

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL MEETING

VOLUME II

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL MEETING

Volume II

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Wednesday, July 22, 1998

8:10 a.m.

Holiday Inn Gaithersburg
Ballroom
Two Montgomery Village Avenue
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
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PARTICIPANTS

Anne B. Curtis, M.D., Chairperson
John E. Stuhlmuller, M.D., Executive Secretary

VOTING MEMBERS

Michael D. Crittenden, M.D.
Tony W. Simmons, M.D.

CONSULTANTS

Salim Aziz, M.D.
Cynthia M. Tracy, M.D.
George W. Vetovec, M.D.

Industry Representative

Mr. Gary Jarvis

FDA

Thomas J. Callahan, Ph.D.

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P R O C E E D I N G S

Call to Order

1
2
3 DR. CURTIS: Good morning. I am Anne Curtis, the
4 Chairman of the panel. I would like to call this meeting to
5 order.

6 The first order of business today is going to be
7 the reading of the conflict of interest statement.

Conflict of Interest Statement

8
9 DR. STUHMULLER: The following announcement
10 addresses conflict of interest issues associated with this
11 meeting as made part of the record to preclude even the
12 appearance of an impropriety.

13 To determine if any conflict existed, the agency
14 reviewed the submitted agenda for this meeting and all
15 financial interest reported by the committee participants.
16 The conflict of interest statutes prohibit special
17 government employees from participating in matters that
18 could affect their or their employers financial interest.

19 However, under the final rule on 18 USC 208, Title
20 the, CFR Part 2640, a special government employee may
21 participate in any particular matter of general
22 applicability where the disqualifying financial interest
23 arises from his or her non-federal employment.

24 Since the agenda item for this meeting involves
25 only a particular matter of general applicability, the panel

1 has determined that Dr. Anne Curtis may participate fully in
2 today's deliberations.

3 The agency has also determined that participation
4 of certain members and consultants, the need for whose
5 services outweighs the potential conflict of interest
6 involved, is in the best interest of the government.

7 Therefore, waivers have been granted for Drs. Tony Simmons
8 and George Vetovec for their interest in firms that could
9 potentially be affected by the panel's decisions.

10 The waivers permit them to participate in all
11 panel deliberations during today's sessions. Copies of this
12 waiver may be obtained from the agency's Freedom of
13 Information Office, Room 12A-15 of the Parklawn Building.

14 We would also like to note for the record that the
15 agency took into consideration other matters regarding Drs.
16 Curtis, Vetovec, Tracy and Aziz. Each of these panels
17 reported past or current interest in firms at issue but in
18 matters not related to the agenda for today's meeting.
19 Since their interests are unrelated to today's agenda, the
20 agency has determined that they may participate fully in all
21 discussions.

22 In the event that the discussions involve any
23 other products or firms not already on the agenda for which
24 an FDA participant has a financial interest, the participant
25 should excuse himself or herself from such involvement and

1 the exclusion will be noted for the record.

2 With respect to all other participants, we ask, in
3 the interest of fairness, that all persons making statements
4 or presentations disclose any current or previous financial
5 involvement with any firms whose products they may wish to
6 comment upon.

7 DR. CURTIS: I would like to have each of the
8 members of the panel introduce themselves.

9 As I mentioned, I am Anne Curtis. I am from the
10 University of Florida and I am a cardiac electrophysiologist
11 there.

12 DR. TRACY: Cynthia Tracy from Georgetown
13 University, electrophysiologist.

14 DR. SIMMONS: Tony Simmons, Wake Forest
15 University, cardiologist, electrophysiologist.

16 DR. AZIZ: Salim Aziz from the University of
17 Colorado, cardiac surgeon.

18 DR. VETROVEC: George Vetrovec, Medical College of
19 Virginia, Virginia Commonwealth University, Chairman of
20 Cardiology and I am an invasive cardiologist.

21 MR. JARVIS: Gary Jarvis. I am the industry
22 representative to the panel.

23 DR. STUHLMULLER: Not here yet but for FDA will be
24 Dr. Callahan. He is Division Director for the Division of
25 Cardiovascular, Respiratory and Neurological Devices. He

1 should be here shortly.

2 I am John Stuhlmuller. I am the executive
3 secretary and I am a medical officer at FDA.

4 DR. CRITTENDEN: Michael Crittenden, cardiac
5 surgeon at Harvard University.

6 DR. CURTIS: Thank you.

7 **Open Public Hearing**

8 DR. CURTIS: We will move on to the open public
9 hearing.

10 DR. STUHLMULLER: We received correspondence from
11 Boston Scientific and Cardima, Incorporated. This written
12 information will be incorporated into the public record and
13 they have been provided to the panel members for their
14 review today.

15 DR. CURTIS: Is there any representative from
16 industry that wanted to make any comments as part of this
17 open public hearing now?

18 [No response.]

19 DR. CURTIS: If not, then what we will move on to
20 the FDA presentation. We are going to be splitting the
21 discussion up today separately between atrial fibrillation
22 and we will be starting with atrial flutter.

23 **Atrial Flutter Ablation**

24 **FDA Presentation**

25 MS. GOODE: Good morning.

1 [Slide.]

2 My name is Jennifer Goode and I am a biomedical
3 engineer in the Pacing Electrophysiology Devices group here
4 at FDA. On my right is Dr. Stuart Portnoy, a medical
5 officer in our group.

6 This morning, I have been asked to provide you
7 with some background information prior to the panel
8 deliberations. As you know, FDA is currently developing
9 guidance for industry on clinical-trial design for catheter
10 ablation systems intended to treat atrial flutter. We have
11 identified several issues where we would appreciate your
12 input.

13 My presentation will include general background
14 information concerning atrial flutter and summary
15 information from studies reported in the medical literature.
16 I will also highlight specific issues for your consideration
17 before you begin your deliberations on the particular
18 questions put forward to you.

19 [Slide.]

20 For the purposes of this discussion, FDA has
21 identified a specific type of atrial flutter which we
22 believe is appropriate for investigation in studies of new
23 ablation catheters. FDA has used a definition of typical
24 atrial flutter from an article by Dr. Olgin in 1996 and this
25 definition states that typical atrial flutter is an

1 anatomically well-defined clockwise or counter-clockwise
2 right macroreentrant circuit.

3 This arrhythmia typically manifests on surface
4 ECGs with a sawtooth pattern and a regular rate, usually
5 between 250 to 350 beats per minute.

6 [Slide.]

7 Atrial flutter manifests as palpitations and
8 presyncope, is not directly life threatening but can
9 diminish the quality of life.

10 [Slide.]

11 In 1995, the American College of Cardiology and
12 the American Heart Association, in collaboration with NASPE,
13 published guidelines for clinical intracardiac
14 electrophysiological and catheter-ablation procedures. I am
15 going to go over their recommendations today just as some
16 background.

17 As stated in this report, catheter ablation has
18 become the treatment of choice for some arrhythmias and an
19 important consideration for others. In a 1992 NASPE survey,
20 it was reported that more than 10,000 ablation procedures
21 were performed in that year with complication rates as low
22 as 2 percent in some patient groups.

23 Catheter ablation has largely supplanted open-
24 heart surgical procedures for several types of arrhythmias
25 and is an acceptable alternative to long-term drug therapy.

1 The role of catheter ablation as primary therapy for several
2 arrhythmias has been described in position papers or
3 technology assessments by the American Medical Association,
4 the American College of Cardiology and NASPE.

5 This report is specific to radiofrequency current
6 for ablation, but we wanted you to also consider what your
7 recommendations for clinical-trial design would be if the
8 ablation catheter used a different energy source. So we
9 would like you to keep that in mind today.

10 These guidelines include three levels of treatment
11 recommendations, Class I, Class II and Class III and I am
12 going to over those quickly for you.

13 [Slide.]

14 For RF catheter ablation of atrial tachycardia,
15 atrial flutter and atrial fibrillation, Class I
16 recommendations include patients where the arrhythmia is
17 drug resistant, the patient is drug intolerant or long-term
18 drug therapy is undesirable.

19 Class I indicate that there is general agreement
20 among the experts that treatment of these patients is useful
21 and patients are likely to benefit.

22 [Slide.]

23 Class II recommendations include those patients
24 experiencing atrial tachycardia or atrial flutter associated
25 with paroxysmal atrial fibrillation or atrial fibrillation

1 with evidence of a localized site or origin. In all of
2 these cases, the arrhythmia is drug resistant. The patient
3 is drug intolerant or long-term drug therapy is undesirable.

4 Class II recommendations indicate that treatment
5 of these patients is usually performed but experts are less
6 certain about the usefulness of the procedure and are
7 divided in their opinion of whether patients are likely to
8 benefit.

9 [Slide.]

10 Class III recommendations include those patients
11 experiencing atrial tachycardia, atrial flutter or atrial
12 fibrillation where the arrhythmia is drug resistant, the
13 patient is drug intolerant or patients prefer drug therapy,
14 and patients with any multiform atrial tachycardia.

15 Class III recommendations indicate that experts
16 agree that treatment of these patients is generally not
17 useful and patients are not likely to benefit.

18 [Slide.]

19 In your deliberations this morning, FDA asks that
20 you consider the role that anti-arrhythmic drug therapy
21 should be in the design of the clinical trial as it relates
22 to the selection of a study population as well as in patient
23 treatment post-ablation.

24 In particular, we would like to know whether the
25 risks of antiarrhythmic drug therapy should be considered

1 versus the unknown risks of an investigational ablation
2 catheter when choosing a study population. We are also
3 asking for your input as to whether previous drug therapy or
4 lack thereof could influence the assessment of the
5 investigational ablation catheter performance, particularly
6 if you agree that it is appropriate to allow treatment with
7 antiarrhythmic drugs during post-ablation follow up.

8 [Slide.]

9 On the next few slides, I summarize data from the
10 medical literature concerning catheter ablation of atrial
11 flutter. On page 6 of your handout package, there is a
12 table with more detailed information for your reference.

13 In these studies, acute success rates range from
14 80 to 100 percent with rates appearing to increase in recent
15 years as knowledge of the arrhythmia and treatment have
16 increased. When the procedure endpoint includes
17 bidirectional conduction block, acute success in these cases
18 was 100 percent.

19 The reported chronic success rates range from 50
20 to 100 percent. When the procedure endpoint includes
21 bidirectional direction block, chronic success rates range
22 from 91 to 100 percent.

23 [Slide.]

24 Unfortunately, these studies of atrial flutter
25 catheter ablation do not generally specify how major

1 complications were assessed and usually only indicate that
2 major complication rates were low to none. However, the
3 literature does indicate that for other well studied
4 supraventricular tachycardias such as WPW or AV nodal
5 reentry tachycardia, the rate of major complications is
6 usually around 2 to 3 percent.

7 In your deliberations this morning, you will be
8 asked to comment on whether it is appropriate to design a
9 study as a randomized trial or whether a single-arm study
10 with objective performance criteria would be appropriate.

11 If you recommend that a single-arm study is
12 appropriate, FDA asks that you recommend an appropriate
13 control for comparison of the study rate of major
14 complications.

15 [Slide.]

16 The current medical literature reports follow-up
17 periods ranging from four to thirty-six months. FDA would
18 like your recommendations for an appropriate follow-up
19 period for clinical studies of investigational catheters for
20 treatment of atrial flutter.

21 While most of the studies found in the literature
22 do not specify when recurrences of atrial flutter occur,
23 Cosio's 1996 paper reported that in 50 percent of his
24 patients with recurrences, the arrhythmia recurred within
25 the first month, 70 percent recurred within six months and

1 90 percent recurred with eighteen months of the ablation
2 procedure.

3 FDA would also like you to consider whether atrial
4 fibrillation presenting secondary to ablation of atrial
5 flutter is important to assess. The medical literature
6 reports that atrial fibrillation has occurred in 6 to
7 36 percent of patients who achieved acutely successful
8 ablation of their atrial flutter. However, these papers do
9 not specify when atrial fibrillation occurred.

10 [Slide.]

11 We would also like to know whether it is
12 appropriate to include in the study population patients who
13 have previously failed any ablation procedures. In your
14 discussion of this issue, we ask that you consider whether
15 data from these patients could bias the results of the study
16 because of the difference in the difficulty of treating
17 these patients in comparison to those who have never been
18 treated with ablation therapy.

19 Would you expect primary endpoints such as acute
20 success, chronic success and major complication rates to be
21 affected is the question that is put before you.

22 [Slide.]

23 It is also important to note that, in order to
24 demonstrate clinical benefit of a particular design feature,
25 the sponsor may also be investigation secondary endpoints

1 such as number of lesions, fluoroscopy time or procedure
2 time. We would also appreciate it if you consider whether
3 these endpoints could be affected by including patients who
4 have previously failed in ablation procedure.

5 At this point, we are going to turn to the
6 specific questions that I think you have copies of. If you
7 like, I can read those or Dr. Curtis can guide the
8 discussion.

9 DR. CURTIS: I think there is no point in reading
10 all the questions up front. I think we should just go one
11 at a time.

12 Do you have any other comments?

13 MS. GOODE: That's all.

14 **Panel Discussion**

15 DR. CURTIS: Then let's turn it over to a
16 discussion of trial designs for atrial flutter. You can go
17 ahead and put up the first question. It is nice and long.

18 "Is a randomized, concurrently control clinical
19 study needed to collect safety and effectiveness data on RF
20 catheter ablation as a treatment for atrial flutter. Are
21 there alternative study designs that would provide valid
22 scientific evidence to support a marketing application.

