 understand the goal of the second protocol,
8 because it seems to me -- and I'll just
9 preface it by saying it seems to me that gives
10 you a lot of safety information comparing to
11 a performance goal, to another non-approved
12 catheter in that area, and it would give you
13 parameters of safety evaluation.
14 But how, in FDA's thinking, does
15 that provide you with understanding of the
16 effectiveness compared to either other
17 approaches or in a general sense? How does it
18 give you an effectiveness when you have a
19 series of similars?
20 DR. AGUEL: I think the idea is to
21 compare the effectiveness to the performance
22 goal, and that's the primary end point. But

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because that performance goal is difficult to derive, we want a check, if you will, that we're not approving a device that's inferior to devices that are essentially what are being used as a standard of care.

DR. SOMBERG: Just -- may I follow that up just for one second?

DR. YANCY: Very briefly.

DR. SOMBERG: The lecture on 101 trial design and all says when you have robust data for -- you can establish the performance goal on the basis of that. At the same time, I heard FDA saying they didn't feel there was much data on the -- on ablation therapy per se in terms of the -- its effectiveness and that there was tremendous variability.

So with that conundrum, how is FDA going to look at this type of performance goal as saying these devices are no different than the other devices that are off-label on the market, and to some goal somebody comes up with in a room, but how does that tell you,

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real life, how is this better than alternative therapies?

DR. YANCY: Dr. Aguel, let's have Dr. Zuckerman respond to this.

DR. ZUCKERMAN: Okay. Dr. Somberg, I think you've put your thumb on the nail per se as to some of the complexities with the hybrid trial design.

But I think we need to take a step back, again, to understand why the agency is presenting this trial design as a potential straw man. And I think you've hit upon some of that.

Previously, you've heard an interesting interchange between Drs. Page and Morrison which really reflect the opinion in this field. There are some who believe that there are adequate data out there when judiciously looked at that could be used to develop a performance goal.

On the other hand, you heard Dr. Yue's presentation whereby a strictly rigorous

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1 interpretation of meaning of performance goal
2 would leave that number that the FDA would
3 generate as somewhat problematic.
4 So we've taken a two-step
5 approach. Certainly, with the initial
6 analysis we would like to see, as Dr. Aguel
7 indicated, superiority to some derived
8 performance goal number at, say, nine to 12
9 months.
10 As a second check, and also to
11 reflect reality, the agency is also suggesting
12 a real non-inferiority comparison to a
13 standard of care approach. It's thought that
14 at this point in time, with the limitations in
15 data, that this would be a reasonable way to
16 assure safety and effectiveness.
17 I would underline the point that
18 you just made, that if we decided to randomize
19 just to so-called standard of care right now,
20 the principal problem with non-inferiority
21 comparisons is that of potential drift.
22 And that's why Dr. Aguel and the

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agency have clearly tried to demarcate this three-armed approach so that at the end of the day we can clearly decide, both sponsor and FDA, where the experimental therapy sits in comparison to what we believe are the best baseline comparators right now, given the limitations of these comparators. It's just one suggestion for an approach.

DR. YANCY: Thank you, Dr. Zuckerman.

We need to address a few more questions from panel members.

Dr. Jeevanandam was first to be recognized.

DR. JEEVANANDAM: I guess the biggest problem here is off-label use of ablation catheters that have de facto become accepted as standard of care or have become standard of care that are preventing these trials from progressing.

Now, of course, that's all based on no randomized trials that they became

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accepted as standard of care. Now, is there any way to limit their use so -- I mean, the second you limit their use in -- for instance, if patients don't get reimbursed for atrial fibrillation unless they join a trial, then all this becomes moot and you can go into a type A trial without a problem, because we haven't really established that ablation is standard of care.

So is there any way to limit their -- it's like carotid stenting. I mean, unless you were part of a trial, you weren't going to get reimbursed for carotid stenting, and a trial was done.

DR. YANCY: We may get some input when we listen to public comments that reflect guideline statements about what is a standard of care and where A.F. ablation sits in this model.

Dr. Neaton?

