

1 one-third of A-fib patients are expected to experience a
2 peripheral vascular event which may or may not include
3 stroke.

4 [Slide.]

5 The initial treatment of A-fib is focused on
6 achieving ventricular-rate control and converting the
7 patient back to sinus rhythm either pharmacologically or
8 with electrical cardioversion. Most patients then begin a
9 course of antiarrhythmic drug therapy to maintain sinus
10 rhythm. The current medical standard of care also specifies
11 that patients should be anticoagulated with warfarin and/or
12 aspirin to reduce the risk of stroke.

13 [Slide.]

14 Therapeutic interventions for treating atrial
15 fibrillation include antiarrhythmic drug therapy as
16 described in the previous slide but may also include more
17 invasive therapeutic modalities such as AV nodal ablation
18 followed by pacemaker implantation to restore ventricular
19 pacing, implantation of an automatic atrial defibrillator
20 which is currently still in investigational therapy, and
21 cardiac ablation which is the subject of our discussion this
22 afternoon.

23 One of the questions that you will be asked to
24 address is what is appropriate patient population to be
25 enrolled in atrial-fibrillation ablation studies. Another

1 question is what is an appropriate control group for
2 comparing safety and effectiveness data.

3 This list of antiarrhythmic drug therapy, AV nodal
4 ablation, atrial defibrillation and convention catheter
5 ablation include some of the control therapies that you
6 should consider.

7 [Slide.]

8 Catheter ablation of atrial fibrillation usually
9 involves creating linear lesions according to anatomical
10 patterns loosely based on the surgical MAZE procedure
11 described by Cox. Many EP cardiologists currently use
12 standard ablation catheters off-label to create drag-burn
13 lesions.

14 The published literature includes discussions of
15 investigations using multiple electrode catheters specially
16 designed to create linear lesions. There are also other
17 catheter designs which are currently being developed for
18 atrial-fibrillation ablation.

19 Lesions can be created in the right atrium or in
20 both the right and the left atria. Several questions that
21 we are asking you to address this afternoon concern right
22 versus left atrial ablations and whether investigators in
23 clinical studies should be limited to only a prescribed
24 lesion set versus choosing which linear lesions they feel
25 are appropriate.

1 [Slide.]

2 The medical literature suggests that creating
3 right-atrial plus left-atrial lesions is more effective in
4 treating atrial fibrillation than creating right-atrial
5 lesions alone. However, there is a potential for an
6 increased risk of thromboembolic complications such as
7 stroke associated with left-heart catheterization
8 procedures.

9 Since catheter designs are still evolving, we may
10 have to wait until several difficulties in creating
11 effective ablation lesions are resolved such as the
12 difficulty in making adequate wall contact before we can
13 adequately determine whether right versus right-plus atrial
14 lesions is optimal in the ablation treatment of atrial
15 fibrillation.

16 [Slide.]

17 This is my last slide and it just shows some
18 preliminary clinical results from a number of atrial-
19 fibrillation ablation studies reported in the medical
20 literature. On average, procedures involving right-atrial
21 lesions alone result in approximately 40 percent chronic
22 success.

23 Investigators performing procedures in the right
24 and left atria achieve 74 percent chronic success. It is
25 important to note that the preliminary results from these

1 studies varied widely as seen by the values in the
2 parentheses. For a more complete description of the
3 clinical data reported in these studies, please refer to the
4 table included in your handout.

5 So that was just a brief overview of some of the
6 clinical issues that the medical community faces and that we
7 face in trying to put together a guidance for manufacturers
8 for atrial-fibrillation ablation studies and we can proceed
9 now to the questions.

10 DR. CURTIS: I wanted to just let you know that we
11 are going to see how this works. If we get through the
12 questions in a reasonably timely manner and it looks like we
13 can wrap up this discussion by, say, 12:30 or 1 o'clock at
14 the latest, we are going to go straight through.

15 If we get bogged down and these issues become very
16 complicated, then we will still need to break for lunch. We
17 are going to see how it goes over the next hour.

18 Next, we have some comments from industry.

19 DR. STUHMULLER: As I noted this morning, we
20 received a written response from Boston Scientific and
21 Cardima. Is there anybody from either of those companies
22 here today that would like to address the information that
23 they submitted?

24 [No response.]

25 I guess, briefly, what Boston Scientific wanted

1 the panel to consider were four questions. Should the
2 primary means to estimate sample sizes required for these
3 trials be based on safety endpoints? Second, is the only
4 appropriate method for analyzing safety data an intention-
5 to-treat analysis? Can a complication's relationship to the
6 procedure investigational device be reasonably assessed by
7 the investigators and, if not, by whom?

8 Can the panel define the difference between major
9 versus minor adverse events for the fib and flutter trials
10 and how should safety and efficacy be determined from
11 approaches that utilize a combined system, multiple
12 diagnostic and therapeutic catheters, to cure fib or
13 flutter?

14 The document for Cardima appears to be just
15 related to the trial-design issues for A-fib. Perhaps, the
16 panel can review those as you go through each question and
17 make a comment on it.

18 During the break, I also received a copy of a
19 statement from NASPE that will also be incorporated into the
20 public record and will be available with the other documents
21 through dockets management with the transcript.

22 DR. CURTIS: Is there any member of the atrial
23 flutter here, public or industry, that wants to make a
24 comment at this point before we start going through the
25 questions? Again, you will be able to get up as we do them

1 if it seems more appropriate.

2 **Panel Discussion**

3 DR. CURTIS: Let's start to tackle this one. The
4 first question we have is related to clinical-trial design.
5 "Is a randomized, concurrently controlled clinical study
6 needed to collect safety and effectiveness data on RF-
7 catheter ablation as a treatment for A-fib? Are there
8 alternative study designs that would provide valid
9 scientific evidence to support a marketing application?

10 "For example, with a single-arm study using safety
11 and effectiveness data from the medical literature as an
12 historical control be appropriate? Is the current
13 literature sufficient to create objective performance
14 criteria? Can major complication rates from ablation
15 studies treating other arrhythmias be used as an historical
16 control?"

17 I think what we are going to find, right off the
18 bat here, is that we are going to wind up looking at this a
19 lot differently than the way we looked at atrial flutter
20 because whereas there is quite a bit of literature about
21 atrial flutter and a consensus among electrophysiologists
22 that complication rates are low and we know what kind of a
23 success to expect, I don't think that is nearly true with
24 atrial fibrillation.

25 I don't believe anybody has quite worked out what

1 lesion sets are optimal, that there are RA versus LA issues,
2 and there have been significant complications reported in
3 some of the early studies that would be of concern.

4 So, in terms of objective performance criteria, I
5 don't think anything exists that you could say, "This is the
6 gold standard or this is the standard by which we are going
7 to judge any new procedure," just to start that off.

8 DR. TRACY: I would completely agree with that.
9 There is not something here that you can turn back to in any
10 sense to say this is the standard by which we should measure
11 thing. Also, I think just to get it right out there, that
12 is true regarding the surgical intervention for atrial
13 fibrillation.

14 I don't think that we have to propose in comparing
15 against a surgical approach to atrial fibrillation. So I
16 don't think there is a catheter. I don't think there are a
17 number of lesions. I don't think there is another therapy
18 that is equivalent and should be used as a control.

19 DR. CURTIS: In addition, the issue about major
20 complication rates from ablation studies treating other
21 arrhythmias, I don't think you can use that at all, either.
22 That would probably be the absolute minimum I would expect
23 from an atrial-fibrillation study but I think it would be
24 expected that the complication rates for atrial-fibrillation
25 ablation are going to be higher than they were for other

1 types of arrhythmias.

2 We know that. We don't know how high or what we
3 really should aim for or expect as a safe procedure and a
4 low enough complication rate. But I certainly would not use
5 results from WPW ablation to tell me what to expect with
6 atrial fibrillation. I don't think that is true at all.

7 There is a risk of stroke that is rarely seen with
8 any other diagnosis. There have been rare reports of WPW
9 having strokes associated with it whereas it wasn't that
10 uncommon in some of the initial studies with atrial
11 fibrillation, for example.

12 You don't have benchmarks to judge complication
13 rates and efficacy for this procedure, so you are starting
14 from scratch, basically.

15 I think that, then, takes you into the first part
16 of the question which is do we need a randomized,
17 concurrently controlled clinical study. Let me try to
18 summarize what Cardima's opinions were. As we said, this
19 information can be obtained, but, basically, what they
20 suggested was that, although a randomized study should not
21 be excluded, "We believe other viable designs are possible;
22 for example, a single-arm, non-randomized study in which
23 each patient serves as his or her own control," kind of what
24 we were talking about with the flutter before. You compare
25 number of episodes before to number of episodes after.