23 "For example, would a single-arm observational
24 study using safety and effectiveness data from the medical
25 literature as an historical control be appropriate? Is the

1 current literature sufficient to create objective
2 performance criteria? What safety and effectiveness data
3 for atrial flutter ablation are available in the medical
4 literature that can be used as an historical control or can
5 rates of major complications from ablation studies treating
6 other supraventricular tachycardia indications be used as an
7 historical control?"

8 So the first question relates to the trial design,
9 the overall trial design, itself, whether it has to be
10 randomized or concurrently controlled, and then what the
11 standards are for complication rates.

12 What we can do is go around the panel and have
13 some comments made about that. I don't know if you want to
14 start, Cindy.

15 DR. TRACY: I think what will come out of it will
16 depend on what it is that you are looking at. If you are
17 talking about going and evaluating what we would now
18 consider a standard radiofrequency treatment for atrial
19 flutter, I don't think that is going to fly in any sense
20 because the cat is out of the bag with that, and that is
21 clinical practice at this point.

22 People are using off-label catheters to perform
23 very successfully catheter ablation of atrial flutter. I
24 think the only issue to deal with is if there is new
25 catheter development or new energy source development, I

1 think that the control, in that case, should be accepted to
2 be what we are doing clinically at this point which is
3 catheter ablation with standard catheters.

4 I don't think we can ever compare this against
5 drugs. I don't think that there is surgery we can compare
6 this to. It is not applicable to compare this to AV node
7 ablation and implantation of a permanent pacemaker. I think
8 we are too far down the road with this to turn our backs on
9 the fact that there are just a whole lot of flutter
10 ablations being done with standard catheters but that this
11 does, if we can accept that, provide a very excellent
12 control group against which to compare any new technology.

13 MS. GOODE: Do you think that it is appropriate to
14 use the medical literature and do a single-arm study or do
15 you want to see randomized trials to ablation?

16 DR. TRACY: I think that it would be reasonable to
17 have it comparing to a randomized controlled study,
18 comparing to the catheters used currently. So I think that
19 would be a reasonable expectation.

20 DR. VETROVEC: Can I ask for a clarification,
21 because yesterday it came up that the FDA didn't want to--
22 this is an FDA question. The FDA did not want to compare to
23 catheters or devices that weren't approved. Is this a
24 problem if we design something like this?

25 MS. GOODE: I don't believe there are any atrial-

1 flutter indications for approved RF catheters.

2 DR. TRACY: I appreciate that, but the reality is
3 that every day we are doing this. Everybody is. It is an
4 FDA question, I guess. I don't see how we can force
5 suboptimal studies by ignoring the fact that this is what
6 people are doing.

7 DR. CALLAHAN: Our problem is we can have a
8 procedure or another technique, obviously. We don't need
9 just another device, so we don't need a device, necessarily,
10 to compare it to. What you are saying is that is the
11 standard of practice but our hands are a bit tied on that
12 because we don't have a device that we can compare it to and
13 condoning off-label use.

14 One of the things that we have wrestled with at
15 various times is, in special circumstances, if the practice
16 of medicine has evolved to that stage without using a
17 specific catheter, then we could consult--that is why we
18 would look at the literature and see whether that is being
19 done or not, and to use other guidelines as sort of a norm
20 for what clinical practice is.

21 DR. TRACY: It is a difficult issue but it is one,
22 I think, we have to grapple with because it is now a
23 Class II indication for ablation. Atrial flutter has at
24 least a Class II indication concerning--as treatment with
25 ablation. So it is something that is accepted by the vast

1 majority of the electrophysiology community as being the
2 appropriate care for these patients or at least a very
3 appropriate form of care for these patients.

4 I don't know what we can do to get past that
5 roadblock. If there is a ten-person study that could be
6 done with standard ablation or something to sanctify the use
7 of standard catheters for a catheter ablation of atrial
8 flutter--but I think to always have your hands tied by
9 saying you can't compare it against standard catheter,
10 catheter ablation of atrial flutter, eliminates an excellent
11 group against which to compare any new technology.

12 It eliminates the possibility of looking at risk,
13 every benefit that you would get out of a controlled study.
14 I would think that a controlled study comparing against the
15 standard catheter would be better than historic control of
16 the literature because you acutely are collecting the
17 information regarding complications, success, et cetera.

18 You have a much better control group than a
19 historic control and it is feasible, I would think, to do a
20 randomized trial if you are allowed to use standard catheter
21 ablation as your other arm.

22 DR. PORTNOY: Cindy, what if the study device is
23 one that is currently approved for SVT ablation and, right
24 now, we know that those devices are also used for off-label
25 ablation so there is no adequate current control under those

1 circumstances because the study device, itself, is the one
2 that is being used today to do off-label A-flutter ablation.

3 So what would be an appropriate control under
4 those circumstances? We are talking about a 4-millimeter
5 conventional RF-ablation catheter.

6 DR. SIMMONS: I think for this particular disease,
7 this atrial-flutter disease, it goes back to--

8 DR. STUHMULLER: Can I interrupt for one second.
9 I think part of what the panel is struggling with and I
10 think I would like to get Dr. Callahan to clarify--one of
11 the issues that came up yesterday is when you are doing a
12 study, you can't compare an investigational device to an
13 investigational device.

14 I think what the panel is asking for clarification
15 on here today from the agency is what do you do when the
16 off-label use of an approved device is considered the
17 standard of care and how can you factor that into a study
18 design potentially against an investigational device.

19 DR. TRACY: That's exactly it.

20 DR. STUHMULLER: That is essentially what they
21 are asking you to give them a cut on. I think that is
22 appropriate for you to respond on that.

23 DR. CALLAHAN: I think in that case--and those
24 cases are unusual and this may be, in fact, one of those
25 cases, the second one is the MADIT indication for

1 defibrillators which one particular company has a labeling
2 for and others don't, yet there doesn't seem to be any
3 difference between the different types of generators that
4 would be used for that.

5 I think, in both of those cases, if we look to
6 things like, perhaps, the NASPE guidelines, ACC guidelines,
7 as to what is practice--but then you wouldn't be able to
8 compare it to a single catheter. You would have to take a
9 broad spectrum of catheters and so we wouldn't be stuck with
10 a case that looked like we were comparing an off-label use.

11 I think there has to be some mechanism like that.
12 Maybe on those rare circumstances where medical practice has
13 gotten to the point where there is nothing out there at all
14 approved, and this may be one, that we can use those kinds
15 of guidelines.

16 But we wouldn't be able to do it in a single study
17 versus a single catheter. We would have to have a broad
18 spectrum of catheters that were used, a single device.

19 DR. PORTNOY: I can give a little bit of
20 historical perspective on this. The FDA has been struggling
21 with this for several years. I remember back in 1995 we had
22 an internal meeting to discuss what would be appropriate
23 clinical-trial design for A-flutter.

24 Bruce Burlington happened to attend that meeting.
25 Bruce Burlington is the Director of the Center for Devices

1 and Radiological Health. He recommended that if
2 investigators and if manufacturers were reluctant to do a
3 randomized study to drug therapy which is what we were
4 trying to pursue at that time that patients could be
5 randomized to what he referred to as deferred ablation so
6 there would be a three-month or so period where they would
7 get antiarrhythmic drug therapy and then they could cross
8 over to get the ablation therapy.

9 So then, at the end, everybody gets ablation which
10 would make the investigators happy. We actually formalized
11 that as a draft policy and made it available to many of the
12 manufacturers. But there has been a lukewarm response to
13 that kind of a clinical-trial design from the clinical
14 community.

15 So it really leads us to where we are today to try
16 and get a good idea for what is going to be the best way to
17 go with this.

18 DR. VETROVEC: For clarification to me, not doing
19 these procedures, can the electrophysiologist tell me if
20 there is a significant difference in the risk or
21 complications or difficulty or success, or anything, of
22 using RF ablation for atrial flutter as opposed to the
23 standard SVT or WPW uses when, then, would come to the
24 question of could you really use established control groups
25 in the literature.

1 I think that is a question that I don't have a
2 feel for.

3 DR. CURTIS: I think for the electrophysiologists
4 here, that is kind of what we are getting at. Flutter
5 ablations have been done for several years, now. We all do
6 them. We use catheters with various sized tips on them.

7 In terms of complication rates, I think what makes
8 flutter so different from ablation of atrial fibrillation is
9 that we already know--I think we could all name numbers here
10 as to what we think would be acceptable complication rates
11 and success rates that you would want to see out of any new
12 catheter.

13 There are a number of publications about flutter.
14 The complication rates are very comparable to other SVTs.
15 They are low and they are expected to be low. And so there
16 would be less of a risk of complete heart block, say, then
17 you would even have with AV nodal reentry in tachycardia,
18 that sort of thing.

19 So I think, knowing the published literature about
20 SVT ablation and knowing what is out there about atrial
21 flutter, I think we do know that any catheter technique that
22 was studied now, we would expect to have a low complication
23 rate, probably on the order of around 2 or 3 percent, the
24 way it was published in the literature.

25 In terms of success, I think that has changed over

1 time. I think the very initial publications on flutter turn
2 out to have lower success rates than what we think would be
3 acceptable now and that is because, over time, we have
4 learned that it is not just enough to burn and have the
5 flutter no longer inducible.

6 There is an additional criterion now that you have
7 to demonstrate what is called "bidirectional block" along
8 the floor of the tricuspid isthmus. Basically, what that
9 means is that if you burn along there and you can prove that
10 if you pace from the lateral right atrium, you can't conduct
11 to the proximal coronary sinus. Of if you pace from the
12 proximal coronary sinus, you can't conduct across to the
13 lateral RA. Recurrence rates are very, very low. That is
14 pretty well looked at, too.

15 So I think that there are acute success rates that
16 we would expect. I think, over all, the success rate for
17 flutter, and if I can get opinions from the other
18 electrophysiologists here--the acute success rates are
19 probably a little lower than some of the other diagnoses.
20 They are not substantially lower. I would have said a couple
21 of years ago, we were all happy with 80 percent. We would
22 probably want a little bit higher now overall.

23 But the acute success rates are pretty good. Some
24 of the patients have to be redone. I think the biggest
25 reason for differences with flutter is that, as opposed to a

1 diagnosis like WPW or AV nodal reentry tachycardia where, if
2 you get that catheter in just the right spot, one burn
3 works.

4 That is not true here. You actually have to have
5 a drag line. It is a line of a burn. If it is not
6 complete, if you leave any hole in there in that line, you
7 don't get your bidirectional conduction block. So I think
8 acute success rates probably will always be a little bit
9 lower than for the other diagnoses. Recurrence risks are a
10 little bit higher than they would be for the other
11 diagnoses.

12 DR. SIMMONS: Technically, the other part of your
13 question is it is a little bit more difficult. I guess we
14 are past that severe learning curve on WPW and AV nodal
15 reentry. We expect to get in and get out of the lab in an
16 hour and a half or two hours at most for one of those cases.

17 You are not at all surprised to be in there for
18 four or five hours sometimes trying to get that drag lesion
19 in exactly the right spot. Of course, that may be because
20 we are tackling different kinds of atrial flutter now, too.
21 We used to be a little bit more selective looking for
22 typical A-flutter and now we take anything that even closely
23 resembles A-flutter and we are trying to do more with it.

24 It is a little more technically difficult.

25 DR. CURTIS: Let me ask you, Tony, what kind of an

1 acute success rate would you expect for a flutter ablation?

2 DR. SIMMONS: I think you are right. I just would
3 disagree with your terms. I was surprised when you said you
4 would almost expect what you would get for WPW or AV nodal
5 reentry because we would really expect 97 or 98 percent
6 success rate.

7 DR. CURTIS: For that; yes.

8 DR. SIMMONS: So I would say 90 percent is
9 substantially lower but it is still--we would expect around
10 90 percent acute success. I guess I don't know what I
11 expect for the long-term success. I think that is something
12 that could come out of this because a lot of those patients
13 do get lost from tertiary medical centers and they don't
14 come back.

15 So I guess I haven't followed them as closely. I
16 guess I would expect around 80 percent or so chronic success
17 but I guess I don't know the real answer.

18 DR. CURTIS: So then you would expect, out of your
19 acute patients, 10 percent might come back and have to have
20 a redo, something like that?

21 DR. SIMMONS: Right.

22 DR. CURTIS: What do you think, Cindy?

23 DR. TRACY: I would agree basically with what has
24 been said. I think that when I am talking to a patient
25 about a flutter ablation, the main thing I tell them is that

1 the worst-case scenario is that this won't work; we are far
2 enough away from your normal conduction system, there is not
3 really a risk of heart block.

4 You are strictly dealing on the right side, at
5 least for typical flutter, so you are not exposing them to
6 the risk of a trans-septal and left-sided energy delivery.
7 We expect at least a 90 percent acute success rate. It has
8 been about a 1 to a 5 percent recurrence rate, at least from
9 what I have seen so far.

10 DR. CURTIS: I was kind of leading everybody on,
11 but what gets to me is that I am not sure that, in order to
12 demonstrate that a catheter takes care of flutter that I
13 have to randomize it against some other technique. I know
14 what I am expecting.

15 I know that I expect a certain acute success rate.
16 I know I expect the complication rate to be low. I think
17 you could set up objective performance criteria that a
18 catheter would have to meet. If you randomize it to another
19 catheter that is an off-label use, you are doubling the
20 number of patients you have to put in and I am not sure it
21 is adding a whole of information to that.

22 DR. SIMMONS: This is kind of what John mentioned
23 at yesterday's meeting. The control has to have equivalence
24 or you are not going to get people in it. You can't
25 randomize people to things that you are not willing to

1 randomize them to, and we are not going to randomize people
2 to drugs. We are just not going to do it. It is just not
3 fair.