DR. NEATON: Maybe just a couple questions to help clarify, I'm sure, which

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1 will be a lot of helpful future discussion.
2 I mean, first of all, I found the
3 statement by the FDA -- maybe this can just be
4 clarified later -- that the -- a limitation of
5 the design against optimal medical therapy was
6 that the device and the therapy had different
7 safety profiles. I think that's exactly what
8 you want to study, and I don't see that as a
9 limitation.
10 But having said that, I wonder if
11 you could comment on whether or not for trial
12 A or something like trial A, a comparison
13 against optimal medical management has been
14 considered for first-line therapy, so
15 essentially take people that have not failed
16 their first-line anti-arrhythmic drugs and
17 randomize them to ablation or optimal medical
18 management.
19 And then secondly, for the -- that
20 same type of trial design that you propose for
21 A, with the target population that's failed,
22 has a design been considered where -- I would

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1 call it an immediate versus deferred ablation,
2 where perhaps a shorter follow-up, where
3 people would be randomized to get the ablation
4 therapy immediately or they have that
5 potentially deferred till something happens or
6 six months later, say.
7 DR. BROCKMAN: With respect to
8 your first question, I think what we're trying
9 to do is to follow the guidelines, the
10 published clinical guidelines, which in my
11 reading refer to A.F. ablation as a second-
12 line therapy.
13 I think there -- there is a -- is
14 an escape clause, if you will, for certain
15 situations. It may be appropriate for first-
16 line. But in general, I believe it says after
17 failure of medical therapy.
18 I suppose if the panel thinks that
19 A.F. ablation is appropriate as a first-line
20 option without use of prior medical therapy,
21 we should hear that.
22 DR. NEATON: Well, I mean, it's

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not a -- I mean, I think -- I think that --

DR. BROCKMAN: That isn't the --

DR. NEATON: -- establish at the trial.

DR. BROCKMAN: That isn't the -- that isn't the approach that we have taken.

DR. YANCY: Dr. Schoenfeld, brief question, please?

DR. SCHOENFELD: Right. I applaud the FDA in terms of their approach to this practical issue, just because I think enrollment has been one of the major concerns, and patients come, as already stated, with the concept that they're going to get a procedure done.

And there is the major concern that we've seen with sham or placebo or what I prefer to call the emperor's-new-clothes approach to patients' response to atrial fibrillation. I think you have to differentiate between the tool concept versus the methodology.

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1 And I think the thing that
2 concerns me still about this is that, really,
3 for the tool aspect, you want to look at the
4 safety and the efficacy. Safety is really
5 clear-cut. That can be defined. But the
6 methodology differs so variably from one
7 institution to another.
8 And my concern is that the data
9 that's been presented in the past has really
10 been single-center trials, rarely meta-
11 analyses in terms of outcomes, and if you
12 allow these studies to go across multiple
13 institutions so as to achieve the accurate
14 numbers that you need, then you may be mixing
15 and matching various types of institutions
16 that have different methodologies, that have
17 different performance expertise.
18 And I just don't know how you can
19 then mix and match the outcomes. I mean,
20 safety, I think, would be easier to evaluate.
21 But in terms of efficacy, when you have major
22 centers that are doing thousands of patients

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versus out in the community where you have much less volume and/or expertise but, in fact, is occupying in some estimates up to 60 percent of their time seeing less device volume, I'm just concerned about this mixing and matching from one center to another in order to achieve adequate numbers, no matter what trial design you pick.

DR. YANCY: I mean, this certainly amplifies the dilemma in establishing a performance goal, because you have very much disparate inputs.

Before we close this discussion section, I want to see if there is a comment from our lay representative -- either a question or a comment. There is not.

In the interest of time, then, and with the indulgence of panel, I'd like to go forward and begin the first open public hearing.

We have five speakers for this session. Each speaker has been allotted a

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maximum of 10 minutes to speak. In the interest of time, we will ask each speaker to be as succinct and brief as possible but certainly as thorough as possible.

I will ask the panel to hold all questions until after everyone has presented, and we'll have another opportunity to address this.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

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1 topic of this meeting.
2 For example, this financial
3 information may include a company's or a
4 group's payment of your travel, lodging or
5 other expenses in connection with your
6 attendance at the meeting.
7 Likewise, FDA encourages you at
8 the beginning of your statement to advise the
9 committee if you do not have such financial
10 relationships.
11 If you choose not to address this
12 issue of financial relationships at the
13 beginning of your statement, it will not
14 preclude you from speaking.
15 I'll ask each speaker to identify
16 themselves and their organization of
17 affiliation. Our first speaker is Dr. Albert
18 Waldo.
19 Thank you, sir.
20 DR. WALDO: Thank you, Dr. Yancy.
21 Good morning, everyone. I'm Al
22 Waldo. I'm from Case Western Reserve