1 They pointed out that there has been some
2 precedent for this with the EPT SVT study which was a
3 single-arm, non-randomized. The VT clinical study started
4 out randomized, became non-randomized. It is hard to have a
5 good control group. Drugs are palliative, although that may
6 be a reasonable way to go.

7 Their suggestion was for a single-arm, non-
8 randomized study with the patient as his or her own control.
9 I think we need to talk about that and whether that is
10 appropriate for this clinical problem as we thought it might
11 be for the atrial flutter.

12 DR. SIMMONS: I think that trying to randomize
13 them to drugs is just not going to work; right? We all
14 agree to that. There is certainly enough historical data on
15 drug therapy of atrial fibrillation to establish criteria
16 for successes on drug therapy, plus it is not a comparable
17 control.

18 So doing a randomized study comparing some
19 ablation technique to atrial fibrillation is kind of a
20 meaningless study. So if you are going to eliminate drugs
21 as your randomized arm, what else are you left to randomize
22 to? I think you have to randomize to the patient, himself,
23 using him as his own control.

24 It is actually a very complicated issue because--I
25 don't want to get into patient selection, but are you going

1 to do permanent A-fib, paroxysmal A-fib, persistent A-fib?

2 It is a very complicated issue.

3 So I think the only way to do it is where the
4 patient has their own control and in a non-randomized trial.
5 I can't even kind of visualize a randomized trial.

6 DR. CURTIS: I agree with what you are saying. If
7 you have a patient--each patient has their own recurrence
8 rates and whether it is persistent or chronic or paroxysmal
9 and all those different terms that we use. It is comparing
10 apples to oranges. I am not sure if you can compare
11 patient A with their own pattern of A-fib to how Patient B
12 does with drug therapy.

13 What drug therapy? How do you adjust for it? How
14 do you keep it constant? So I think comparing a patient to
15 his or her own history would be the better way to go in
16 terms of efficacy. Really, the bottom line with this is,
17 again, if you are ablating atrial fibrillation, then the
18 ideal goal or the thing you would like to aim for is having
19 no more atrial fibrillation.

20 We can get into partial successes and success with
21 drug therapies and all that sort of thing, but I think a
22 single-arm, non-randomized would be acceptable. That may be
23 the easy answer, though. The much tougher questions may be
24 what you were alluding to about which patients and how
25 persistent is it and that sort of thing.

1 DR. TRACY: I agree with all those comments. The
2 only place I can see any possibility of randomization would
3 be within a study, if you were going to study right-atrial
4 lesions versus right-atrial plus left, versus left,
5 something on that order.

6 But that would be within the study. And I think,
7 still, at some point, the patient then becomes their own
8 control, pre-ablation number of episodes versus post-
9 ablation and only within looking at the different
10 approaches.

11 DR. CURTIS: So I think we have an agreement that
12 using a single-arm, non-randomized study with the patient as
13 his or her own control would be a valid way to go. There
14 are many other clinical issues that have to be addressed,
15 but, as a basic study design, that would be a good first
16 step.

17 DR. VETROVEC: Would you require these patients
18 to, let's say, have three months of medical therapy before
19 they got treated and is that how you would establish their
20 baseline control? How would you establish their baseline
21 control?

22 MS. FLEISCHER: We have some questions later about
23 that.

24 DR. CURTIS: Let's take it one step at a time. I
25 guess that is what I was getting at with the first one. We

1 can answer the question. We have a consensus there. I
2 think there are a lot of other tough issues and we will take
3 them one at a time here.

4 No. 2. "Should factors such as the evolving
5 technique of A-fib ablation and new catheter designs for
6 creating linear lesions--that is, loop catheters, multiple
7 electrodes, et cetera, influence the choice of the control
8 group? If so, how?"

9 I think we just decided there wasn't a control
10 group. So we don't have to worry about that.

11 No. 3. "If randomization is the optimal study
12 design, what is the most appropriate control therapy?"
13 Again, we got away from that.

14 Let's go to No. 4, because then we start getting
15 into these other issues. "If a single-arm study is the
16 optimal study design, how should ablation effectiveness be
17 defined? For example, should it be defined as a percent
18 reduction in frequency of symptomatic episodes? If so, how
19 should this percent reduction be assessed? For example, is
20 a baseline observation period necessary?"

21 So that starts getting into what you said, George.
22 Frequency of episodes; that assumes paroxysmal atrial
23 fibrillation. Some people have classified atrial
24 fibrillation into various groups; chronic, paroxysmal and
25 persistent, persistent meaning that if you don't convert it,

1 they will become chronic.

2 Would all of those patients be candidates for
3 atrial-fibrillation ablation? I am not sure I see why not.
4 Any one of them could potentially be symptomatic that you
5 would want to include them in a study.

6 In that case, then, before you started the study,
7 you could have anywhere from a patient persistently being in
8 atrial fibrillation to having paroxysmal atrial fibrillation
9 and then some sort of a defined number and frequency of
10 episodes.

11 DR. TRACY: What about chronic atrial
12 fibrillation? I don't know if this is going to be addressed
13 at another point, but what if you have a patient who has
14 been in atrial fibrillation for an extended period of time,
15 months, ten or twelve months, and has very large atria. Is
16 that a reasonable patient to include in a study like this,
17 in atrial-fibrillation ablation? Is that a reasonable
18 person to be doing an ablation in or surgery in?

19 DR. CURTIS: I think that is a good question.
20 Personally, I think most patients who are chronically in
21 atrial fibrillation aren't that hard to manage, really. I
22 have more trouble and more complaints from the patients when
23 they are in and out of atrial fibrillation and have a lot of
24 complaints like that.

25 Many of the ones who are persistently in atrial

1 fibrillation, if it has been for some period longer than six
2 months to a year, if they have got adequate rate control,
3 that is usually the thing that is key to me.

4 DR. TRACY: So, within the confines of a study to
5 evaluate a new technology, would it be more reasonable,
6 then, to just talk about people with persistent and
7 paroxysmal atrial fibrillation as being appropriate
8 candidates?

9 DR. CURTIS: And then exclude patients who have
10 been in atrial fibrillation for six months, something like
11 that? I think that might be reasonable.

12 DR. SIMMONS: I think that would give you your
13 best chance of getting some answer at the end of the study.
14 Actually, if you are going to allow patients in who have
15 been in A-fib permanently for over six months, you are
16 really biasing the study against the catheter.

17 So I would say paroxysmal or persistent atrial
18 fibrillation would be your goal and then that would help
19 answer the question about follow up and how many months free
20 and definitions of successes.

21 DR. CURTIS: Okay.

22 DR. TRACY: The other issue that came up in the VT
23 study was quality-of-life assessment following the ablation,
24 comparing pre-and post-ablation because we can anticipate
25 from what we see in the literature that some of these

1 patients are not going to be completely free of arrhythmia,
2 yet their arrhythmia may become much more tolerable.

3 So I think this would be a very valid endpoint in
4 a study like this where you are not necessarily expecting
5 100 percent free-from-arrhythmia episodes.

6 DR. AZIZ: Can I ask a question. Why not include
7 them as a separate group, have people with chronic AF,
8 because you will have a huge population. It may not work,
9 but why not allow them to be used and analyze them
10 separately?

11 It looks like you are going to have four or five
12 different categories of AF anyway. It probably won't work
13 in that setting, but those people should be given a chance
14 to be included.

15 DR. SIMMONS: I guess there is no problem with
16 that if you declare up front which group they are going to
17 go into, respectively, and declare that this is a permanent
18 A-fib and I have got documentation that they have been in it
19 for six months. But then your endpoint is going to be
20 different.

21 DR. CURTIS: I would expect your chances of
22 success are lower. I am trying to think of why. I can
23 think of some reason why I would have to exclude them and I
24 don't think so.

25 DR. AZIZ: The operator will get experience with

1 doing patients like that. Basically, you are going to have
2 a learning curve of people who are using the catheters. It
3 may be that people who have been in A-fib for more than two
4 years may not work out. I think it is a point where you are
5 gathering data and if the patients are willing to take that
6 chance--

7 DR. PORTNOY: Do you think patients with a certain
8 left-atrial size enlargement should be excluded?

9 DR. TRACY: The bigger the chamber size, the
10 longer the arrhythmia, the less likely you are going to be
11 able to establish sinus rhythm and, if you do, the less
12 likely that it is going to be a functional contractile left
13 atrium.

14 I don't know that there is an absolute number that
15 you would have to invoke here but I think we can look at the
16 surgical literature to get some idea about atrial transport
17 and success in larger chambers.

18 I think you have to always bear in mind if you can
19 do something it doesn't mean you should do something. I
20 think we have to exercise some judgment about doing
21 something--that we wouldn't consider doing surgery on this
22 patient, we wouldn't consider another trial with
23 arrhythmics.