4 And you do have performance criteria and the
5 patient can be his own control, or her own control. So I
6 think there are ways around it without having to try and do
7 a study that none of us are interested in seeing the results
8 of in the end.

9 DR. TRACY: The only thing that continues to
10 bother me is the fact that we continue to call this off-
11 label use. Why are these catheters being held hostage? Why
12 is this technology--

13 DR. SIMMONS: I guess I am more anti-manufacturer
14 than you are. It is the company's problem, not the FDA's.
15 Let them come up and do the study. They just haven't been
16 willing. They have actually offered them an opportunity to
17 do it without even having to put any money into it and they
18 still haven't come forward.

19 DR. TRACY: That is the community's fault for
20 having created this scenario, somehow, I think because we do
21 this. We know it can be done. We do it. It works. It's
22 great. People go home and they are happy.

23 So is there any way around this so that this can
24 be--I mean, anything that is developed in the future should
25 be compared against what we do. I think it is an injustice

1 to the whole field of electrophysiology not to be able to
2 use this as a control. This is what we do.

3 And yet, we struggle to know what is our long-term
4 success, what is our long-term recurrence rate. This is
5 information that we could gain if this catheter, the
6 standard catheters that we use, are not somehow vilified but
7 are allowed in a study where we are comparing it to a new,
8 novel-design, catheter or a new delivery sheath or something
9 different.

10 If we are using a standard catheter, and it
11 doesn't have to be any manufacturer in particular--it could
12 be several manufacturers. I am sure they would all throw in
13 a few dozen catheters to be included in somehow devilifying
14 them.

15 Or, alternatively, is there any historic
16 perspective on something that is currently--that has been
17 used so much by the community that it just simply doesn't
18 make sense to go back and put it through some kind of a
19 process to approve it. Is there any historic way of doing
20 this?

21 DR. CALLAHAN: I think, as I alluded to before,
22 there are a couple of situations now that are forcing that
23 we relook at things. In my recollection, we have not done
24 it before but the history of ablation has been unique,
25 anyway. It started as a diagnostic catheter and then went

1 from there, and we have been doing it for ten or fifteen
2 years.

3 So one thing that we have thought about doing is,
4 if it is so widespread, which it is, that we could use
5 something like NASPE and the ACC guidelines if it is part of
6 medical practice to say that it is medical practice, not
7 compare it to a single catheter but to compare it to a host
8 of catheters and lump them together which is, essentially, a
9 literature control, using those same catheters that have
10 been out and reported in the literature and letting them all
11 be used in a trial.

12 We haven't done that. As I say, we are looking at
13 that with even the MADIT indication for defibrillators as
14 well.

15 DR. TRACY: That seems to me, perhaps, to be the
16 quickest way out of this problem. Enough of these things
17 are being done that if the companies could cooperate and
18 could, say, each donate a dozen catheters to twelve or
19 thirteen centers, you would have, very quickly, a group of
20 patients were you could at least, very quickly, make some
21 kind of assessment.

22 And then you could go forward. You could then
23 struggle with newer catheter designs to decide, what design
24 do I use at this point? Do I use a historical control? Do
25 I now have all of these different companies' approved

1 devices. I can incorporate them as my control arm.

2 Then you would be in a lot better position, I
3 think, to do science because, right now, we are not in a
4 position to do anything--to me, you are limiting your
5 scientific ability if you don't get these things somehow
6 approved and okayed to use in other studies as a comparative
7 standpoint.

8 I favor doing it very, very quickly.

9 DR. PORTNOY: How does the panel feel about simply
10 establishing an objective performance criteria based on your
11 experience, based on data reported in the medical
12 literature, and use that as a control so there would be no
13 concurrent control?

14 DR. TRACY: For the currently off-labeled
15 catheters or for some new catheter?

16 MS. GOODE: Booth.

17 DR. TRACY: Both? I think you are tying your arms
18 if you use some kind of historic control for a new catheter
19 device.

20 MS. GOODE: If the new catheter device doesn't
21 perform as well as current RF catheters, then do you want it
22 to go on the market?

23 DR. TRACY: How would you know unless you are
24 comparing it directly. I think you have to compare it
25 directly to the currently used catheters. So the steps

1 would have to be--just as Tom is saying, take the currently
2 used catheters and, sure, compare them against the historic
3 control, NASPE registry, and so on, get that out there, make
4 that okay.

5 I guess there may be some disagreement in the
6 panel, but I think at least you, then, have the opportunity
7 of having that serve as a control group. I think it is not
8 okay to use, for all the things we have seen yesterday,
9 historic controls against NASPE literature for a novel
10 technology.

11 DR. CURTIS: I guess we are going to have to agree
12 to disagree here because I really feel strongly differently
13 about it. I think there is so much information in the
14 literature about atrial flutter already, I think we know
15 what kinds of goals we would want to set.

16 You can quibble about numbers. We think, in good
17 labs, we can hit 90 percent for flutter. Maybe a minimum
18 for catheters should be, I don't know what, 80 or 85, to be
19 marketable. You could quibble about that, but I think we
20 know what the numbers ought to be.

21 I, personally, don't see the point of getting a
22 bunch of standard catheters together to show that your new
23 catheter performs the same as something where there really
24 isn't a study that has been done on that already.

25 To hold up doing flutter studies because you have

1 to collect this other information that you are talking
2 about--I think you could use objective performance criteria.
3 I think you could spell out what those things are and you
4 could go ahead and use a patient as his or own control,
5 knowing historically how much flutter they have had before,
6 with the expectation that the flutter would be gone.

7 That would be your endpoint.

8 DR. SIMMONS: I think I would agree with that,
9 too. I would like that. I think that is something that
10 would be effective, safe and could rapidly be done. I
11 agree.

12 DR. TRACY: But yesterday, struggling to figure
13 out what the acute success rate was--it was around
14 60 percent, depending on who they put in or whatever--say,
15 60 percent. Then that catheter is worse than what is
16 reported in the literature. So that is the problem.

17 DR. CURTIS: I think, though, for ventricular
18 tachycardia, there are all sorts of other issues like the
19 multiple morphologies. Obviously, I didn't hear the
20 discussion yesterday, but I think flutter is a different
21 entity, too, in that counterclockwise flutter is in one
22 place, you go after it, you should cure it.

23 Most of the time, there are not different flutters
24 in different locations that we are looking for. Clockwise,
25 counterclockwise, it is the same target you go after. So I

1 think the endpoints are a little bit cleaner than they would
2 be for V-tach.

3 Are we going to have some of the non-
4 electrophysiologists make some comments?

5 DR. VETROVEC: Is there an ongoing registry that
6 NASPE runs in terms of outcome for these things? One
7 compromise might be to use concurrent registry data. One
8 concern I have is these techniques continue to evolve. If
9 you use the current literature to set your standards, but
10 the time a study is done three years from now on a new
11 catheter, the numbers may actually be better than where you
12 set the standards.

13 So, using some type of concurrent registry data
14 might get you more in real time. I remember when balloon
15 angioplasty catheters were starting and, even into the late
16 1980s, they were using--I hate to say this--a study that we
17 had done in 1983 as the success rate that was not what the
18 success rate was in 1987 for a balloon catheter.

19 There is a little risk to that. Maybe some type
20 of concurrent registry would be the compromise to this.

21 DR. CURTIS: I am not aware of a registry going on
22 right now.

23 DR. TRACY: There actually is. Is it Scheinman
24 that is running it? It is Mel Scheinman.

25 DR. CURTIS: I thought it was going to do it. Is

1 he doing it?

2 DR. TRACY: It is actually--we have been sending
3 somebody data for about eight months. I don't know where it
4 is going, but it going somewhere.

5 DR. CURTIS: You are right. You have a moving
6 target there, although I am not sure with the flutter--I
7 think we are not on the steep part of the learning curve.
8 We may not be totally flat, either. There may be some room
9 for all of us to improve a little bit.

10 DR. PORTNOY: You know, with SVT ablation studies,
11 we have actually raised the bar over the last couple of
12 years because we read the medical literature and we get a
13 sense for what is the expected performance of these devices.
14 As you know, nobody has ever randomized for SVT ablation
15 because it was approved using single-arm studies.

16 So we keep an eye on that and we have raised it
17 accordingly.

18 DR. TRACY: Michael wants to say something, but I
19 just keep thinking that, if we don't, somehow, have this
20 standard approved against which to compare, there are going
21 to be times where we are going to wish that we had something
22 else to compare a new technology against.

23 Whether that is a new energy source or a new
24 total-catheter delivery system, there are going to be times
25 where it would make sense to have something concurrent to

1 compare it against. The cool-tip ablation; bigger is not
2 necessarily better at all times.

3 Is a giant linear lesion necessarily better? Is
4 it associated with a higher incidence of heart block? I
5 think there are going to be times where we may want to have
6 the ability, the freedom, to make a comparison without
7 having to go back to something that is less well quantified.

8 DR. CRITTENDEN: I don't have much to add except
9 that I am kind of trying to understand the debate, being a
10 non-cardiologist and non-electrophysiologist. But it seems
11 that there are two concerns. We are trying to look for
12 science and we are also trying, as Cindy says, to devilify
13 these catheters so that we can move things along and treat
14 the patients the way they ought to be treated.

15 So the question I would pose to the
16 electrophysiologists on the panel is which is the more
17 pressing concern? Are we trying to make scientific
18 breakthroughs or prove it beyond a shadow of a doubt, or do
19 we want to get the off-label use of these things devilified
20 so we can do what we need to do.

21 DR. TRACY: I don't think people care right now.
22 We are doing it. We are just doing it.

23 DR. CRITTENDEN: So then, if the science is not
24 important, then the most important thing to me seems that we
25 just get these things on market and on-label rather than

1 debate the science and objective performance criteria. It
2 sounds like the fastest way to do that because it looks like
3 you are looking for randomized, controlled trials or some
4 standard to make this thing pure from the scientific point
5 of view so that, when you come back for panel debates, we
6 can decide on the data because it is nice and pure data.

7 I understand that. I don't like debates that we
8 can't really decide on either. However, if we are trying to
9 devilify these catheters, then I think the fastest way is to
10 use the objective performance criteria.

11 One more comment I want to make about registry. I
12 like that idea and I was thinking about that, too. But,
13 unless everybody who is doing ablations puts every single
14 patient in there--you don't have your private patient that
15 you are doing it for or some referral, and you don't send
16 those in but you are doing in for this special study, that
17 the registry may not really give you a true reflection of
18 what is going on.

19 DR. CURTIS: That is a good point.

20 DR. TRACY: I think that is absolutely true. I
21 think the centers that are more likely to sending in forms
22 are centers that are interested in this kind of thing.
23 There are going to be a lot of people who are not sending in
24 forms, or an outside physician comes to Georgetown and we
25 don't put it--do we or don't we send his form in.

1 We do, but that may not be universally true. We
2 are considering ourselves a center, not an operator.

3 DR. CURTIS: Is there anybody in the audience who
4 wanted to make any comments? It is a little less formal,
5 perhaps, than yesterday's discussion. You do need to
6 identify yourself when you come up.

7 DR. MYERS: My name is George Myers, MedSys,
8 regulatory consultant.

9 DR. STUHMULLER: Do you have any financial
10 interest in any of these devices?

11 DR. MYERS: I do consulting for a company that
12 makes these catheters, but none of the companies here. It
13 seems to me that if you use the objective criteria and get
14 some of these catheters approved, which is about all that is
15 on the horizon right now, then you will have some of them,
16 as you have put it, devilified, a few catheters.

17 Then, in the future, anybody who comes up with
18 novel technology will have loads of catheters to compare
19 them with and the problem will just solve itself within a
20 few years.

21 DR. CURTIS: Does anybody else on the panel want
22 to make any comments about this first question? I think we
23 have all stated our opinions.

24 DR. STUHMULLER: From an agency perspective, what
25 kind of data would you put into the OPCs? The reason I ask

1 this is if you look at the transcript for the valve meeting
2 last fall, the panel members conceptually agreed that OPCs
3 were a valid way to evaluate safety and effectiveness of the
4 valves. But one interpretation of their comments also was
5 that the data that the OPCs were generated on didn't reflect
6 the current standard of practice at the time the valves were
7 being approved and, therefore, they didn't think the numbers
8 in the OPCs were necessarily valid.

9 They, therefore, then, one way to interpret it,
10 made a decision that, in their clinical judgment, this is
11 what they thought was a reasonable thing and that is how you
12 might interpret the way some of those valves were approved.

13 So, from the panel's perspective, the bottom line
14 is, conceptually, you agree, but what data would you
15 actually use so that, if one of these devices came for
16 evaluation, you are going to say that this is a valid
17 standard for comparison?

18 DR. CURTIS: I will take a crack at that.
19 Acutely, in the lab, I would say that you would want to
20 demonstrate bidirectional block along the isthmus and there
21 would have to be--it is always hard to put percents on these
22 things. It should be close to 100 percent if you are going
23 to be successful but at least, certainly, probably at least
24 90 we would be looking for.

25 Bidirectional block; the question is whether you

1 would have to look for acute noninducibility of flutter. I
2 would say probably yes, that that would be true, that you
3 cannot induce flutter at the end of the procedure. So those
4 would be the two criteria you would use for acute success.

5 In follow up, what you would be looking for is no
6 recurrence of atrial flutter, possibly over a six-month
7 period of time, and you would have a recurrence rate that
8 you would be watching and see how many patients actually had
9 to have the procedure done a second time.

10 Does anybody else want to make any comments on
11 that?

12 DR. SIMMONS: I think that is what you would want
13 in a very good lab. I am not sure that you want to set the
14 bar--I mean, if you are asking what is the criteria that you
15 would accept to pass this catheter, I don't think
16 90 percent, that you would demand that they got 90 percent.