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1 University and University Hospitals in
2 Cleveland, Ohio, and I'm a cardiac
3 electrophysiologist. And I'm speaking on
4 behalf of Biosense Webster this morning.
5 Here are my disclosures. I'm a
6 consultant to Biosense Webster, who paid for
7 the travel costs of this meeting. I'm also a
8 consultant to additional drug and device
9 companies, including Astellas Pharma U.S.,
10 sanofi-aventis, Solvay, Biotronik, CryoCor,
11 and St. Jude Medical.
12 Also, I'm a Speaker=s Viewer for
13 Reliant Pharmaceuticals and have a research
14 contract with Boehringer-Ingelheim
15 Pharmaceuticals.
16 So Biosense Webster has the
17 NaviStar ThermoCool Catheter for the
18 radiofrequency ablation of paroxysmal atrial
19 fibrillation study, and I'm going to be
20 presenting on Biosense Webster's experiences
21 as sponsor of this IDE trial.
22 I chaired the data safety and

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adverse events committee for the ThermoCool catheter IDE studies. I have previously chaired similar committees for Biosense Webster for the previous studies, including use in atrial flutter in particular tachycardia.

Both those indications are now approved and the ThermoCool catheter is widely used for both right- and left-sided procedures, especially atrial procedures, and that will have an implication.

By the way, if I could just interject -- I hadn't planned to say this, but in the hybrid study, the comparator's going to be Biosense Webster's device and how would Biosense Webster compare their device to their device. I think that's an interesting problem.

Biosense Webster's commitment to the AFID is clear. The company recognizes the potential benefit to public health and to practitioners for on-label procedures with

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1 attendant arrhythmia specific instructions for
2 use, and the company also recognizes the
3 importance and value of rigorous critical
4 examination of both efficacy and safety of the
5 product by the FDA.
6 It's currently enrolling patients
7 in a third IDE ablation trial, as I just
8 indicated, using the NaviStar ThermoCool
9 diagnostic ablation deflectable tip catheter,
10 this time seeking to demonstrate its efficacy
11 and safety in the treatment of atrial
12 fibrillation.
13 But it's encountering major
14 challenges not previously seen in the atrial
15 flutter and atrial -- and the ventricular
16 tachycardia ablation studies, and I'm going to
17 address that specifically with some data which
18 I think will help you to craft your charge
19 this morning.
20 So the study design -- the radio
21 frequency ablation used in the ThermoCool
22 ablation catheter is randomized against anti-

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1 arrhythmic drug therapy, all in accordance
2 with current FDA guidance. Inclusion and
3 exclusion criteria specify minimum number and
4 frequency of pre-enrollment atrial
5 fibrillation episodes, the need for previous
6 anti-arrhythmic drug usage, except -- one of
7 the points we'll address -- you can't use a
8 patient who's had amiodarone in the previous
9 six months.
10 The ablation arm treatment
11 approach and procedural end points are
12 specified in the protocol. We're trying to
13 address that, too, because it's a specific
14 technique for doing the ablation.
15 So study designs based on current
16 FDA guidance directly cause the majority of
17 screening failures, thereby prolonging trials.
18 We'll show you those data. Some of this is
19 inevitable, and some of this seems reasonable
20 to modify.
21 And here are the data. This is
22 the patient screening results. Now, it has

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1 taken three-plus years of intensive, truly
2 intensive, effort to approach the required
3 number of study patients for this trial.
4 And what I want to share with you
5 are some of these data. Only three percent of
6 those -- of the very, very, very large number
7 of patients have been enrolled. In previous
8 studies -- Biosense Webster -- the lowest
9 they've ever had is about 30 or 40 percent.
10 Most of their studies are 70 to 80 percent.
11 They've even had 90 percent enrollment after
12 screening. So this is a dramatic and
13 difficult thing.
14 Now, it's interesting. Refused
15 randomization -- you've heard the studies.
16 You already expected that would be very high.
17 It's only 11 percent. That's really
18 misleading, and I'll show you why in a moment.
19 It's still very high.
20 Really, 62 percent of the patients
21 were excluded by protocol requirements, and so
22 when the screeners saw the patient, they never

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1 even bothered to ask them if they wanted to be
2 into the trial, and I believe that's why
3 that's so low. It really represents about a
4 quarter percent of the 38 percent who are left
5 over here after the -- originally rejected by
6 screening criteria.
7 Now, I mean, some of this you
8 expect -- for instance, unable to return for
9 follow-up, for personal reasons. Of course,
10 those patients can't be in the trial. That's
11 just one obvious example.
12 But now, if we look at the reasons
13 in that 62 percent for exclusion, I want to
14 point out a couple of things. First, 13
15 percent -- well, almost 50 percent involved --
16 this 42 percent -- previous -- previously on
17 amiodarone within the past six months, and too
18 few atrial fibrillation episodes.
19 And when you realize that probably
20 it's -- and most studies would suggest at
21 least two-thirds of the people being treated
22 for atrial fibrillation with drug therapy on

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