24 Should we be putting a catheter in this person?
25 There has to be some sense to the doing of it. I would

1 think, and I am, unfortunately, not familiar enough with,
2 even though he is at my institution, Cox's data to know
3 that, are there upper limits to the atrial dimension at
4 which he would not consider a MAZE procedure.

5 I don't know but I think we have to be very
6 careful that we are not just saying do it in anybody for any
7 reason.

8 DR. CURTIS: I think you get back to if you have
9 that kind of data, if we knew that he has not been able to
10 maintain sinus rhythm if the atria were larger than
11 55 millimeters or something, then that would be reasonable
12 not to include those patients.

13 If you don't know, then is there a reason to
14 exclude the patients? The worst of it is is they may not
15 have the success rate you want. Should we be learning?
16 Maybe we want to learn that. Maybe we will find out we can
17 do just as well if we get patients--that they may not do
18 quite as well as the people with the left-atrium below 40
19 but they do reasonably well and it is a good treatment for
20 them.

21 I don't know. The reason you would exclude them
22 is if it was so unlikely it would work and the complication
23 rate was high enough that you don't want to do that to the
24 patient. But I don't know the answer to that, so it is hard
25 to exclude them.

1 DR. SIMMONS: It may really boil down to how much
2 is the company willing to do. You start including these
3 groups of people, you are going to have to have larger
4 numbers of patients to actually show some benefit because
5 your failure rate has got to be higher.

6 So if they are willing to pay for it, I would say,
7 "Great; let's do it."

8 DR. VETROVEC: These are what we would agree to
9 include. They are not requirements.

10 DR. CURTIS: That's right.

11 DR. VETROVEC: They could do a more isolated study
12 if they chose.

13 DR. CURTIS: And they may want to limit the upper-
14 -the larger the atria, the more lesions you are going to
15 have to put in, too, in order to create linear lesions and
16 have block. So I think there is no reason, a priori, to
17 exclude somebody but they want to limit the group that has
18 the ablation done to start with to some extent.

19 DR. TRACY: It seems like you are really pushing
20 the limits of the technology which isn't even established at
21 this point at all when you start opening the door to bigger
22 and more diffusely diseased atria.

23 Just because we can do something does not mean
24 that we should do it. I just don't know that we are going
25 to get good answers here. I would favor not starting with

1 chronic A-fib, not starting with big atria. I would favor
2 starting with something that is going to be definable,
3 persistent of paroxysmal atrial fibrillation.

4 I think that we are still so early in the learning
5 curve with atrial fibrillation, we don't know anything about
6 what lesions we really need, anything about what locations
7 we need, whether they need to be transmural or not. We
8 don't know anything about it at all, so far, as far as I am
9 concerned.

10 So I just worry about going too far with our
11 looseness of allowing patients in.

12 DR. CURTIS: In terms of this question, one of the
13 issues was brought up about a baseline observation period
14 and percent reduction in symptoms. I think this potentially
15 gets a lot messier than the atrial flutter because we may
16 wind up with some definitions of partial success; arrhythmia
17 controlled with antiarrhythmic drugs whereas it wasn't
18 before as a partial success; complete success is somebody
19 who never has the arrhythmia again.

20 So if things are going to get a little messier, we
21 probably do need a baseline observation period. I think
22 that would be essential here to know what it is you are
23 dealing with ahead of time.

24 I think that would get into question No. 5, "If a
25 baseline observation period is needed, how long should this

1 period be; one month, three months or other, for example a
2 certain number of episodes?"

3 Does anybody want to comment on that?

4 DR. TRACY: Does anybody know what the AFFIRM
5 entry--is it within one year?

6 DR. CURTIS: Funny you should ask. I don't think
7 it is within one year. I think it is a lot shorter than
8 that.

9 DR. TRACY: Is it shorter than that?

10 DR. CURTIS: Yes.

11 DR. TRACY: Again, if you are doing things for
12 people who have one episode of atrial fibrillation a year,
13 should you really do that?

14 DR. CURTIS: That's right.

15 DR. TRACY: I don't think so. I think it has got
16 to be a higher density whether it is paroxysmal or
17 persistent. It has to be a higher density so maybe you
18 don't need such a long period of observation. They should
19 prove that they are having lots of episodes.

20 DR. CURTIS: I am nearly certain that that study
21 requires documentation within something like six to twelve
22 weeks of enrollment in the trial. You have to actually have
23 your documented episode. How much other than that, I don't
24 recall offhand.

25 DR. PORTNOY: Would it help if we looked at

1 question 8 which actually asks you to specify how many
2 episodes and then come back to the baseline period?

3 DR. CURTIS: It could. It just depends on how you
4 want to look at it. Is it just a particular duration of
5 time you look at or how many episodes?

6 I just want to mention, since we brought up the
7 AFFIRM trial, something that NASPE has in their statement to
8 the panel. The AFFIRM trial is the atrial fibrillation
9 follow up investigation of rhythm management. It is
10 sponsored by the NIH. The goal of the trial is to determine
11 the relative benefits of treatment strategies directed at
12 rate control or rhythm control.

13 So there is going to be a lot of information there
14 collected about patients with atrial fibrillation and what
15 we could expect. I might also mention now other comments
16 they made. They suggested that, for atrial fibrillation, it
17 would be appropriate to begin with small, non-randomized
18 groups of patients before expanding to large randomized
19 clinical trials.

20 They suggested with a large trial there must be a
21 sizeable randomization against conventional therapy to
22 maintain sinus rhythm. I think that is a little bit farther
23 down the road than what we were talking about here in terms
24 of what our goal would be.

25 I might also mention the Cardima information that

1 I had. There rely was far too long to just read out, but
2 they were suggesting that establishment of baseline data
3 would first be necessary in terms of designing a study and
4 so I think there is general consensus that you have got to
5 know what you are dealing with before you do the ablation.
6 So I don't think there is any disagreement there.

7 In terms of baseline observation period, in terms
8 of time, they were suggesting one month might be adequate
9 for most patients but patients who have low frequency might
10 need a baseline period of at least three months before
11 starting the study.

12 They were also suggesting, in terms of question 8
13 that you put up there, that any patient with one or more
14 episodes per month should be allowed to enroll but if
15 patients had a low frequency, they might need a longer
16 pretreatment baseline monitoring period.

17 So kind of to sum up what they are saying, one or
18 more episodes a month would be enough to get you in the
19 trial or three months baseline period of observation if you
20 had less than that. But, even then, you have to get some
21 frequency in there to know what you are doing.

22 DR. ECHT: Debra Echt, Cardiac Catheters. I just
23 wanted to say that I seem to remember now, since I am on the
24 data monitoring board for AFFIRM, that it was within the
25 last six months that you had to have--and you had to have

1 either, I think, one episode that was at least twelve hours
2 in duration or X number of episodes that--

3 DR. CURTIS: It had to be sustained enough to
4 warrant enrollment.

5 DR. ECHT: Right. It was six months.

6 DR. CURTIS: Thank you.

7 We are trying to get some ideas here about what
8 kind of baseline period you would need. One problem with a
9 long baseline period is sometimes you will have patients who
10 are referred in and they have been on drugs, and they are
11 failing them and you want to do something about them.

12 To take somebody who is highly symptomatic and
13 say, "We have got to wait three months and let you have
14 fifteen episodes of A-fib and then we will be able to do
15 your ablation," may be too much. Patients are anxious to
16 get in there and get treated.

17 On the other hand, there are some patients who
18 don't have that much. If you have a one-month observation
19 period and they do absolutely nothing, then what do you do
20 after that because some of those patients could wind up
21 being arrhythmia free for some period of time after the
22 ablation and you don't know that is a result of your
23 ablation, itself.

24 DR. SIMMONS: I guess I didn't realize you were
25 talking about prospectively deferring treatment for a

1 baseline period.

2 DR. CURTIS: No; it doesn't have to be that. That
3 is one way to look at it, or you could say retrospectively.
4 It is always hard to document something retrospectively,
5 though, exactly how many episodes did somebody have back in
6 April.

7 DR. SIMMONS: I guess I would say it has got to be
8 more than two episodes and maybe in a three-month period and
9 documented, something like that, and then you at least have
10 got something that is a clinically relevant tachycardia to
11 attack, something of a reasonable expectation over the next
12 year, would reasonably be expected to occur.

13 DR. CURTIS: I would think, too, that we want
14 something reasonably serious to be going after. If it is
15 the kind of patient who has palpitations and you never seem
16 to be able to catch them, is that the sort of patient who
17 should be going through the initial A-fib ablation trials
18 where there is a potential risk we don't know about yet?
19 Shouldn't they be more symptomatic?