17 DR. CURTIS: What would you demand?

18 DR. SIMMONS: I would demand 80 percent. I would
19 say to demand that they have to have at least 80 percent and
20 expect 90 and that an 80 percent success rate chronically,
21 but at least demand 70 percent. I would say six months is
22 the minimum follow-up time.

23 And then the complication rate--I don't know;
24 3 percent sounds high to me. I guess you could say
25 3 percent and expect 2 percent.

1 DR. PORTNOY: I just want to jump in here one
2 second. Some of the issues you just raised are questions
3 that we are going to be discussing later on.

4 DR. CURTIS: Okay.

5 DR. WHARTON: Marcus Wharton, Duke University,
6 investigator for several different catheters, for SVTs. I
7 guess I would argue, Tony, in contradistinction, that the
8 present results, and I agree with Anne here, for flutter
9 ablation are almost 100 percent and really reflect
10 supraventricular tachycardia ablations.

11 So if you set that bar too low, I think that is
12 not right because it is not what is being practiced
13 presently in the community. So I would accept at least a 90
14 percent, but I would argue that that is too low, preferably
15 95 percent or something like that with a 1 to 3 to 5 percent
16 late recurrence rate at six months.

17 But recurrences, as was noted in the comments, can
18 be very late. The bigger issue is what the A-fib recurrence
19 rate is after a successful flutter ablation.

20 DR. CURTIS: I think part of what has to be
21 considered here though is that it is operator dependent,
22 too. The more experience you have doing flutter ablations,
23 your success rate is going to be higher independent of the
24 catheter.

25 So I think what we are trying to get at is what is

1 enough to prove a catheter works well enough to do flutter
2 ablations. So, in that case, is 89 percent not good enough
3 that you wouldn't want the catheter marketed?

4 DR. WHARTON: I guess one of the issues is you are
5 not going to be comparing it to catheters that are in
6 skilled hands, which is where these studies are going to be
7 done anyway. You can set the bar too low and make it too
8 easy for a catheter to come around that may be okay for
9 doing flutter but standard catheters do it better or easier
10 or whatever so it, in some ways, argues for a control.

11 But I would argue that it is probably too late for
12 a control.

13 DR. SIMMONS: Don't you think, Marcus, it depends
14 on--if you were really looking for 90 to 100 percent success
15 rate, you are really talking about--or at least I think you
16 are really talking about--typical flutter in good hearts.

17 If you are talking about atypical types of flutter
18 and scar-type tissue and you are talking dilated hearts and
19 things like that, I think that the rate is going to go down.

20 DR. WHARTON: Atypical flutter was specifically
21 excluded from this discussion but for typical isthmus-
22 dependent flutter, even if they are bit hearts, particularly
23 with the concomitant use of sheaths now. It is a relatively
24 simple procedure. There are the exceptions and this is why
25 I wouldn't say 100 percent success rate where it is going to

1 be applied.

2 But the majority of cases, it is a two- or three-
3 hour procedure at the present time.

4 DR. TRACY: Where we are with open feed, that may
5 be okay for something--RF being delivered through a new
6 catheter of some shape or another. When somebody wants to
7 hook a new catheter of some shape or another up to an
8 ultrasound, then what are we going to compare it against?

9 I just think very, very strongly that there will
10 come circumstances where we have to be comparing it against
11 something that we know works very, very well and we know is
12 safe. And we have to have that as a control group inside
13 the study against which the new, completely novel, solar-
14 powered linear catheter must be compared.

15 So I think to not address this fundamental issue
16 of getting these catheters approved for the indications that
17 we are actually using them and to do that as quickly and as
18 painlessly as possible for the community is doing an
19 enormous disservice to any future technology because we will
20 always be comparing apples and oranges, and, "Well, maybe if
21 we had done this."

22 It is going to go on and on like this.

23 DR. SCHWARTZMAN: My name is David Schwartzman. I
24 am from the University of Pittsburgh. I am also involved
25 with several different SVT trials. I wanted to raise the

1 question at this point because I think I am much more
2 interested in the answer with respect to atrial
3 fibrillation, but that is the fact that atrial flutter is
4 the first, and should be used as a teaching tool regarding
5 an anatomical solution for arrhythmia.

6 This means, specifically with respect to atrial
7 flutter, there are well developed databases showing that, in
8 many patients, it is a very paroxysmal disease and there
9 could be, based on the patient, long intervals between
10 episodes of flutter making a clinical follow up alone
11 potentially misleading, particularly in that the well-
12 developed reports of standard atrial flutter which we are
13 all doing have shown a very significant recurrence rate of
14 isthmus conduction far beyond that of clinical recurrence of
15 atrial flutter.

16 So the question I wanted to bring up to the panel
17 was this issue of we, at this point, with respect to isthmus
18 block, have a very well-developed simple tool to determine
19 whether the lesion that we set out conceptually to achieve
20 was actually achieved and was maintained.

21 For flutter, it may not be as important as for
22 atrial flutter where our understanding of the underlying
23 pathophysiology, which will impact on the clinical outcome
24 is much more important. So, with respect to evaluating
25 technology, it seems more reasonable to adhere to the goal

1 that was set out in the beginning which was an anatomic
2 lesion.

3 So I guess my specific question is with respect to
4 follow-up testing of these devices, we can start now for
5 flutter and readdress this issue for fib, which is should
6 not there be more than a clinical follow up--that is, should
7 we not be able to assess whether the anatomical lesion that
8 we set out to do and that we documented acutely is
9 maintained.

10 DR. CURTIS: I think that is a good question.
11 Basically, what it should be getting down to is restudying
12 people at some period of time afterward, three, six, months
13 later and saying is there still bidirectional block. So the
14 patients would have to go through an invasive study;
15 limited, but invasive with catheters in order to demonstrate
16 that.

17 So it is one thing, patient acceptance of that.
18 Secondly, if you see that there is not complete
19 bidirectional block but yet the patient is doing well, do
20 you burn again? What do the patients want done?

21 DR. VETROVEC: But this is really crossing over
22 beyond saying whether a catheter is safe and efficacious for
23 what we are currently comparing to, existing catheters, to
24 doing an NIH-type scientific study to understand the
25 mechanism of what you are doing.

1 I think there are two different things here, it
2 seems to me. I think it is a great question and I think I
3 understand what the issue is, but the question is is that
4 the purview of this group or the FDA when it is comparing it
5 to catheters where that has never been tested. And that
6 seems to be unfair.

7 DR. SCHWARTZMAN: I agree with respect to flutter.
8 The problem is then when you start dealing with the atrial-
9 fibrillation problem and you add on an unknown substrate or
10 a little-known substrate in the context of a large
11 denominator of patients that we deal with every day, you
12 really have two different independent variables that you
13 can't assess.

14 So if you are looking at a technology, in my
15 opinion, you really have to reflect to the long-term
16 anatomical goal and let the underlying pathophysiology speak
17 for itself.

18 DR. VETROVEC: It would seem to me, though, that
19 flutter is markedly different from fibrillation.

20 DR. CURTIS: Yes; and we will spend plenty of time
21 talking about fibrillation. I am beginning to feel like we
22 beat the first question into the ground. I think what you
23 have been hearing is that there are numbers that could be
24 thrown out in terms of what kind of expectations you would
25 have for acute success rates.

1 Probably the minimum number would be somewhere
2 around 80 percent. Desirable would be something like
3 90 percent. I think if you demand the catheter as
4 98 percent successful, it is going to be unrealistic. So
5 you are somewhere in that ballpark for acute success.

6 Recurrence rates ought to be possibly somewhere in
7 the 5, 10, 20 percent range, certainly no more than
8 20 percent but maybe 5 percent is a little bit too strict.
9 And then the goal would be, to me, that a patient would
10 serve as his or her own control, and we are going to be
11 talking about how to select the patients, but that they
12 wouldn't have a recurrence of flutter afterwards as your
13 primary endpoint and that complication rates ought to be low
14 with Dr. Tracy mentioning her concerns about that isn't the
15 best way to do the study and that looking at some of the
16 currently used catheters would be a better way to go.

17 If that kind of sums up where we are, I think I
18 would like to move on to the next one.

19 DR. WHARTON: Anne, could I ask one question?

20 DR. CURTIS: Sure.

21 DR. WHARTON: Would the FDA accept, let's say, if
22 they randomly selected four or five institutions that do
23 flutter ablations, to ask for their last years' experience
24 in complication rates with atrial flutter which would not
25 assume any sort of standard catheter use. It would be a

1 mixed bag depending on how you pick your institutions.

2 I say non-published, because I think there are
3 biases that go into publications.

4 DR. PORTNOY: I don't know if that would be
5 considered valid scientific evidence. That is our standard.
6 That is what the statute says that we are supposed to use in
7 making comparisons.

8 DR. STUHMULLER: I think the question you are
9 asking is can you take that information and develop a
10 registry out of it.

11 DR. WHARTON: Right.

12 DR. STUHMULLER: That is essentially what you are
13 asking and can that be used as the control data.

14 DR. WHARTON: I worry about the Scheinman registry
15 because of the issues that were raised that it is kind of
16 what people decide to turn in so there is too much
17 randomness to that.

18 But if you go to institutions and say, "I want
19 your last year's results for flutter including
20 complications," or something like that, that gives you a
21 concurrent standard thing. We save a lot of trouble of
22 having control arms for flutter. I think most of us would
23 be more than willing to share that kind of data.

24 DR. STUHMULLER: Do you want to answer that, Tom?

25 DR. CALLAHAN: Yes. It is possible but the

1 problem would be we would have to go and verify, validate,
2 that the database--see are all the patients included, and
3 things like that.

4 DR. VETROVEC: What about requiring a six-month or
5 one-year retrospective database from each of the
6 investigators in an ongoing trial that is going to look at
7 a new device. That would create a registry from the same
8 operators and would come closest to getting around the issue
9 of operator variability affecting catheter success because
10 you would have the same operators.

11 If you took it a year back, you would be pretty
12 close in time to the expected success rate which is one of
13 the things that has worried me a little bit about using sort
14 of what is in the literature because that is always a few
15 years behind in terms of what is really state of the art.

16 That might come closer to fixing it and it is kind
17 of a composite of your idea.

18 DR. STUHMULLER: But, to clarify, from Dr.
19 Callahan's point of view, the agency would be open to
20 looking at that type of data in a registry format but the
21 sponsor, or whoever, would have to demonstrate poolability
22 of the data and that there is a uniform definition of
23 success in complications and so forth.

24 DR. CALLAHAN: Right.

25 DR. TRACY: Does that, in any way, serve to gain

1 approval for use of those catheters we are using off-label
2 now?

3 DR. CALLAHAN: I think it was mentioned before,
4 the catheter usage is dependent upon the companies to come
5 forward and ask for it. We haven't seen that up until now.
6 That is why we are seeing these right now.

7 You could make the argument that they could have
8 come forward long ago and we wouldn't have the problem. But
9 they haven't. And so we do have the problem. But we can't
10 do things retrospectively like that. First, they have to
11 come forward and they will need some database.

12 That is what we are struggling with. Usually,
13 what we have is another technique out there that was the
14 tried and true technique up until now. What you have had,
15 obviously, with these kinds of--a lot of the ablation issues
16 is a big paradigm shift where everybody is doing something
17 totally different.

18 There was no treatment before and so when you look
19 at what is the comparative treatment, you don't really have
20 anything. So it is getting them off the ground in the first
21 place. So historical controls are not bad for the first
22 few. As you come along, objective performance criteria are
23 even better. Registry is probably even better than that.

24 But once we get them off and running, and a few
25 companies come forward with those for legitimate uses, then

1 I think we will get beyond this initial hurdle. But if the
2 companies don't come forward with the data, they are not
3 labeled for that and we don't have the data to do anything
4 further with other companies.

5 DR. CURTIS: Let's move on to No. 2. Now we are
6 getting into patient-selection criteria.

7 "Given what is known about the safety and efficacy
8 of current drug therapy and off-label use of RF ablation to
9 treat atrial flutter, what is the appropriate patient
10 population for a study of an investigational ablation system
11 used to treat atrial flutter?"

12 I think this is basically getting at how many
13 recurrences, how much trouble does a patient have, how many
14 drugs do they have to have failed, if any, before they can
15 be approached with a catheter ablation system knowing what
16 we know about off-label use of this.

17 DR. TRACY: I think anything goes, any typical,
18 atypical, flutter would be reasonable to include whether
19 they had or had not ever seen a medication.

20 DR. CURTIS: That is actually what I wanted to see
21 what people would say. Ablation for flutter is done so
22 commonly now and it works so well, and the complication
23 rates are so low that it has become--if you have a clear-cut
24 flutter, it has become a lot like AV-node RT and WPW. If
25 you have the tachycardia, you don't need to have failed two

1 and three medications before you go ahead and have an
2 opportunity to cure it.

3 I think that is a lot of how we practice
4 medically. For a study of this, would that also be true? I
5 am not sure we have to fail drugs in order to go ahead and
6 offer it to a patient.

7 DR. SIMMONS: I agree.

8 DR. VETROVEC: What percentage of patients, after
9 you do an ablation, wind up on some antiarrhythmic?

10 DR. CURTIS: For flutter, and we are going to get
11 into this in some of the other questions, the big question
12 is how much fibrillation somebody has in addition. So I
13 think I will save it for then. But if it is clean-cut
14 atrial flutter and the patient has never had anything else,
15 and you can burn and get rid of the flutter, the chances are
16 that the patient is not going to have any more rhythm
17 problem and not require any drugs.