20 DR. SIMMONS: So you want to put a time on how
21 long the A-fib spell has to last or a symptom score or--

22 DR. CURTIS: I think documentation would be
23 something that would be important because that is one issue--
24 -it is one of the reasons it is unusual for me to do a
25 radiofrequency ablation on somebody I have never documented

1 an arrhythmia on because I figure, if it is bad enough, they
2 need me to put a bunch of catheters in and do something
3 about it. It ought to be something I can catch.

4 There are exceptions to that, certainly, but I
5 think it is nice to be able to see it. For atrial
6 fibrillation, if it is so evanescent you never catch it, is
7 that the patient who should be going through a potentially
8 risky ablation?

9 DR. SIMMONS: No.

10 DR. VETROVEC: One thing I just want to clarify,
11 though, if you are using a retrospective entry criteria,
12 let's say somebody has had three episodes in the last six
13 months and they are even documented. The problem you always
14 get into is, at least for our center, they were documented
15 in some other institution, you can't get the documentation
16 but somebody said they saw X, that is a certain problem
17 about, "what do you mean by documentation?"

18 But then the patient is finally put on amiodarone,
19 let's say, and he sees you in the office. And those three
20 episodes didn't occur on amiodarone. Do you have to show
21 that he is an amiodarone failure before you can ablate him?
22 You see the problem, because you might just leave him on the
23 amiodarone and you will never have another spell and you
24 will credit it to ablation, and it really had nothing to do
25 with that.

1 So one of the advantages of having a prospective
2 period would be that you would presumably have stable
3 therapy during that time with continued--it wouldn't require
4 any therapy but you would have some stable condition that
5 would then be continued, or potentially continued, into the
6 follow-up period.

7 That period might not be a fixed period of time
8 but might be a period of time based on the severity of the
9 arrhythmia so that somebody who had infrequent spells, you
10 would require two spells within that three-month period.
11 And, on the other hand, somebody who had 48 hours of
12 continued arrhythmia on whatever therapy you had would
13 qualify without further ado because they would be in the
14 persistent category.

15 Something like that with a rolling entry criteria
16 but requiring some prospective follow up would seem to me to
17 give you your best baseline data.

18 DR. SCHWARTZMAN: I would like to elaborate on
19 that a little having had some experience with a feasibility
20 study with respect to patients like this. In order to
21 define entry criteria, I think you have to look at the
22 literature and anticipate what it is going to mean to define
23 success.

24 There are two areas I would like to talk about.
25 One is with respect to the monitoring issues. Now, there is

1 monitoring and then there is monitoring. The monitoring
2 that we are talking about here can be construed as very
3 unelaborate, one documentation of atrial fibrillation.

4 Again, this gets very complicated. For example,
5 it is really simple to take someone who always is in atrial
6 fibrillation, you document it however, and they go into the
7 trial. It is very difficult to document patients with
8 paroxysmal and even more murky for patients with persistent
9 AF that have long inter-AF intervals after you intervene
10 with pharmacologic or direct cardioversion.

11 So the monitoring issue is something that is
12 important and so a retrospective control, I think, is out of
13 the question. I really think you need to monitor them the
14 same way before you intervene and after.

15 Now, with respect to the success issue, I think
16 this comment of partial success is important, particularly
17 in unilateral ablation, most importantly the right side.
18 You have to anticipate that there are going to be people who
19 are not cured with this and that the addition of a
20 previously ineffective but well-tolerated drug may be the
21 norm, particularly if you want to stay out of the left side.

22 So, for those patients, it is really important to
23 expose them to that drug prospectively prior to entering
24 them into the ablation trial because the comment from
25 another clinician that the patient failed quinidine carries

1 with it a lot of subtleties in terms of how much quinidine,
2 whether they really failed or whether they had some
3 palpitation or were construed to have failed.

4 So I think that is really important to focus--in
5 order to focus on inclusion, you really have to anticipate
6 how we are going to define success.

7 DR. CURTIS: That would be kind of tough, though,
8 because you can't exactly say, well, we are going to have a
9 prospective period of observation during which we are going
10 to use the drug that we are going to wind up using later on
11 if the patient fails. I think that would be hard to do.

12 It sounds like it probably would be best to have
13 some sort of prospective baseline observation period just so
14 that you don't get into the problems--as you said, somebody
15 in the other city said the patient had a documentation but
16 we don't have any record of it, and what does that really
17 mean.

18 So, if it is a prospective observation period, the
19 longer it is, the longer you are delaying until you start
20 the procedure and do something about it. What is enough?
21 Is one month enough if a patient has a documentation of an
22 episode? What if a patient goes three months and has
23 nothing?

24 I think it is really hard to know what the right
25 answers to these things are but they are really critical in

1 terms of designing a trial.

2 DR. SIMMONS: There is probably enough A-fib that
3 it is not going to limit enrollment. What we heard
4 yesterday was trying to delay therapy after somebody is
5 referred to you is difficult. And it is difficult. Most of
6 these places are going to be tertiary referral centers.

7 There is a lot of A-fib out there. Maybe it won't
8 reduce enrollment that much but if patients are getting
9 referred to you and you are telling them, "Well, let's just
10 wait three months," or six months, is that going to decrease
11 your ability to get these people in here?

12 I think it is.

13 DR. TRACY: I think it is early enough in the
14 whole A-fib ablation arena that you can say whatever--we can
15 say more definitely whatever we think is the right thing. I
16 really think we don't know much about atrial fibrillation
17 ablation despite what is out there in the literature.

18 We just really don't. I think we should really
19 take a stand, whatever we feel--if we feel, and I do think
20 it is appropriate to have a prospective period of
21 observation, and I think it is very important that we define
22 carefully the entrance groups that we want.

23 I think we have to just stick by our guns and say
24 this is what we, as an EP community, feel is important and
25 not feel pushed around by referring physicians. I have a

1 sense that we wouldn't have the same push. We are not
2 dealing with recurrent episodes of potentially life-
3 threatening VT.

4 We are dealing with a different uncomfortable
5 arrhythmia but an arrhythmia whose prognosis is defined by
6 the underlying cardiac condition not by the arrhythmia,
7 itself.

8 So I think we have to take a stand. I think it
9 would be important to say prospectively, here is day 1 of
10 looking at you as a candidate here. Let's gather the
11 information over the next three months.

12 Presumably, by the time the patient is referred to
13 you, they will already have had something going on. They
14 are not going to just presumably come in on their first
15 episode of atrial fibrillation. If they do, that is not the
16 kind of patient we should enroll here. One episode of
17 atrial fibrillation is not an appropriate person to be doing
18 an ablation on in an entity where the entire prognosis is
19 solely dictated by the underlying cardiac condition,
20 assuming that they are properly cared for, if they have risk
21 factors for stroke, they are anticoagulated.

22 We can't prove--we don't know yet that making
23 people be in sinus rhythm is going to prolong their lives.
24 We won't know that until the information from AFFIRM is
25 analyzed several years from now. So I think we have to take

1 a stand and this is a group that we are really doing, I
2 think, largely for palliative purposes.

3 DR. SIMMONS: Let's say you have a patient
4 referred in for this study. A typical patient is going to
5 come in--they have probably already had a couple of
6 episodes. They have probably already been on beta blockers
7 or calcium channel blockers and dig.

8 They have probably already failed at least one
9 antiarrhythmic drug. Whether or not they have truly failed
10 it is, again, a question. And they are probably going to be
11 on Rhythmol, propafenone. Now, you want to set up your
12 prospective trial of baseline follow up. Are you going to
13 stop all the drugs, stop the Rhythmol, stop the--

14 DR. VETROVEC: No.

15 DR. SIMMONS: So you are going to leave them on
16 that drug and follow them for three months. If they have
17 one episode of A-fib or two episodes of A-fib--if they have
18 one episode of A-fib and it lasts more than X minutes, that
19 is an occurrence. So then you are going to have two
20 episodes of A-fib lasting X minutes in three months and that
21 is going to be your inclusion criteria?

22 But then are you going to stop the propafenone
23 before you do the ablation? Do the ablation and leave them
24 off all drug? Is that the kind of a trial that you are
25 thinking of doing?

1 DR. TRACY: The kind of trial that I think would
2 be interesting would be to tag this on to something like the
3 AFFIRM study and say, if you are randomized to the group
4 that you want to have in sinus rhythm, then to have that as
5 a potential way of achieving a sinus rhythm.

6 But within there, you are still stuck thinking
7 through the issues of how many drugs do you have to fail or
8 what kind of intolerance do you have to have, or this ever
9 going to be a first-line therapy for atrial fibrillation?

10 I just feel uncomfortable enough with atrial
11 fibrillation ablation at this point with what we know to
12 think of it as an alternative to drug therapy. But the
13 scenario that you have, the patient is referred, they are
14 already on propafenone or something.

15 Then you have to decide that you really do want
16 them in that--do they and do you want to pursue ablation,
17 not necessarily force them to go onto another drug but to
18 use that period of time of observation on whatever.

19 DR. CURTIS: I don't think we have to worry so
20 much about changing drug therapy here because I think we are
21 going to expect that--the patients have to have failed
22 something. We are not going to take anybody who has never
23 been on drug therapy and to an atrial fibrillation ablation.

24 So they have to be having episodes on
25 antiarrhythmic drugs. Whether they are on antiarrhythmic

1 drugs today and having recurrences or they are not on them
2 today and having recurrences, I am not sure that really
3 matters so much.

4 The key thing is that, for a complete success
5 afterwards, it would be no more atrial fibrillation. And
6 then we could discuss about the issues about if it is now
7 controlled on propafenone whereas you were having
8 recurrences before--so I don't think that is so much of a
9 problem.

10 I think what I am having a hard time pinning down
11 in my own mind is how much of an observation period you need
12 altogether, how much of it must be prospective, how much of
13 it could be retrospective.

14 Let's say you had two perfectly well-documented
15 episodes of A-fib in the past three months. Do we still
16 have to wait and keep documenting on a patient?

17 DR. VETROVEC: I wouldn't have a problem with that
18 provided you didn't change therapy.

19 DR. CURTIS: One way of changing therapy, though,
20 would be they are on propafenone, I have got the documented
21 two episodes. I stop the drug, do my ablation and follow
22 them up like that.

23 DR. VETROVEC: Stop is one thing. I just don't
24 want you starting the drug and then ablating them and
25 keeping them on the drug and saying it is a success.

1 DR. CURTIS: No.

2 DR. VETROVEC: I just want to make sure we define
3 it that way.

4 DR. CURTIS: Sure.

5 DR. VETROVEC: Within three months, two episodes.
6 The other thing I would say is that if you want to have a
7 prospective period for those people that you haven't
8 documented it in, it is two episodes within three months.
9 But if they have their first two episodes in the first two
10 weeks, they have fulfilled it and you go to study.

11 It is just that it has to be within--it has to
12 have that kind of frequency to it.

13 DR. CURTIS: You need that kind of frequency
14 because the follow-up period is going to probably be
15 something like six months again. So you have to have
16 enough--or longer. But, certainly, you have to get yourself
17 an observation period that makes some sense for those kinds
18 of numbers.

19 At least two episodes documented within three
20 months, whether prospectively or retrospectively? Would
21 that work?

22 DR. VETROVEC: On stable drug therapy.

23 DR. CURTIS: On stable drug therapy. I don't have
24 a strong opinion about this.

25 DR. TRACY: I don't have a strong opinion either.

1 I just don't want to have a design set up where you can't
2 really know if you have made a difference. And that is the
3 advantage of a prospective three-month observational period.

4 I just think it is not like the VT density concept
5 where you have a device and you can just interrogate the
6 device and see how many therapies it has delivered. You
7 have to have some kind of way of documenting how many
8 episodes pre versus how many episodes post.

9 If you are very confident that you have captured
10 all the episodes--I don't know.

11 DR. CURTIS: I guess one of the values of--AFFIRM
12 was a little bit more liberal if you are saying six months.
13 But, there, you were trying to decide which kind of drug
14 therapy you were using. Here, it is going to be a catheter-
15 based system where there are risks associated with it.

16 So we want to try to get patients who have more
17 episodes. So demanding a little bit more frequency to allow
18 somebody into the trial would be good whether it is
19 retrospective or prospective.

20 DR. ABATI: This is Allan Abati from Cardima.
21 Getting back to the frequency issue, we find that there are
22 a lot of patients that have frequent episodes per day, per
23 week. They are easy to measure. Then, statistically, it
24 would be easier to measure an effect.

25 You could look at patients that have infrequent

1 episodes, once per month, twice per month, and so forth.
2 But they should be separated out as a separate group and
3 they are going to be fewer in number. And you are going to
4 look at them for a much longer period of time to get a
5 comparison of whether the treatment had an effect or not.

6 So I think we, at Cardima, are more interested in
7 the higher frequency patient group initially.

8 DR. CURTIS: What you have there is the tradeoff
9 between--if you have somebody with very frequent episodes,
10 it is going to be easy to measure a statistical effect but
11 it is going to be harder to find the patients to enroll
12 versus the tradeoff of enrolling lots of patients but then
13 having them have a longer follow up where it is more
14 difficult to tell what you have done.

15 DR. TRIEDMAN: John Triedman from Boston
16 Children's Hospital. We have looked at patients who have
17 atypical atrial tachycardia--

18 DR. CURTIS: Do you have any financial interest in
19 these products?

20 DR. TRIEDMAN: No. I have been sponsored for
21 research with Cordis Webster. We have done some research on
22 patients who have atypical atrial tachycardias after
23 congenital heart disease. In some ways, the measurement of
24 symptoms and recurrence of those tachycardias is not
25 dissimilar from atrial fibrillation in adult patients.

1 One of the problems that you have with taking a
2 retrospective baseline is you are making the presumption
3 that the frequency of your events is more or less constant.
4 One of the phenomena that we definitely observe in our
5 practice, and I think anybody will admit is true in their
6 practice, is that patients who have more symptoms come to
7 ablation when they have more symptoms.

8 There is very little data on fluctuation of event
9 frequency of these types of arrhythmias and the advantage of
10 having a prospective run-in period is that you are not going
11 to artificially elevate your estimation of the frequency of
12 occurrence by the fact that a patient presents to you or is
13 referred to you with a sudden increase in frequency of
14 symptoms or arrhythmia occurrences, you ablate them and
15 then, just by regression of the mean, many of those patients
16 will have a quiescent period afterwards.

17 By setting yourself back from the timing of their
18 ablation and forcing yourself to rigorously look, you can,
19 over your entire population, probably get a more accurate
20 sense of the true frequency of events you would like to
21 alter by your ablation.

22 DR. CURTIS: Any other comments on this? I think
23 it is hard to come up with one answer here that is the right
24 way to go on this. There are pros and cons to prospective
25 and retrospective analyses.

1 Retrospectively, you could get your patients into
2 the trial faster but it may be less reliable. A prospective
3 observation period for three months would be pretty strict.
4 I don't know.

5 Are there any other comments you want to hear
6 about this?

7 DR. PORTNOY: I think that there was a range of
8 ideas here and we will have to see what we can do with it
9 from here. But it didn't sound like there was a consensus
10 from the panel on this.

11 DR. CURTIS: Not really. I am having a hard time
12 coming up with one on this. There are different ways to go.
13 As the gentleman from Cardima said, you could opt for
14 somebody with lots of episodes of atrial fibrillation and it
15 is easy to tell what is happening. It is just that it is
16 going to be harder to find those patients.

17 So it depends on if you want to enroll lots of
18 patients quickly and go for infrequent episodes of atrial
19 fibrillation, then it is harder to make statistical sense
20 out of it and you have to follow them up longer. Or else
21 you can enrich your population by taking people who are
22 highly symptomatic and know you are going to look long and
23 hard for them. But then it is probably pretty easy to tell
24 what you have done with them.

25 So you may want to get some of the industry input

1 on that.

2 Let's go to No. 6, go backwards now. "If symptoms
3 are not monitored during a baseline period using Holter,
4 trans-telephonic, et cetera, how should ablation
5 effectiveness be defined? For example, could it be defined
6 as complete absence of arrhythmia in the acute and/or
7 chronic setting?"

8 What gets hard here, too, is we know patients have
9 little episodes of atrial fibrillation. How many of our
10 patients with PAF, if you would put a Holter on them, have
11 ten-beat runs and that sort of thing that they are not even
12 aware that they are having, and is that a success or not?

13 At what point do you decide that a patient has had
14 a recurrence of atrial fibrillation and how do we define
15 that?

16 I would not want it to be simply, as I said, a
17 Holter showing they had little runs of it because unless you
18 have really intensive monitoring ahead of time, you wouldn't
19 know the patients weren't doing--it is hard to make any
20 sense out of that.

21 I guess my first thought on this would be
22 symptomatic, something that a patient is aware of, calls in,
23 documents that they are having a recurrence, that would--

24 DR. SIMMONS: I think that is not the question.
25 We have already agreed, kind of, for this question, they

1 have to be monitored. We have to have documentation and we
2 wouldn't accept it otherwise.

3 I think they are talking about the baseline entry
4 criteria in that question.

5 DR. CURTIS: All right.

6 DR. SIMMONS: I think you were talking about
7 outcome criteria.

8 Did I misinterpret that?

9 DR. PORTNOY: No; you are correctly interpreting
10 it. And we are actually going to get to outcome measures
11 later on.