18 The patient who also has atrial fibrillation in
19 addition to the flutter, it is a very different entity.
20 Then you could start talking about who should you include in
21 the study and what is going to happen afterwards.

22 But the patients who are going to wind up on drugs
23 later tend to be the ones who already had some fibrillation
24 in addition to the flutter.

25 DR. VETROVEC: The only reason I asked that is if

1 a fair number of them wind up on some drug, and your
2 intention-to-treat, however you set this up, includes late
3 complications, they are going to be corrupted by the
4 complications related to drug therapy. That is the only
5 concern, the only reason I raised it.

6 DR. CURTIS: Let me ask should patients be
7 excluded from these studies of investigational devices if
8 they have had any fibrillation?

9 DR. TRACY: That's tough. I think there are a few
10 things that we have suffered from from not having done this
11 right from the get-go with flutter. I hate to get
12 anecdotal, but I saw a guy who had his first episode of
13 flutter in 1993. If I had ablated him in 1993 and then
14 followed him for the next three years, I would have been
15 happy.

16 He came back in 1996 with his second episode of
17 flutter. I wasn't involved in his care at that point, but
18 flutter, in a way, doesn't have to happen all the time. It
19 can go away and it can come back three years later and then
20 now, a couple of years later, he is having his third run-in
21 with it.

22 So that is part of our problem with understanding
23 success with flutter. Acutely, all these acute measures,
24 noninducibility, bidirectional block, are reasonable. What
25 we suffer from is never having studied the problem

1 particularly well to know sort of the variability in the
2 occurrence of flutter and then not having a long enough
3 registry to know that the people that have been ablated,
4 five years later, or three years later, are they coming back
5 again with flutter again.

6 So there is that problem of the tremendous
7 variability of the entity and the second problem is the
8 problem of concurrent atrial fibrillation. Curing atrial
9 flutter doesn't necessarily cure atrial fibrillation. Would
10 I exclude a patient because they have had atrial
11 fibrillation? No, because if I can be very confident that
12 the flutter is the primary problem, I would not.

13 But it is again sort of like yesterday's
14 discussion with VT, if they have got four or five different
15 VTs and they are shocking for the "not a clinical VT," what
16 does the patient care. If they are having racing in their
17 chest, what do they care if it is flutter or fibrillation?

18 DR. SIMMONS: I think it is a difficult question.
19 We don't want to limit the patient population that is
20 available for the therapy. So if you eliminate anybody who
21 has ever had A-fib or eliminate people who have a tendency
22 to A-fib, you are really going to shrink the A-flutter
23 population down.

24 Maybe that is a good thing because then you get
25 cleaner data in the long run. If you have to have a normal

1 left atrium and a normal ventricle and be under 60 years of
2 age and not have any comorbidities and you do atrial-flutter
3 on those patients, you should get very clean results.

4 But you are really going to shrink the patient
5 population down. What happens if they have never had A-fib
6 and they have to get started on drugs for A-fib? Are you
7 going to call that a failure? Are you going to censure them
8 from the database and just end their follow up at that point
9 but don't call them a failure?

10 How are you going to handle that? That is a
11 difficult question.

12 DR. CURTIS: Maybe I am sorry I brought it up.

13 DR. DeCARLO: Hi. Larry DeCarlo from Guidant.
14 Like many of you, I have been an electrophysiologist for
15 fifteen years. I joined Guidant just two months ago. I
16 have been listening, thinking back about my clinical career
17 and I think identify with everything that has been stated so
18 far today.

19 The problem seems to me to be trying to objective
20 endpoints in a disease that is a moving target, number one,
21 and may have a continuum when one considers atrial
22 fibrillation.

23 The other issue I struggle with is that, many
24 times, having published quite a bit as well, you publish
25 something; it looks like it works. You think you gave

1 adequate follow up. The patients start dribbling back a
2 little bit later; idiopathic VT, RV-outflow-track
3 tachycardias come to mind where sotalol, amiodarone starts
4 getting brought back into play late in the game for the
5 patient.

6 From my standpoint, I don't think we really have
7 any objective, quantifiable endpoints in ablation when we
8 compare it to drug therapy with control arms, flecainide,
9 propafenone, for examples.

10 The other thing I struggle with is what is going
11 to be our endpoint. If a patient has a racing heart in my
12 practice, and I have done an AV node ablation and I really
13 think those palpitations represent a recurrence, I bring the
14 patient back to the lab and try to ablate them a second
15 time. I see if they are inducible and see if I can ablate
16 them again because they want satisfaction.

17 I think we are struggling with all these issues
18 and, at the same time, trying to identify objective
19 measures. What I would suggest we at least consider the
20 first go-around is perhaps what we really need since this is
21 a first-line therapy that is under consideration for
22 flutter.

23 Perhaps what we really need the first time is a
24 true controlled trial where patients get randomized to
25 ablation or a drug and we look for follow up, understanding

1 that some of that follow up may, unfortunately, be
2 symptomatic. We may not have anything on the patient at the
3 time they have their 20- or 30-minute episode of rapid
4 palpitations following the ablation.

5 I would encourage that, rather than arguing what
6 is the bar here, is it 80 percent, 90 percent, 100 percent,
7 that you simply do a randomized trial the first time so you
8 can establish the bar and go forward from there.

9 DR. VETROVEC: This is an FDA question. If that
10 is the way we do it for the first company, unfortunately, it
11 has to be for the next four, doesn't it? Isn't that the
12 "rule of four," or something that I have heard?

13 DR. CALLAHAN: That rule is, at that point, we can
14 use the data garnished in the first study to make decisions
15 on the subsequent ones. But if, in fact, our main concern
16 is a little bit separate from that, is just keeping an even
17 playing field.

18 Usually, what happens is these companies don't
19 come through serially. They come sort of in packs. So you
20 are usually starting three or four trials at the same time
21 and you are getting one result finished while there are
22 three others in the pipeline. And then my question is, I
23 guess you are asking can we change things in midstream.

24 Certainly, none of the investigators like to do
25 that, and we like to be able to give some prediction to the

1 companies. There is nothing legally that says we can't
2 change it if the results of the trial are so outstanding,
3 for example, and they got published.

4 We are not bound. It is merely a level playing
5 field that we try to keep. So that is a bit separate from
6 being able to use the database. Especially if that first
7 study was a breakthrough and got published and it became
8 sort of a turning point in medical practice, I'm sure we
9 could use it.

10 DR. TRACY: I personally would think that that
11 would sort of be in an ideal world that you could go back
12 and so something like that. But the problem is the guy that
13 I saw who may go many, many years between his clinical
14 recurrences anyway. So, in order to do a study, a drug
15 study, at what year is the study done? How long would it
16 take to compare to drug management?

17 I don't think we can afford to do--things happen
18 in the atria. The milieu changes. The electrophysiology
19 changes. I don't think we can afford to do something that
20 would take that long and has such a tremendous variability.
21 I don't think that would be practical, unfortunately, at
22 all.

23 DR. CURTIS: I think, too, if we had the control
24 group, we would have to go back to the idea that was
25 mentioned earlier where you would allow patients to

1 crossover after some finite period of time, three months or
2 six months or something like that, because people do want
3 that therapy.

4 I think that the consensus here on this question
5 is that you don't need to fail drug therapy, that if
6 somebody has typical atrial flutter, that they are a
7 reasonable candidate for an ablation procedure to cure the
8 flutter.

9 If we go on to No. 3, we have basically answered
10 that. "Should patients who have not previously been treated
11 with antiarrhythmic medication be included in a clinical
12 study of an investigational catheter?" Again, we think that
13 would be legitimate, that they do not have to fail drug
14 therapy first.

15 If there are no other comments on that, let's move
16 on to No. 4.

17 "How should atrial flutter be defined for
18 inclusion-criteria purposes?" which, I think, gets right
19 into what you were talking about your patient. "For
20 example, is the following appropriate: a., two or more
21 patient-reported symptoms of atrial flutter during the last
22 twelve months and one or more documented episodes of atrial
23 flutter by ECG, Holter monitor, rhythm strip or ICD
24 electrogram?"

25 The question is how much atrial flutter should

1 somebody have before they get into the study. In some ways,
2 the more the better because then you get away from the
3 patients who were not going to have a recurrence for years,
4 anyway.

5 If you make it too strict, though, it becomes very
6 hard to find patients who can be put in. Is what is
7 outlined there reasonable? Would we want to see something--

8 DR. SIMMONS: I think this is the minimum. If you
9 don't have at least two episodes in a year, then it is going
10 to be very hard to define success without doing an invasive
11 study and looking for bidirectional block and trying to do
12 it on some sort of anatomical grounds.

13 I would say that is the minimum that you have to
14 have.

15 DR. CURTIS: Okay. Would anybody want to argue
16 strongly for a lot more than that? No? It sounds like that
17 would be a reasonable starting point, that you would have to
18 have at least one documented episode and at least the two.

19 DR. AZIZ: At least two episodes.

20 DR. CURTIS: At least two episodes reported, at
21 least one documented is the way it is written there.

22 DR. PORTNOY: It is two in one year's time. Do
23 you like the time limit?

24 DR. CURTIS: I guess I am kind of thinking that
25 you would be better off in terms of endpoints in the trial

1 or demonstrating efficacy if you weren't quite that liberal
2 with it. Two in six months? Is that too much?

3 DR. VETROVEC: But, practically, aren't a lot of
4 people being treated that fall into the criteria that you
5 defined? It seems to me what you are saying is this kind of
6 works. And that isn't the issue as much as maybe how much
7 atrial fib they are going to have.

8 It seems to me that the atrial-fib risk is
9 probably there whether they have one spell every two years
10 or one spell every six months. Isn't that correct?

11 DR. SIMMONS: It is there but I guess the question
12 is if you are going to accept one episode of A-fib a year,
13 and you do your ablation and you are going to follow them,
14 how long do you have to follow them before you can say that
15 your ablation was a success?

16 With only two in a year, how long are you going to
17 have to follow them? They may not have another one for a
18 year. So that means you are going to have a minimum follow
19 up of a year for the patients, then, to see if the thing
20 worked. So the more spells they have, the better study you
21 will be able to do in a shorter period of time.

22 Unfortunately, the more spells you require, you
23 shrink the patient population down that you are going to be
24 able to put into the trial and your numbers are harder to
25 achieve. So it is a real balance. I think two in a year is

1 probably a reasonable kind of compromise.

2 DR. CURTIS: I think another issue, too, though,
3 is the documentation of what is going on. Having at least
4 one flutter documented would be important but patients don't
5 always know whether they are having fib or flutter.

6 DR. SIMMONS: Or nothing.

7 DR. CURTIS: I just had a gentleman come back whom
8 we ablated in March, successfully, with a clear-cut type 1
9 flutter. We were getting called about a recurrence. The
10 transmitted ECG was A-fib. It was a different problem. We
11 are not going to ablate him again, but you have to be very
12 careful about that because the patients are not always aware
13 of it.

14 DR. SIMMONS: Having looked at a lot of monitor
15 strips, there are a lot of patients who call in with
16 palpitations or sinus rhythm as well.

17 DR. CURTIS: Then we would accept that as a
18 minimum necessary, the way it has been spelled out.

19 No. 5. "Should patients who have previously
20 failed ablation therapy be excluded from a clinical study of
21 an investigational ablation system?"

22 DR. TRACY: It doesn't seem like we have done that
23 with other investigational--or have we--with other
24 investigational ablations. If you go in and you do a study
25 and you define, pretty much--you don't find, obviously,

1 bidirectional block, I would think that you could include
2 them.

3 Your chances of success are probably lower than
4 with the patient who has a pretty normal heart and it has
5 never been touched before. But I think, again, it comes
6 down to a little bit of looking at not wanting to limit your
7 patient population too excessively by excluding people who
8 had had prior attempts with other devices.

9 So I would, realizing that there is some
10 difficulty with that kind of population, still think it
11 would be appropriate to have them in there.

12 DR. VETROVEC: What about analyzing that data,
13 including them but analyzing that data separately, because
14 you have to assume that once they fail that is somehow
15 stacking the deck a little bit against the product.

16 It would be good to have it in there to kind of
17 know what the success is but probably handle that data
18 separately.

19 DR. CURTIS: I think that is an excellent idea.
20 There is no medical reason to exclude patients from access
21 to an investigational system like that, but, as Dr. Tracy
22 said, the success rate is going to be lower and you want to
23 look at that separately.

24 DR. SIMMONS: I think, also, your problem is once
25 you have done multiple ablations on somebody, your chances

1 of getting other arrhythmias may go up. I don't know that
2 for a fact, but that may complicate interpretation of the
3 results. They are probably going to be a very small number.
4 Shoot them in a different slot. Don't exclude them from the
5 study.

6 DR. CURTIS: Okay.

7 No. 6, endpoint questions. "How should acute
8 success be clinically determined? For example, is it
9 appropriate to define acute success as the demonstration at
10 the end of the ablation procedure of both noninducibility of
11 atrial flutter and bidirectional conduction block?"

12 DR. TRACY: I am thinking about AVnRT. I am
13 thinking about that and I am thinking about knowing that
14 even if you see an echo beat that that doesn't predict a
15 clinical recurrence. So I am thinking that maybe the
16 bidirectional block isn't--I think it is something that
17 should be looked for but I am thinking that maybe we
18 shouldn't count that as success or failure.

19 It shouldn't hinge on that. Does that make sense?
20 Because we don't know for sure that the patient would have a
21 clinical recurrence if you could not definitely demonstrate
22 bidirectional block. We know that the recurrence rate is
23 likely to be higher but we also know that there are people
24 who walk out of the lab without bidirectional block who
25 don't have recurrences.