12 DR. SIMMONS: So we are saying we wouldn't accept
13 symptoms as an entry criteria. We want paper.

14 DR. CURTIS: Thank you.

15 No. 7 "Given what is known about the safety and
16 efficacy of current drug therapy and off-label use of RF-
17 ablation to treat A-fib, what is the appropriate patient
18 population for a study of an investigational ablation system
19 used to treat A-fib? For example, should patients who have
20 not previously been treated with antiarrhythmic medication
21 be included in the clinical study of an investigational
22 ablation system or do you have to have failed antiarrhythmic
23 drugs?"

24 I don't think anybody ought to be in who hasn't
25 tried medical therapy. It is too risky up front and we

1 don't know what the risks are to the patients. Failing
2 arrhythmic therapy, to me, means failing membrane-sensitive
3 antiarrhythmic drugs. Beta blockers alone or digoxin alone
4 is not antiarrhythmic therapy to me for atrial fibrillation.
5 I think they would have to have been on one of the 1C or 1A
6 drugs or amiodarone, sotalol, something like that.

7 DR. TRACY: I would agree with that completely.
8 We just don't know enough. We know that it is potentially a
9 very unsafe procedure so far as what we know, potentially.
10 We need to feel that there is a good justification for doing
11 this. Until we define exactly the safety and efficacy of
12 this, I think it should be reserved to after a patient has
13 failed antiarrhythmics--antiarrhythmic.

14 DR. CURTIS: I think they should have failed two
15 drugs. What does everybody else think?

16 DR. SIMMONS: I guess I would have accepted one.
17 I would rather they didn't go on the amiodarone, frankly,
18 because that is probably going to be the second drug most
19 people are going to pick. And then there are going to be
20 all those questions of when you stop it, when is it not
21 around anymore. I guess I would accept one.

22 DR. CURTIS: You would?

23 DR. TRACY: I think I would not accept one. I
24 think I would want more than one unless there is an absolute
25 contraindication, like a patient has some other--I don't

1 know, hepatic dysfunction or some reason they can't take
2 amiodarone or they can't take one drug or another.

3 Then I think you want them to be reasonable. But
4 there are the vicissitudes of amiodarone, but you can deal
5 with it. You continue observation long enough until you are
6 reasonably assured that amiodarone is no longer in the
7 system after an ablation.

8 DR. CURTIS: I guess I do have to rethink that. I
9 don't think people have to fail amiodarone in order to be
10 able to get an ablation because amiodarone does have
11 potential problems with it. And how many other choices do
12 we have?

13 You are talking sotalol right now, one of the 1Cs
14 or a 1A drug. I don't too many of us are that thrilled
15 about the way the 1As work anyway.

16 DR. TRACY: I think it would be probably not
17 unreasonable to say that you don't have to fail everything
18 including amiodarone. However, I think it would also be--I
19 wouldn't exclude somebody from the study because they had
20 been on amiodarone.

21 DR. CURTIS: I think that is true if they are
22 having recurrences.

23 DR. TRACY: I think that you should be allowed to
24 satisfy some definition of drug failure and that you should
25 be allowed to include amiodarone therapy in drug therapy

1 that the patient can have received.

2 So just being concerned that you are not going to
3 know when it is out of the body and when you have to start
4 worrying about recurrences because of drug withdrawal versus
5 failure to the therapy, that is not enough reason to exclude
6 patients who have previously received amiodarone because, in
7 fact, many patients who currently are referred for things
8 like the MAZE procedure or AV node ablation and implantation
9 of permanent pacemaker are people who have already failed
10 amiodarone.

11 It is, in many places, the first-line therapy for
12 atrial fibrillation that we feel needs to be treated by
13 antiarrhythmic therapy. So I don't think it is necessary
14 that you failed it, but I also think I would not exclude it.
15 Because it does muddy the waters a bit, I wouldn't exclude
16 it.

17 DR. SIMMONS: I guess the question would be if you
18 get referred a patient who has already failed quinidine, are
19 you going to make them fail procaine amide. Or are you
20 going to make them fail Rhythmol or propafenone?

21 DR. CURTIS: Maybe we should.

22 DR. TRACY: Yes.

23 DR. SIMMONS: You think they should fail two
24 drugs.

25 DR. CURTIS: Maybe they should because, again,

1 this is a potentially risk procedure. We don't know what
2 potential complications are going to be. Is that so
3 unreasonable to say that they would have to fail a second
4 drug?

5 I think if you fail one--if you fail flecainide, I
6 don't see a real reason to go to propafenone, that that is
7 going to help anything. I also agree, though, that as some
8 patients get put on amiodarone right up front because they,
9 let's say, have poor LV function.

10 I think if you fail amiodarone, I think that would
11 be good enough. I don't think I would backtrack and say,
12 "Well, I am now going to try my quinidine."

13 DR. TRACY: That is good point. If you have used
14 first amiodarone on the other line, then--it probably should
15 be failing two antiarrhythmics if one of them is not
16 amiodarone, or failing amiodarone therapy.

17 DR. VETROVEC: Failed or couldn't tolerate.

18 DR. CURTIS: Or couldn't tolerate. That would be
19 reasonable, too.

20 DR. SIMMONS: I just have low faith that if they
21 failed propafenone putting them on quinidine is going to be
22 successful, that they are going to tolerate or that there is
23 going to be long-term success. I just have a low faith.

24 DR. CURTIS: I do agree with you that if you
25 failed something that sounds good to you and your next line

1 of therapy would normally be amiodarone, that you don't
2 really want to have to do that instead of being able to
3 ablate.

4 DR. WHARTON: I just want to make one point of
5 clarification because when we talk about A-fib ablations, it
6 gets somewhat more complex nowadays if you start breaking
7 down atrial fibrillation by different potential mechanisms.

8 Up until this point, we have been talking,
9 basically, about atrial fibrillation very generically. We
10 have been talking about MAZE-type procedure, be it right or
11 left atrial. I just want to make the point of clarification
12 that if we also talk about ablation procedures for atrial
13 fibrillation for focal atrial fibrillation that some of the
14 inclusion criteria that have been made up to this point may
15 not be applicable to that group, in particular, how many
16 antiarrhythmic drugs you are going to make them fail before
17 you take them for focal ablation.

18 Focal ablation and the issues of risk and
19 complications may be dramatically less. I just wanted to
20 make that point of clarification.

21 DR. SIMMONS: It also would make a big difference
22 in what kinds of catheters you would be using. If you have
23 had them enrolled in some sort of linear ablation protocol
24 and you ended up with a focal lesion, then they would drop
25 out of the protocol; right? You wouldn't give that linear

1 lesion just to be--

2 DR. WHARTON: I didn't want to bring this up at
3 this point but one of the issues that is going to have to
4 made clear as you start designing protocols, and this came
5 up actually with some of Dr. Haissaguerre's work with right-
6 sided linear lesions, but you have to define what you are
7 doing.

8 In Dr. Haissaguerre's work, when they did a
9 multivariate analysis of what predicted success from a
10 right-sided-only procedure, it was who had a focal fib
11 ablation which raises the issue that it wasn't the right-
12 sided lesioning at all. It was the focal-fib ablation that
13 was the success.

14 So, again, that is another issue in terms of
15 outcomes and procedural methodology. At this juncture,
16 though, I just want to make sure that FDA is clear that
17 there are different types of fib ablation potentially that
18 you are going to be presented protocols for, and they may
19 not have the same protocol designs or the same type of
20 inclusion criteria applicable, the two types, or three
21 types.

22 DR. CURTIS: Let's move on to the indications for
23 use, No. 9. "How should the patient selection criteria
24 impact the labeling indications for the study? For example,
25 if the sponsor chooses to enroll only patients with one type

1 of A-fib--for example, paroxysmal--should the labeling
2 include only the type of A-fib treated in the study, include
3 other frequencies of atrial fibrillation--that is,
4 persistent and/or chronic--or not specify the type of A-fib
5 and the indications for use but describe the study in the
6 clinical trials section?"

7 DR. TRACY: I think the point that Dr. Wharton
8 raised that focal A-fib is probably very different from
9 either chronic or persistent or even paroxysmal--so I think
10 if you are doing a study for focal fib ablation that that is
11 going to end up with a different outcome and is going to end
12 up with a different labeling.

13 But if you are doing ablation and you have
14 included a variety of frequencies and presentations, episode
15 duration, et cetera, I don't think that you need to get very
16 specific in the labeling but you do need to describe the
17 types of patients that were actually enrolled in the study.

18 DR. CURTIS: There is a good likelihood that
19 chronic A-fib may be excluded. We don't know. If it is,
20 then should there be some statement when the labeling comes
21 out that patients that we don't have any data on, patients
22 with chronic A-fib, we probably would say that. That would
23 be pretty typical.

24 DR. SIMMONS: But it may not have to be in the
25 indications section. You could put it in the

1 individualization-of-patient section. Just in the
2 indications could be that the A-fib was treated and was
3 shown to be effective, but in the other subsection say, "The
4 only patient study were patients with paroxysmal and it is
5 unknown whether the results or complications would be
6 different in chronic."

7 DR. TRACY: I don't want to be sitting here, or
8 have another group sitting here in five years, debating
9 about, "Well, if only we could go back now retrospectively
10 and approve this catheter for this chronic atrial
11 fibrillation." I don't want to be there in the future, so I
12 think this is a good time to think about it.

13 I guess that is why you are bringing this up. I
14 think not being that specific, except for probably the very
15 different entity that Dr. Wharton was talking about, the
16 focal atrial fibrillation.

17 I think, other than that, I wouldn't be all that
18 specific in the indications but would be very clear in the
19 description somewhere in the patient cohort, or whatever.

20 DR. VETROVEC: But, remember, you are always
21 trying to gather extra scientific data and if you make it
22 easy to get--not easy, but you make it so that one can get a
23 broad indication with a fairly limited study, you will never
24 have any data on the more complicated circumstances.

25 DR. TRACY: I would imagine that these studies

1 will include not only paroxysmal A-fib but the patient who
2 is, by definition, persistent; in other words, needs to be
3 cardioverted to get out of an individual episode but is not
4 chronically in A-fib.

5 So think almost however you do it, you are going
6 to wind up having data on those two. What you may or may
7 not have data on is what happens to somebody who has been in
8 chronic A-fib and, if they are not included in the studies,
9 you don't know what kind of outcomes to expect.

10 In this case, then, if you have good results for
11 somebody with paroxysmal atrial fibrillation, I don't think
12 you can extrapolate and say, "I would have just as good a
13 result with a chronic A-fib if I did the ablation." You
14 don't know that. It is a supposition.

15 So you wouldn't be able to make the claim. You
16 would have to possibly specify it or describe it in the
17 clinical-trials section. But I think if you want to say
18 that, "If I do linear ablations for chronic A-fib, I am
19 going to keep people in sinus rhythm," that has to be
20 demonstrated. You can't just make the assumption one from
21 the other.

22 DR. TRACY: I think that there is the issue of
23 acute procedure and then there is the issue of follow up.
24 And then there is the whole definition problem of if I just
25 don't do something about the person with persistent

1 episodes, they, before long, become chronic.

2 So there is a lot of gray zone in there. But I
3 think the point is well taken that if you are not fairly
4 rigorous ahead of time, you are not going to end up with
5 information on the more difficult situations. But I still
6 think that there is a lot of gray zone in atrial
7 fibrillation and forcing somebody to not treat so that they
8 can say that now this person is chronic doesn't make sense
9 to me either.

10 I think we would be better served by setting the
11 study up carefully ahead of time but not being unbelievably
12 specific in the indications, if that makes any sense.

13 DR. SCHWARTZMAN: I am a little confused and I
14 wanted to kind of get the pulse of the panel. Are you
15 tending towards excluding patients with chronic atrial
16 fibrillation defined as those with pharmacologic or direct
17 current cardioversion attempts cannot hold sinus rhythm for
18 a period of time?

19 DR. CURTIS: No; I don't think there is any reason
20 to exclude them from the studies if the sponsors want to put
21 them in. That is no problem. We are just saying that if
22 they were not any part of the study then you can't a claim
23 that it works for that condition.

24 DR. PORTNOY: Just before we go on, I am hearing
25 consensus that option No. 3, at a minimum--let's say chronic

1 A-fib patients aren't included so somewhere it would say,
2 "There is no data on this."

3 DR. CURTIS: That's right.

4 DR. PORTNOY: But then what about the indications?
5 Can you comment? Do you think it should just say A-fib or
6 should it, as in options A and B, get more specific in the
7 indications for use?

8 Yesterday, we talked about VT and it said, it was
9 ischemic or from dilated cardiomyopathy. So it got very
10 specific there what was the etiology. This is somewhat
11 similar. Should it actually say persistent paroxysmal, et
12 cetera?

13 DR. SIMMONS: Do you want the indication to say,
14 "This device is intended for the use in patients with
15 paroxysmal and/or persistent atrial fibrillation?"

16 DR. CURTIS: What do you think?

17 DR. SIMMONS: Or do you want it to just say atrial
18 fibrillation? I think the definitions are so vague for
19 atrial fibrillation in the first place that, at this point
20 in time, to make that kind of a black-and-white decision is
21 asking a lot.

22 Patients sort of go between persistent and
23 paroxysmal and, on a drug, they were chronic--

24 MS. FLEISCHER: What about defining it, instead of
25 paroxysmal, persistent and chronic, as number of episodes?

1 I think that is what we were trying to get at instead of--

2 DR. CURTIS: I don't think I would do that because
3 I think what is going to happen if you are going to have
4 different definitions of how many episodes and that sort of
5 thing.

6 Maybe it would be best to just say it is indicated
7 for the cure of atrial fibrillation and then be specific in
8 your clinical trials saying what patients were studied and
9 which ones were not.

10 DR. TRACY: You can envision, however, a totally
11 different type of catheter that you would use for focal
12 ablation as compared to a persistent or a paroxysmal or
13 chronic. So, if the only patient where that catheter or
14 that delivery system has been studied is the focals, well,
15 then, that is what the indication states very specifically.

16 But, other than that, you get into these gray
17 zones so tremendously that I think you can't be too terribly
18 specific. I think there is going to end up being a lot of
19 considerations that this has not been studied in the
20 presence of whatever, valvular heart disease or whatever the
21 exclusions are at the time that the study is set up.

22 Those will be listed as situations that have not
23 been studied, whatever that would turn out to be. But I
24 think to very clearly state in whom the device has been
25 tested is probably reasonable.

1 DR. HALL: Jeff Hall, Guidant Corporation. A
2 point for your consideration, though. If you exclude your
3 dilated atria and your chronic patients, that is a different
4 catheter in size and shape than your other patients. So I
5 think that is an important consideration in your
6 indications.

7 DR. CURTIS: I don't think any of us are saying
8 that those patients have to be excluded from trials. They
9 could be included easily. It is just that if you don't have
10 them in there, then it is hard to make an assessment as to
11 how well it would work in patient populations like that.

12 DR. AZIZ: Can I just sort of interject? I know
13 you are basically talking from the catheter point of view.
14 In most institutions, particularly a university like
15 Georgetown where you have surgeons that also do the MAZE
16 procedure, if a patient came to you, you would offer them as
17 an arm of therapy surgical intervention?

18 DR. TRACY: Having the luxury of having a surgeon
19 who does this on site, I would offer them. I don't think
20 that this would--at this point, it certainly doesn't replace
21 the MAZE procedure and, yes, I would continue to offer them
22 MAZE if I felt that they merited going on to that type of
23 procedure but I think there would be still a place for doing
24 a study like this even in an institution where you do have a
25 surgeon available.

1 I suppose, in fact, it might be a reasonable
2 knowledge for an investigator to have that there is a
3 surgeon available who can perform a MAZE procedure if the
4 catheter procedure didn't work.

5 DR. AZIZ: Your results could be compared to a
6 surgical approach.

7 DR. TRACY: Well, it could but I don't think that
8 that is true in every center.

9 DR. CURTIS: Let's move on to the next question.
10 "How should acute success be clinically determined? For
11 example, is it appropriate to assess acute success as
12 noninducibility of A-fib post-ablation?

13 I would imagine if you could still induce atrial
14 fibrillation at the end of your procedure, it would be hard
15 to define that as a success.

16 DR. TRACY: I think what you see in the lab is not
17 necessarily going to be predictive of what you see. There
18 is just so little that is known about what atrial-
19 fibrillation ablation is. Even with the MAZE procedure, we
20 have been seeing people out months later in sinus rhythm--to
21 see them come up with atrial-stuff rhythm that they come out
22 of the OR with that becomes sinus rhythm and maintains a
23 sinus rhythm.

24 I know that when the patient rolls out from the
25 OR, I cannot predict, on the basis of what I see at that

1 moment, what is going to happen six months down the road. I
2 am betting that it is going to be the same scenario with
3 atrial-fibrillation ablation that we can't predict on the
4 basis of what is seen.

5 I don't think we know enough about whether lesions
6 have to be transmural, whether they have to be contiguous.
7 I don't think we know enough even to put--I think we are in
8 an observational period where we just have to figure out
9 what it is that we want to look at and then use clinical
10 follow up.

11 I don't think that inducibility of atrial crap is
12 an appropriate--or noninducibility of some non-specific
13 stuff--is an endpoint that I would insist on.