1 I think that when there is a lot of unnecessary
2 energy delivery going on in AVnRT to try to eliminate that
3 last little pop out or that last little echo beat, that was
4 creating more damage than was necessary to be done.

5 And we have found that it is not necessary to
6 eliminate every single echo beat. Is it necessary in all
7 cases to create bidirectional block? I don't think that we
8 know that for sure. I think we should look at it, but I
9 don't think that we should make that as the hinge point to
10 say that this thing worked or didn't work.

11 DR. CURTIS: I see your point. You are making the
12 analogy to AVnRT. We do know that, in that diagnosis,
13 though, if you still have single echo beats, if you are--the
14 way I do it is if I am still noninducible despite isopril,
15 even though I have single echo, it is good enough. I am out
16 of the lab and I don't have those patients come back,
17 period.

18 I have been going more, really, for bidirectional
19 block. If I have got that, I am happy enough. But let's
20 say you don't acutely. Would that, plus noninducibility of
21 atrial flutter be good enough? Could that be defined as a
22 success?

23 DR. SIMMONS: Inducibility of atrial flutter
24 sometimes is a little more "iffy" than inducibility of--

25 DR. CURTIS: Sure it is. And you may get some

1 other rhythm.

2 DR. SIMMONS: And then trying to follow clinical
3 occurrences which, again, is a little "iffy." I think you
4 have to have bidirectional block to call it a successful
5 procedure.

6 DR. TRACY: I don't know. I don't know whether
7 you have to say--if you can't demonstrate bidirectional
8 block, do you have to say that you have failed, then?

9 DR. SIMMONS: I think so.

10 DR. SCHWARTZMAN: Again, to echo some of the
11 members, I would argue that inducibility is the weak link.
12 There are several issues. One is, obviously, again,
13 particularly for a well-circumscribed area of anatomy such
14 as that we were talking about this morning, this offers a
15 wonderful opportunity to have a clinical-issue-free
16 endpoint, unlike AVnRT, as you know, because there is no
17 anatomical endpoint.

18 You have a clear, distinct endpoint here with
19 respect to what you had set out to do. Now, clinically, as
20 was mentioned, if you try to induce flutter, you more often
21 induce atrial fibrillation, even in those who have perfectly
22 pristine isthmus conduction.

23 I would argue that that leads to more morbidity
24 than it is worth when you have a well-defined anatomical
25 endpoint to chase. In addition, there are several reports,

1 albeit not concurrent, showing that the recurrence of atrial
2 flutter is significantly higher in patients in the same
3 hands and when they ended up without complete isthmus block
4 as when they ended up with complete isthmus block.

5 So my argument would be you have an anatomical
6 endpoint. It is very straightforward. It is very simple.
7 It eliminates a lot of the difficulties with program
8 stimulation. It would be a step backwards to hinge things
9 on program stimulation again and ignore the anatomical
10 issue.

11 DR. TRACY: The only question I have is, of the
12 people who are here, how many people have ablated somebody
13 who came to you with an EP report from another institution
14 stating that they had achieved bidirectional block following
15 ablation of atrial flutter? I have. So how is it being
16 defined in Gainesville versus Washington, D.C.?

17 DR. CURTIS: There is no question it depends on
18 what kinds of catheters you put in, and you can fool
19 yourself sometimes, depending on how you have put the
20 catheters in.

21 DR. TRACY: Right.

22 DR. CURTIS: The way I do it is if I get
23 bidirectional conduction block and it looks clear-cut to me,
24 I am finished. It is like not having a slow pathway present
25 anymore in AVnRT. If there is no slow pathway there, I am

1 not going to get AVnRT. And I don't spend a half an hour
2 trying to figure that out.

3 So I think if you have complete bidirectional
4 block, that is a very clean-cut endpoint. And I don't do
5 program stim on those people either. If you have partial
6 block, or you are not quite sure, there are problems with
7 program stimulation.

8 The question here is, I think all of us would
9 agree that, if you have bidirectional block, that is a
10 success. That works. In everything we do, there is a
11 certain recurrence rate. You do WPWs and, every now and
12 then, somebody can come back even though you had the delta
13 wave going and everything looks good.

14 So I think, as an acute success, that would be
15 fine. Do we not need noninducibility of atrial flutter? Is
16 that an unnecessary thing to ask during these
17 investigational studies?

18 DR. SIMMONS: Do you not need it. I always do it.
19 You don't do it? After you get bidirectional block, you
20 don't do program stim?

21 DR. CURTIS: No; I don't.

22 DR. SIMMONS: I always do it. I don't know why, I
23 guess. I always look. It certainly doesn't hurt to ask for
24 it. If you get it, like you said, putting those catheters
25 in, sometimes you are not putting them exactly sometimes.

1 Sure. Yes. Let them do program stim.

2 DR. CURTIS: If I have got block in one direction
3 and the other direction looks like I might but I am not
4 sure, or it is slower but it is not complete, and it is the
5 best I can do, I will do the program stim. I will add that
6 on.

7 DR. SIMMONS: Sure. Put it in there. I would
8 like to see it.

9 DR. CURTIS: Okay.

10 DR. WHARTON: One thing, in terms of inducibility,
11 and I agree with Dr. Schwartzman, really, and you that
12 looking at this bidirectional isthmus block is fine but one
13 of the practical issues would be in including inducibility
14 as an endpoint is defining what you mean and how do you do
15 it? Do you ramp pacing, burst pacing? How many times do
16 you have to induce fib before you do it?

17 You are trying to have a standardized protocol
18 that makes any sense in terms of what inducibility means is
19 really very difficult for this type of situation whereas
20 bidirectional block, like you said, is clean. If you have
21 multipolar catheters, at least, it is clean. You can tell
22 you have clear-cut block or no block.

23 I don't think sitting there after you have got
24 bidirectional block bursting people into fib makes much
25 sense.

1 DR. TRACY: I would argue exactly the opposite,
2 that it is not so easy to see, necessarily, bidirectional
3 block, how many catheters is Cardima--I think it is done
4 very, very differently. I don't care, frankly, which or
5 both you do. I generally don't do program stim and do rely
6 on block, but I know what I am defining it as.

7 I don't know, when I get in these reports from
8 other institutions, what they were defining it as. And
9 there have been people who have come from very good places
10 who come back and, "Did they do it different from me? Did
11 they have their catheter positioned someplace and they had
12 bidirectional block here when they really needed
13 bidirectional block here?"

14 I don't know. So all the ambiguities of program
15 stimulation also exist with the definition of bidirectional
16 block, I think. Neither is perfect. I, frankly, don't care
17 which but I don't think it is fair to say that ramp--how do
18 you define your induction protocol for atrial flutter as
19 making it, excluding that as an endpoint that you would look
20 at because I would argue that the same ambiguities exist
21 with the definition of bidirectional block.

22 It is there.

23 DR. WHARTON: But, see, I think the thing is it is
24 easy to handle the question that you raise, and this is one
25 of the things that I think that is an important issue, and

1 that is how do we define bidirectional block. How many
2 catheters? What types of catheters? Where do you place the
3 catheters? All of those things can give you the appearance
4 of bidirectional block or not.

5 So that is important to define. But that is easy
6 to define in the protocol, defining how many beats at
7 180 milliseconds I burst somebody in to try to burst flutter
8 and, again, how many times I will take fib and cardiovert
9 the patient before I give up and say, "I can't induce
10 flutter."

11 Those are all very subjective, very difficult,
12 things that frequently result in morbidity for the patient
13 in terms of repeated cardioversion and is unnecessary when
14 you have a more objective and easier-to-obtain endpoint as
15 long as you define that endpoint well.

16 I think that is the bigger issue is how do we
17 define bidirectional block. What are we going to set as the
18 gold standard, what type of catheters do we put in.
19 Personally, I think that just putting a bipolar on one side
20 or the other and showing it is late in the lateral portion
21 of the isthmus is inadequate.

22 You have to have a multipolar catheter.
23 Otherwise, you can have really slow conduction to the
24 isthmus and think it is late in the isthmus but not truly
25 have bidirectional block. So I think we need to be more

1 precise in how we define that block.

2 DR. PORTNOY: Aside from the definitions, would it
3 help if we changed the word "and" to "or?"

4 DR. TRACY: That would be nice.

5 DR. PORTNOY: So that if they demonstrated one or
6 the other--

7 DR. SIMMONS: No; I don't think so. I agree that
8 the bidirectional block has got to be there. I probably do
9 the program stims just because I am insecure, or obsessive-
10 compulsive, or whatever. I always do it. If I had to give
11 up one, I would give up the program stim. I wouldn't give
12 up the bidirectional block. It shouldn't be "or."

13 DR. CURTIS: If you couldn't demonstrate
14 bidirectional block but you were noninducible with your
15 flutter, is that a failure or a success?

16 DR. SIMMONS: Say that again; I'm sorry.

17 DR. CURTIS: You can't be sure you have
18 bidirectional block or you think you have got it in one
19 direction and slow to the other. It is something that is
20 not clean-cut bidirectional block, but you can't make
21 flutter happen any more. Is that a success or a failure?

22 DR. SIMMONS: Oh; I don't know. Induction of
23 flutter is very tough sometimes.

24 DR. CURTIS: I don't know the answer either. That
25 is why I asked the questions. I don't have to answer them.

1 DR. TRACY: I don't know the answer. I have
2 pretty much given up on program stim but if somebody asked
3 me to collect that information and I wasn't repeatedly
4 putting it, I wouldn't repeatedly put somebody into fib and
5 keep shocking them over and over again.

6 But if somebody asked me on a protocol to gather
7 that information, I would be happy to do so.

8 DR. CURTIS: I think what you are hearing is that
9 bidirectional block should be the gold standard. That is
10 the goal of the studies that you want to end up with that.
11 Some of us do program stim in addition. Some of us don't,
12 partly because if you really have the bidirectional block,
13 it shouldn't happen that you can have the flutter occur.

14 So I agree with Dr. Tracy that if I have
15 bidirectional block, I am happy I have got a good outcome.
16 If somebody says, "Would you please do program stim and show
17 me you can't get flutter," okay, fine. I'll do it. And
18 you're right; it doesn't take that long.

19 EP procedures are so long I try not to do things I
20 don't think are going to add anything to what I'm doing but
21 if it were part of a protocol, we would do it. It should
22 never happen, actually, that if somebody had bidirectional
23 conduction block that you would get flutter. It should
24 never happen.

25 So that is why there is some debate about the

1 necessity for that endpoint.

2 Any other comments on that?

3 No. 7. "How should chronic success be clinically
4 determined? For example, is it appropriate to define
5 chronic success as being arrhythmia free for a certain
6 extent of time? What is an appropriate follow-up period for
7 evaluating recurrences of arrhythmias; three months, six
8 months or more than six months?

9 DR. TRACY: It has got to be more than six months.
10 At some point, you are going to be worried that you are
11 seeing something that is different, that you are seeing some
12 other arrhythmia in somebody who really didn't have all that
13 normal of a heart or an atrium to begin with and that this
14 is something else other than what you were targeting.

15 But, of course, at that point, you don't really
16 know whether you have created a focus someplace else that is
17 irritable. But I think there has to be some, given the
18 variability of this and depending on how tightly you are
19 defining your entrance arrhythmia, you are going to have to
20 follow them at least, I would say, more than six months,
21 probably up to a year.

22 If you are taking two episodes within a year, I
23 would think it would be at least reasonable to go a year out
24 from the ablation to declare them arrhythmia free.

25 DR. SIMMONS: It kind of depends on how you define

1 it. If you follow patients for a minimum of six months,
2 then your mean follow up is probably going to be over a
3 year. Or are you going to say you have to follow patients
4 for a minimum of a year in which case, your mean follow up
5 is going to be a year and a half or two years.

6 Which one are you saying?

7 DR. CURTIS: I'm sorry; I'm missing you, Tony.

8 DR. SIMMONS: It depends on whether you say is it
9 a minimum of six months and then your mean follow up is
10 going to be over a year, probably. If you say a minimum of
11 a year, then your mean follow up is going to be a year and a
12 half, two years, more by the time you get the study done.

13 DR. CURTIS: I think I would go for a minimum of
14 six-months follow up.

15 DR. SIMMONS: Minimum of a mean of at least a year
16 or something like that.

17 DR. VETROVEC: Can I ask about the term
18 "arrhythmia?" Do you mean arrhythmia including a few PBCs
19 or should that be defined as some type of arrhythmias?

20 DR. CURTIS: Flutter ablations can cure flutter,
21 period. They don't necessarily cure anything else. So, to
22 me, what I would be looking for is not having a recurrence
23 of atrial flutter.

24 DR. VETROVEC: I guess I am arguing it should say
25 that.

1 DR. CURTIS: Okay.

2 DR. VETROVEC: Suppose you got a Holter on him
3 because he was having palpitations and he had V-tach. Would
4 that mean it was a failure?

5 DR. CURTIS: Or PACs. That is not a failure.

6 DR. VETROVEC: Okay. That is why I am just
7 arguing that it should define specifically what arrhythmia
8 makes it a failure.

9 DR. CURTIS: It should be free of recurrent atrial
10 flutter.

11 MS. GOODE: Later on, we are asking a question
12 about A-fib secondary to A-flutter. The question is if we
13 define a study for A-flutter, is that going to be long
14 enough to look for A-fib if you want to.

15 DR. CURTIS: We will get to that.

16 DR. DeCARLO: How are you going to handle a
17 patient that has sustained palpitations lasting twenty
18 minutes? How do you handle that clinically now, when a
19 patient comes in, has SVT, talking generically. The patient
20 has SVT, rapid palpitations, feels a little woozy.

21 You do an EP procedure. The patient calls you
22 back two months later and says, "I just had twenty minutes
23 of identical symptoms to what I had before." Looking at it
24 in terms of endpoints, we are looking for arrhythmia
25 recurrence, but how are we going to define that?

1 DR. TRACY: I think it has to be
2 electrocardiographically defined because we all know
3 patients who have palpitations that are not related to an
4 arrhythmia, as Dr. Simmons had said. So what we do now I
5 think would be a reasonable approach.

6 Before you would take a person back to the lab,
7 unless they came back and back and back and back with
8 something you couldn't catch and you finally sort of had
9 your arm twisted into it, I would like to see that there is
10 some documentation, the loop recorders or something, to
11 define that there is actually recurrence of the clinical
12 arrhythmia.

13 DR. DeCARLO: Perhaps, I could try to pin you down
14 a little further. In a patient that has had two episodes of
15 sustained palpitations in one year, and one episode,
16 fortuitously, was recorded as atrial flutter who then has a
17 procedure in clinical practice presently, what happens to
18 that same patient who goes on within six months to have two
19 sustained episodes of palpitations that are identical to the
20 symptoms that the patient had before the procedure?

21 DR. TRACY: I would define what it is. I
22 clinically would make every effort possible to define what
23 the rhythm is after their first event. I would give them a
24 loop recorder that I could keep renewing and renewing and
25 renewing, or I would tell them that they have to get--I

1 would do something to define what it is that they are
2 feeling.

3 DR. DeCARLO: Are we going to hold the patient and
4 you to the same standards before the procedure is done,
5 then, so that we are certain that we have ablated for two
6 sustained episodes of atrial flutter before? I am really
7 struggling with objective criteria.

8 If we are going to hold anything, whether it is a
9 drug or a device, I am trying to think very generically
10 here. If we are going to hold the drug or device to any
11 standard, it seems to me the standard has to be similar
12 before and after what we are going to do.

13 If we are starting off by saying you could have
14 two episodes of something and one of them is documented to
15 be flutter, there are two chances. They had two episodes of
16 flutter or they had flutter and something else. Whatever we
17 consider to be standard at that end seems to me needs to be
18 similar at the other end.

19 So I am just seeking with you some sense of
20 balance here in terms of what we are going to consider to be
21 a recurrence--an occurrence as well as a recurrence.

22 DR. CURTIS: One way to handle potential issues
23 like that would be to have the patients go home with an
24 event monitor. That way, that would enable them to record
25 something. Or, if you don't want to do that for every

1 patient going home--something I would normally do--
2 especially since, in flutter, there is always that
3 possibility that they are having another rhythm-like fib, if
4 they had one episode of palpitations, probably give them an
5 event monitor then to document what is going on.

6 The other possibility is if you are so worried
7 that it is a recurrence, that would be the time that you
8 possibly could bring a patient back into the lab and see if
9 they have got the bidirectional block.

10 DR. DeCARLO: That is a discussion in clinical
11 practice but we are now trying to measure objectively and in
12 a scientific fashion what this patient has after an
13 investigational procedure is done.

14 So I appreciate what you are saying, Dr. Curtis,
15 in terms of how you practice clinical medicine and how I
16 might practice clinical medicine but that is something that
17 may be separate from trying to satisfy a scientific
18 objective for the FDA. That is why I am struggling and
19 trying to pin you down in terms of how would you handle data
20 streams before and after an investigational procedure.

21 At one end, you can have a mixture of either
22 symptoms and/or documentation. I am trying to look for the
23 balance on the other side so that when we come back to the
24 FDA and say, "Yes; a patient had five episodes of sustained
25 palpitations while they were on a lengthy six-week hiatus

1 from our medical center but we are going to claim success
2 because we didn't document any of those spells."

3 Do you see what I am saying? I think I am
4 struggling a little bit for how we are going to represent
5 these endpoints to the FDA once we, as clinical
6 investigators, have finished this investigational procedure.
7 I am really hoping that I might pin you down in terms of not
8 how you would practice clinically but how you are going to
9 count that event, how it is going to register up when you
10 are trying to answer a question that requires some
11 scientific endpoints.

12 DR. CURTIS: We normally are not talking about
13 huge numbers of patients in any of these trials. It is
14 very, very common in pharmaceutical studies of drugs for
15 rhythms that patients are given the event monitors. And
16 they transmit everything.

17 They will transmit palpitations. There are
18 certain things you call an endpoint. For instance, if you
19 are treating atrial fibrillation and they have atrial
20 fibrillation, that's an endpoint. If they transmit PACs and
21 they are having palpitations, that is not an endpoint.

22 The data is recorded--maybe I am not understanding
23 what you are saying but I think one way to handle it would
24 be to give all of the patients event monitors coming out so
25 that way, if they do have these sorts of things, palpations,

1 you have the opportunity to record what happened then and
2 then you have got the hard data to say yes it was or was not
3 flutter.

4 DR. SCHWARTZMAN: I am going to ask a question,
5 but I am going to start with two assumptions based on my own
6 experience. One is that when patients are involved in
7 studies such as this, they are more than willing to come
8 back for a repeat invasive procedure.

9 The second is because of the fib problem in the
10 context of flutter ablation, we are descending into a very,
11 very difficult area that I think simply saying we are going
12 to monitor these patients until we get the answer is not
13 going to work.

14 Again, I am naive to the ways to how companies
15 would think about this and I would certainly like to hear
16 the opinions of other investigators but I come back to the
17 point that we have an anatomical definition of an endpoint
18 here. I think the greater good for both the patients
19 involved in the study and, more importantly, the patients
20 who are waiting for this technology to become approved so we
21 can move forward here, in my opinion, based on those
22 considerations, we should use this anatomical endpoint as a
23 gift and move forward as quickly as possible by pinning the
24 success of the technology to that anatomical endpoint rather
25 than descending into this clinical problem that is really

1 going to be a major issue and prolong these studies forever.

2 DR. WHARTON: I beg to disagree. Having been in a
3 number of trials earlier with SVT, and the one that kind of
4 comes to mind is the cardiorhythm trial where we were asked
5 to do these hard anatomic endpoints for three PDP studies at
6 some follow-up point.

7 The data is worthless because the patients are not
8 going to come back to you. You cannot get them to come in
9 because they are fine. They are asymptomatic, for the most
10 part. You are talking about the 3 or 4 percent who have
11 palpitations and the rest of them are asymptomatic. You
12 have got to try to convince them that they need to come in
13 and have an invasive study so that we can prove some
14 scientific point.

15 It just doesn't fly and, for that reason, the data
16 is worthless because the noncompliance rate is going to be
17 so high.

18 DR. SIMMONS: I would have to agree. My
19 experience trying to get people to come back for SVT, WPW or
20 repeat ablations when they are asymptomatic is miserable.
21 And then, if you end up with one person who gets hurt, you
22 feel really bad yourself. To do that to find that one guy
23 or that two people out of 100 patients that have
24 palpitations and you could have done a king of hearts.

25 As far as I am concerned, I think maybe the

1 protocol could be read that every effort will be made to
2 document symptoms; king of hearts, loop monitors, those
3 kinds of things will be provided but, in that absence of
4 documentation of symptoms and an arrhythmia, then the
5 arrhythmia didn't happen.

6 DR. TRACY: I agree with that. I think it is too
7 hard to get people to come back. And it is too hard to
8 justify exposure to the risk of an invasive procedure albeit
9 very low. But there is risk. Any time you put any needle
10 into anybody's body, there is some risk involved. I don't
11 think that is reasonable.

12 DR. CURTIS: We have got three out of three on the
13 panel agreeing. From electrophysiology, that is wonderful.

14 All right. No. 8.

15 DR. PORTNOY: Before we go on, can you just
16 clarify what do you expect for chronic follow up? For
17 example, you say you don't want patients to come back. Are
18 they going to come back for an office visit, for physical
19 exam and for interview?

20 DR. CURTIS: Oh; I would expect you would be able
21 to--

22 DR. PORTNOY: We are talking no EP studies.

23 DR. TRACY: No EP study; right.

24 DR. CURTIS: That is what people don't want to do.
25 They go, "I'm fine. Why do you want stick catheters in me

1 again?"

2 DR. TRACY: They are all more than happy to come
3 back for follow-up visits because they are all full of
4 propafenone and fentanyl when they leave the hospital and
5 they don't remember anything about anything anyway. They
6 and their wives and thirteen children want to come and ask
7 you every question that has ever been thought of by mankind.

8 So they always want to come back and meet with you
9 and talk with you. If they have palpitations post-ablation
10 they are also very anxious to understand what it is and
11 whether or not it is something that is a problem.

12 There is not a single person who is not going to
13 be on the phone real quick to call you and say, "I felt
14 something and it felt very similar to," maybe slower or
15 whatever. But they are going to get back in touch with you.

16 I have not had any difficulty in defining
17 recurrences in that fashion. I think if you stick with a
18 very similar definition to what you have done here pre, you
19 may be missing that 50 percent of the pre-ablation episodes
20 may have been atrial fibrillation and 50 percent of the
21 post-ablation episodes may be atrial fibrillation.

22 But you have got to work with what is reasonable
23 to expect patients to comply with. They do want to comply
24 with clinical follow up. I think that as long as you are
25 kind of looking at the same things post, it is reasonable.

1 Yes; they will come back easily.

2 DR. VETROVEC: It is a little bit like restenosis
3 in interventional cardiology. We are all anxious to know
4 whether the blockage came back or not but all anybody really
5 cares about is is the patient at risk and are they having
6 chest pain. This is really an analogous situation.

7 DR. PORTNOY: So if chronic success points were
8 defined as freedom from recurrence of A-flutter and maybe
9 there would be some transtelephonic monitoring or something
10 like that?

11 DR. CURTIS: Yes.

12 DR. PORTNOY: How long would you want to follow up
13 the patients? That is what the question asked, for that
14 endpoint.

15 DR. CURTIS: I think six months would be a
16 reasonable goal.

17 DR. SIMMONS: Minimum of six months.

18 DR. CURTIS: Minimum of six months.

19 DR. TRACY: I would like to mean to be longer than
20 that.

21 DR. PORTNOY: Okay.

22 DR. CURTIS: No. 8. "If acute success is achieved
23 but atrial flutter recurs during follow up, how should the
24 patient be treated? For example, can antiarrhythmic
25 medications be offered during the study. If so, how should

1 the success of these patients be assessed? Should this
2 patient be considered a chronic failure or is there some
3 definition of partial success that would appropriately
4 include these types of patients? How can this be
5 determined? Can repeat ablations be offered during the
6 study? If so, how should the success of these patients be
7 assessed?"

8 I think if you have one recurrence of flutter, you
9 have failed. I don't think you want to get into, "Well, you
10 they had four the year before and now they have only had
11 one, so, therefore, that is a partial success." I think if
12 you have flutter again, you have failed and that is your
13 endpoint.

14 Then, at that point, whatever you are going to do,
15 if you put them on antiarrhythmic drugs or whatever, you are
16 treating them because they failed the endpoint of your
17 study.

18 Could repeat ablations be offered? I am not sure
19 why I see why not.

20 DR. SIMMONS: Once they are a failure, you can do
21 anything you want.

22 DR. CURTIS: I think you could have a repeat
23 ablation in there. Again, success should be--if you have to
24 do it a second time then your success on that second
25 procedure is going to be if they have no flutter after that.

1 I don't see a definition of partial success.

2 DR. SIMMONS: I agree. It is just those patients
3 seem to be put in that same group as not followed in the
4 same way as the way we described it before. That is a
5 separate group if you are going to repeat ablate them.

6 DR. CURTIS: That's right.

7 DR. TRACY: What if it is a different looking
8 flutter?

9 DR. SIMMONS: We always said we are not going to
10 atypical flutters.

11 DR. TRACY: What if it is a typical flutter that
12 you successfully ablated, had bidirectional block,
13 noninducibility, and they come back and they have atypical
14 flutter? Is that a failure?

15 DR. PORTNOY: Do you see that frequently in
16 clinical practice?

17 DR. TRACY: No. It could happen.

18 DR. CURTIS: Do you think we should be going after
19 the rhythm they were treated for?

20 DR. TRACY: But what if you didn't really have
21 bidirectional block and it is just kind of oozing around the
22 other way now.

23 DR. CURTIS: I don't know what to do about the
24 oozing.

25 DR. TRACY: I don't either. I don't know. But we

1 are going to, at some point--and I don't know that we can
2 really come up with an answer right now, but we will see
3 this.

4 DR. CURTIS: Then what is your definition of
5 atypical flutter and when is something a coarse fib and it
6 is not quite the same? You have got to be very careful
7 about those sorts of definitions, too. I don't have a good
8 answer for that.

9 I think the primary thing should be recurrence of
10 the original arrhythmia. I think most of the recurrences
11 are going to be something else. They are going to be atrial
12 fibrillation or something that just doesn't look the same.
13 I don't think I can answer that.

14 Now we get into the A-fib issues. "Is A-Fib
15 secondary to atrial flutter a clinically relevant issue that
16 should be addressed during the clinical study? If so, how
17 should patients that develop atrial fibrillation during
18 follow up be assessed? For example, should atrial
19 fibrillation secondary to atrial flutter be considered an
20 adverse event, a chronic failure, a separate outcome measure
21 to be assessed during analysis of something else?"

22 I think there is a real problem with the atrial
23 fibrillation secondary to atrial flutter phrase there. It
24 is awfully hard to know that in many patients. I think when
25 we have patients who have atrial fibrillation as well as

1 flutter--it depends on how you pick patients, too.

2 I would be somewhat stricter in a clinical trial
3 about trying to aim for patients who are more clear-cut
4 flutterers, but any time you have someone who has
5 fibrillation as well, is it an independent problem or is the
6 fibrillation occurring because they have atrial flutter?

7 We know that in patients who have previously had
8 atrial fibrillation, and you do a flutter ablation, then
9 there is some risk of recurrence of atrial fibrillation
10 afterwards. At least one study I am aware of said it was
11 about a 50 percent recurrence rate whereas in patients who
12 didn't have any history of fibrillation, there was a very
13 low risk of having atrial fibrillation afterwards.

14 So that means that in some patients, the
15 fibrillation may be secondary to flutter because if you
16 ablate the flutter, they never have the fib anymore. In
17 other patients, it may be a different problem and that you
18 ablate the flutter and you have cured that but they are
19 still going to have fibrillation afterwards.

20 So I would tend to look at it as a separate issue.
21 For a patient, they want to be arrhythmia free, and that is
22 clear. Myself, if I have somebody who has an awful lot of
23 atrial fibrillation, I don't like to do flutter ablations
24 because I have got people who, no matter how much I tell
25 them, are expecting to be cured by a procedure.

1 And it is not reasonable to expect that if they
2 have a lot of fibrillation as well. So I tend not to do
3 that. I prefer to do a flutter ablation on somebody who has
4 a lot more flutter than fib if any at all.

5 I would tend to think that the fib is a separate
6 issue and that it is not a failure of the procedure. I
7 would be interested to hear other viewpoints here.

8 DR. SIMMONS: The way the question is phrased, it
9 is kind of ambiguous. If a patient has an ablation and
10 comes back with A-flutter that goes into A-fib, that is just
11 a failure. It is a failure of the procedure; right?

12 DR. CURTIS: That's true.

13 DR. SIMMONS: So it is not an adverse event or a
14 complication or anything. That is just a failure. If they
15 had A-fib before and A-flutter and A-flutter causing A-fib
16 and they have A-fib after, that is not a failure of the
17 flutter ablation unless you document atrial flutter causing
18 the fib. That is probably not a failure of the flutter
19 ablation. That is just maybe poor patient selection or just
20 bad luck the patient's got a dilated atrium.

21 DR. CURTIS: Right. It almost sounds to me like
22 what this question is saying is that atrial fibrillation in
23 patients with flutter is due to the flutter. And that is
24 true in some cases but not in many. So I would call it a
25 separate outcome measure but I wouldn't call it an adverse

1 event or a chronic failure.

2 DR. PORTNOY: Would it be important to try and
3 document, during enrollment, whether the patient had A-fib
4 going in? Is that going to make a difference?

5 DR. CURTIS: Oh, yes. I think you want to know
6 that because if somebody has a previous history of atrial
7 fibrillation and they have it afterwards, you say, well, bad
8 luck, poor selection, as we said there. If you, for
9 example, had a bunch of patients who have never had any
10 fibrillation at all and they are all turning out to have it
11 after your procedure, well, then, maybe you have got a
12 problem with the catheter procedure. It is causing too much
13 damage or something that is aggravating the situation.

14 So I think knowing up front whether the patient
15 had any fibrillation would at least be useful for analysis
16 purposes.

17 DR. TRACY: I agree and I think that the criteria,
18 the entrance criteria that we sort of talked about before
19 would be the minimal needed to get into the study. But I
20 think you realistically know a lot more about the patients
21 before you bring them into the lab even on a clinical basis.
22 I think that information would not necessarily be entrance
23 criteria that they have to meet, but you should know things
24 like whether they had had fib before.

25 You probably do know that to a large extent, so I

1 think that is important and I agree with everything that
2 Anne has said about them often being totally separate issues
3 and not the occasional patient having flutter that
4 degenerates to fib but possibly existing as totally separate
5 entities in the same individual.

6 DR. SIMMONS: I guess the next two or three
7 questions are kind of like how to handle that A-fib if it
8 occurs and maybe this is the time to bring it up.

9 DR. CURTIS: Go ahead.

10 DR. SIMMONS: If they had A-fib and they had A-
11 flutter and you ablated the flutter and the A-fib reoccurs
12 and you have got to start them on medication, what are you
13 going to do about that? How are you going to handle that?
14 Are they going to stop follow up at that point?

15 It is tough to call it a failure of the procedure
16 but, at the same time, you have got to start somebody on
17 flecainide or you start them on propafenone or--I mean, that
18 is going to affect the flutter recurrence rate, too.

19 DR. CURTIS: That is very true.

20 DR. TRACY: I think it is a minority of patients.
21 I think you can't withhold therapy that you might feel is
22 appropriate to put a patient with fib on an antiarrhythmic.
23 You might not. But you are going to have to make an
24 individual decision and that patient, as far as--
25 fortunately, that doesn't happen terribly often.

1 It probably does mean that that is the point at
2 which you can't continue to rely on clinical evidence of
3 flutter recurrence but you can't deny that patient, you
4 can't just shock the patient and, if you felt it was
5 important to put them on an antiarrhythmic, deny them an
6 antiarrhythmic for the sake of following them for their
7 flutter.

8 DR. VETROVEC: Can I ask a practical question,
9 though. Let's say you have a patient who has some atrial
10 fibrillation but predominantly flutter before you do an
11 ablation. Does that, in any way, affect whether or not you
12 are going to keep that patient on antiarrhythmics after the
13 flutter ablation and is that something we should address?

14 DR. TRACY: I think it would be a mistake to get
15 somebody that complicated in a study. I think if you have
16 one episode of atrial fibrillation that may have been
17 defined at one point and it is not clear how that person got
18 into it, but you have then fifteen episodes of atrial
19 flutter that are documented, I think you could allow that
20 patient in.

21 But if you have somebody that is a mixed bag and
22 flutter ablation is almost palliative because it seems that
23 most of the episodes are flutter, but there is a very
24 reasonable likelihood that they will end up having fib or
25 something else afterwards, I don't think that is a good

1 person for a study like this.

2 DR. VETROVEC: Should our definition, then, for
3 acute and long-term success relative to flutter include no
4 antiarrhythmic and, if they required an antiarrhythmic, that
5 would somehow either put them in a separate category? It
6 wouldn't necessarily make them a failure but it would put
7 them in a separate category?

8 Then, if they develop atrial fib after the study,
9 it goes in this category secondary--it would be an outcome
10 measure. And then you could treat them any way you wanted.
11 I think this is tricky, because if you start putting
12 background antiarrhythmics in here, then you may be
13 affecting the incidence of flutter, also.

14 DR. CURTIS: Yes. I think you don't want patients
15 in the study who are likely to require chronic
16 antiarrhythmic drug treatment for fibrillation. I just
17 ablated somebody within the past couple of weeks who was on
18 chronic treatment for atrial fib and then, on his drugs,
19 starting having type 1 flutter. They got him into the ER,
20 like, three times within a month.

21 They wanted to get rid of the flutter. We did.
22 We put him right back on the antiarrhythmic drugs because I
23 knew he was going to need the there for the fib.

24 DR. VETROVEC: My question is how would that
25 patient be handled. I think, by what you said, that patient

1 wouldn't be included in the study.

2 DR. CURTIS: We wouldn't want to put him in. I
3 think you would want to exclude somebody who chronically
4 required drug treatment for atrial fibrillation unless you
5 were pretty darned clear that the flutter caused the
6 fibrillation.

7 In terms of afterwards, I don't know. If you had
8 an episode of atrial fibrillation afterwards, some of the
9 patients are going to be paroxysmal. Maybe you wouldn't
10 have to treat them with anything, get out to the six months.
11 That would be cleanest thing is not to have to put any
12 antiarrhythmic drugs on board that were possibly mask
13 flutter.

14 If you did have patients who sustained an atrial
15 fibrillation, I suppose you could cardiovert them. I think
16 some goal of minimizing the use of antiarrhythmic drugs in
17 that first six months of follow up would be a good idea.
18 So, partially, patient selection and partially trying to be
19 clean about not putting the patient on drugs.

20 I think if you put them on antiarrhythmic drugs
21 for fibrillation, it is not necessarily--you can't call it a
22 failure of the flutter ablation, but I don't know how you
23 analyze it either.

24 DR. TRACY: I think you are right. We sort of,
25 for a second, there, were making the assumption that

1 automatically you would put them on an antiarrhythmic. But
2 you would go through the same decision process you make with
3 any patient with atrial fibrillation and certainly not all
4 of them are going to end up on an antiarrhythmic.

5 But if they do end up on an antiarrhythmic, I
6 think you have lost the endpoint of looking for flutter
7 recurrence. They would have to not be included in that
8 analysis.

9 DR. CURTIS: I guess those might be the patients
10 where that would be nice, if you could see the bidirectional
11 block. I agree with all the things you said before about
12 it. It is hard to get patients convinced to come back in.

13 But before you started your antiarrhythmic drugs,
14 that would be the one way to be sure about the success of
15 your flutter ablations if you still had that bidirectional
16 block, although I wouldn't insist on it, myself.

17 DR. PORTNOY: Can we get you to clarify what you
18 would want as an exclusion criteria? For example, I have
19 seen some manufacturers simply propose, "Exclude patients
20 with atrial fibrillation." That is kind of vague. What
21 would you recommend? With a significant history of atrial
22 fibrillation?

23 DR. VETROVEC: Atrial fibrillation requiring drug
24 treatment?

25 DR. TRACY: You are talking about exclusion

1 criteria to get into a flutter-ablation protocol.

2 DR. CURTIS: That's right.

3 DR. PORTNOY: Or do you think you are going to
4 lose too many patients and companies won't be able to get
5 adequate enrollment?

6 DR. TRACY: I don't think you are going to lose
7 too many patients by putting a pretty strict requirement on
8 that. I think most of us would not have a huge enthusiasm
9 for ablating patients and we probably have a little bit
10 different threshold, each one of us, as to what we
11 considered too much.

12 I would think that there could be some definition
13 of what is too much documented atrial fibrillation before we
14 would not consider doing a flutter ablation within a
15 protocol. Within a protocol, it may be reasonable to say no
16 documented atrial fibrillation.

17 I don't know. I would think that there probably
18 could be a way of reaching a consensus of what is too much.

19 DR. CURTIS: You really do have to think that out
20 carefully ahead of time. Possibly atrial fibrillation
21 requiring antiarrhythmic drug therapy? Because then you
22 don't know whether or not that patient is going to require
23 it later on. PAF that doesn't require treatment; maybe that
24 is not an issue because if they didn't require treatment
25 beforehand with antiarrhythmic drugs, I think they would be

1 no more likely after an ablation and possibly less likely to
2 require treatment afterwards.

3 So it may be the patient who has required
4 cardioversion previously or treatment with antiarrhythmic
5 drugs for atrial fibrillation specifically. That would be
6 the kind of patient you would want to exclude.

7 DR. SIMMONS: Of course, if they are having
8 recurrent PAF, it may be difficult to figure out was it
9 atrial flutter or--

10 DR. CURTIS: That is why they are going to have an
11 event monitor.

12 DR. SIMMONS: Right.

13 DR. CURTIS: I think that covers all those issues
14 on No. 9 because I think we all basically agree that it is a
15 separate outcome measure and not a failure.

16 That basically addresses the flutter questions.
17 Is there anything you are not clear about or want us to go
18 over any more?

19 If not, what we are going to do is we are going to
20 take a fifteen minute break now. When we come back, we will
21 get into atrial fibrillation.

22 MS. GOODE: I am wondering if the industry has any
23 other issues besides the ones we raised. That is the only
24 question.

25 DR. CURTIS: I don't see any rush to the

1 microphone so we will take a break now.

2 [Recess.]

3 **Atrial Fibrillation Ablation**

4 DR. CURTIS: Now we are going to switch over to
5 atrial fibrillation. So we will have the FDA presentation
6 first.

7 **FDA Presentation**

8 DR. PORTNOY: Good afternoon.

9 [Slide.]

10 My name is Stuart Portnoy and I am a physician
11 with the FDA. I focus on clinical issues which arise during
12 the review of manufacturers' submissions for cardiac devices
13 including pacemakers and cardiac ablation systems.

14 My associate, Dina Fleischer, and I prepared this
15 presentation and we also prepared the questions regarding
16 atrial fibrillation ablation which were included in your
17 panel pack.

18 [Slide.]

19 Atrial fibrillation is the most common chronic
20 tachycardia. It is also the most common cardiac cause of
21 stroke. In the United States, approximately 6 percent of
22 people who are greater than 60 suffer from atrial
23 fibrillation. For these reasons, the disease process of
24 atrial fibrillation is considered a significant public-
25 health concern.

1 [Slide.]

2 Patients with atrial fibrillation may experience
3 palpitations, shortness of breath, presyncope and/or
4 syncope, fatigue and other symptoms. Episodes of atrial
5 fibrillation usually occur intermittently. New-onset A-fib
6 is frequently classified as paroxysmal but, as the disease
7 progresses over several years, the frequency of episodes
8 usually increases resulting in what is finally called
9 chronic atrial fibrillation.

10 It is important to recognize that, in contrast to
11 yesterday's discussion of ventricular tachycardia which is a
12 life-threatening arrhythmia, atrial fibrillation is not
13 directly life threatening. However, because of an increased
14 risk of stroke, A-fib is considered indirectly life
15 threatening.

16 Finally, many patients with atrial fibrillation,
17 especially those who experience hemodynamic compromise
18 during symptomatic episodes, suffer from a diminished
19 quality of life because the arrhythmia interferes with their
20 day-to-day functioning.

21 [Slide.]

22 As previously mentioned, patients with atrial
23 fibrillation are subject to an increased risk of stroke. A-
24 fib patients have a five-times greater risk of stroke than
25 non-A-fib patients. In addition, during their lifetime,