14 DR. CURTIS: I might mention Cardima's response to
15 this question. "We believe that noninducibility of A-fib
16 during an EP study doesn't mean that treatment is
17 successful." There may be a typo in here. I am just going
18 to read it the way it says. "And if the A-fib can be
19 induced, this can't necessarily be extrapolated to later
20 success.

21 "Furthermore, patients are very uncomfortable
22 during this kind of procedure and cardioversion, which may
23 be required multiple times, should not be conducted. Thus
24 it is felt that there is inadequate evidence that this is an
25 appropriate indicator. Other indicators may be explored

1 such as the appearance of split potentials and changes of
2 signal amplitude or pacing thresholds."

3 I think the bottom line here is that, as opposed
4 to flutter where we know that if you get bidirectional
5 block, you are not going to have a problem, we have no idea
6 what the right endpoint for this is.

7 So I think it is true that if you can't induce A-
8 fib acutely, that doesn't necessarily mean that is going to
9 translate to a long-term success. So what does that tell
10 you?

11 On the other hand, if you can induce it acutely,
12 does that mean it is not going to work over the long haul
13 without the stress that you are putting on the system by
14 doing the program stimulation. I don't know the answer to
15 that either.

16 The business of appearance of split potentials and
17 changes in signal amplitude, you are talking about this in
18 multiple locations in the heart because these are multiple
19 linear lesions. So how you would assess that, I am not
20 sure.

21 One way I know people are exploring looking at
22 this would be to create the linear lesions and have some way
23 of looking at it as to whether or not it appears to be a
24 complete line of block or not. I think acute
25 noninducibility of atrial fibrillation--I don't know what it

1 tells us. I really don't know if that is going to be a
2 helpful sign.

3 DR. VETROVEC: I agree with everything you said.
4 The other thing is that it might, in some way, bias
5 decision-making about adjuvant drug therapy which wouldn't
6 be bad but, unless you control that prospectively, it might
7 muddle your data later if people said, "Oh, well; we didn't
8 get as good a result here so we are going to leave them on
9 X."

10 That might influence things but it wouldn't be
11 perfect and so then it would get confusing.

12 DR. CURTIS: I guess the question is how do you
13 know when to leave the lab? How do you know when you have
14 done enough, got a good enough result, or you think that you
15 can stop and you are going to say, "Well, now I am going to
16 see if my patient is cured."

17 DR. SIMMONS: It is going to depend on what kind
18 of catheter they brought. If they bring some basket barbed-
19 wire thing that you put the pulse through and you take it
20 out and you are done, then that is the end of the procedure.
21 But if they are asking you to do something anatomical that
22 is descriptive, maybe repetitive fluoro-images or something.

23 The study is yet to be defined. We can't answer
24 that question. Nobody has brought forward anything for us
25 to look at.

1 DR. CURTIS: That's right. I don't think there is
2 an acute outcome that you can say is the gold standard that
3 people are going to have to adhere to in order to know
4 whether the procedure works. Maybe none of those are
5 important. I don't know.

6 I would imagine each company designing a study is
7 going to want some goals to come out of the lab with and it
8 may be inducibility or not. I think the gold standard still
9 here is going to be whether patients suffer symptomatic
10 recurrences. With some of these studies, we may learn what
11 matters more.

12 If one company goes for noninducibility and that
13 helps or doesn't help and another one goes for evidence of
14 block with linear lesions and that helps, that would give
15 you some answers there. But there isn't anything in the
16 literature that tells us what the right answer to this is
17 right now.

18 You have to say that we don't know that
19 inducibility or noninducibility at the end of the procedure
20 is going to make a difference.

21 Is everybody okay with pushing on right here? All
22 right. No. 11. "How should chronic success be clinically
23 determined? For example, are any of the following endpoints
24 appropriate to define chronic success and you can choose
25 more than one: absence of A-fib for the first Y months;

1 increased time to first recurrence of A-fib; percent
2 decrease in frequency of symptomatic episodes over so much
3 time; percent decrease in frequency of symptomatic episodes
4 while the patient is on antiarrhythmic drug therapy; or
5 improved quality of life?"

6 I think increased time to first recurrence of
7 atrial fibrillation isn't particularly helpful. Absence of
8 atrial fibrillation for a period of time would be wonderful.
9 That would probably be your best answer, that if a patient
10 has absolutely A-fib for whatever your follow-up period is,
11 you have got a success. Nobody would argue with that.

12 I think quality of life would be interesting. I
13 don't think that that is going to tell you any answers as to
14 whether or not the procedure works. So you have got one
15 extreme which is that the patient has no recurrence of A-fib
16 over, say, six months after the procedure. That would be
17 great. That is a success. Nobody would argue with that.

18 The question is if somebody starts having any
19 kinds of recurrences, what is a partial success, what is
20 better. I am not sure.

21 DR. SCHWARTZMAN: I would like to bring up an
22 observation here that was actually first observed by the
23 surgeons, recapitulated in animal models related to catheter
24 ablation and since observed, in my experience, with right-
25 sided linear ablation, and that is the concept of delayed

1 gratification with respect to AF ablation.

2 If you watch what is happening to the atria when
3 you ablate the bejeezus out of them, which is what we are
4 doing, they swell like crazy. If you look at potentials
5 away from the linear lesion, there is effect if you simply
6 measure amplitude at a great distance.

7 So there is a huge amount of inflammation that
8 goes on, an evolutionary period, just like you made an
9 incision in the atrium. So this concept of looking
10 immediately after the procedure, in terms of time to first
11 recurrence, frequency of recurrence, et cetera, I think is
12 going to artificially make the procedure look less
13 attractive.

14 So what we built into our study and what I would
15 remind the panel of is the need for a blanking period, if
16 you will, a time between the actual ablation and the
17 beginning of clinical assessment because, as I said, for
18 many of the procedures, both human and animal, efficacy is
19 really demonstrable only down the road.

20 DR. TRACY: I think that is absolutely true. I
21 think that when you are looking at--you can even see atrial
22 fibrillation following a successful MAZE procedure with a
23 very rapid ventricular response. You get a real short, real
24 rapid, atrial activity, very tiny circuit within the MAZE.

25 So the measurement of the acute success is going

1 to be difficult. It is what happens down the road after
2 inflammation and healing has taken place that is going to be
3 more important. I have put in pacemakers and some of the
4 people who have the MAZE procedure because of either
5 underlying sinus-node dysfunction predating--that led to the
6 atrial fibrillation, I know that the p-wave amplitudes, when
7 I first put the pacemaker in, are very, very tiny.

8 And I know that when I do the check, the chronic
9 check, a couple of months down the road, the p-wave
10 amplitude is perfectly fine. So I know that there is a
11 period of time that it is going to take for healing to take
12 place, so I think that the definitions that we use for
13 determining success are going to have to be a little bit
14 broader than we are comfortable with for other forms of SVT.

15 I think that improved quality of life may be a
16 very important outcome. It is not a concrete thing but,
17 from the patient's standpoint, it is really what counts. In
18 a disease, once again, that we are not doing this for
19 longevity but we are doing this for palliation, that is
20 really the bottom line.

21 Are we really providing a service to these
22 patients? We are not making them live longer. We can't be
23 under the illusion that we are. I think that yes, sure, if
24 you get past this healing phase and then you never have A-
25 fib again, well, absolutely, that is a very excellent

1 outcome, excellent success.

2 But to have less frequent episodes or greater time
3 between episodes or better control on antiarrhythmics, all
4 of those, I think, are viable endpoints for this.

5 DR. CURTIS: What kind of a blanking period do we
6 need? What period of time would you wait before you started
7 to assess a patient?

8 DR. TRACY: I can't answer that.

9 DR. CURTIS: You would have to have experience
10 with the MAZE procedure or with the right-sided ablation, I
11 think, to know what is appropriate there.

12 DR. TRACY: For surgery, I would say it would be
13 really a couple of months before things seemed to be pretty
14 much steady-state.

15 DR. SCHWARTZMAN: I think if you depend on
16 pathological data, based on animal models--we have looked at
17 lesion evolution and swelling, echocardiographic,
18 demonstrable swelling related to linear lesions over a
19 period of up to 110 days.

20 By six weeks, in healthy animals, the swelling is
21 gone related to the lesion and in the periphery. The r-wave
22 amplitudes unrelated to the lesion have returned to
23 baseline. And the lesion histology, itself, is largely
24 collagenous. There is very little chronic inflammation
25 left.

1 So what we have built into our clinical study was
2 at least a month, assuming that the human condition is
3 similar which is somewhat of a leap.

4 DR. TRACY: That would kind of go along with the
5 clinical experience that we have had with pacemakers in
6 these patients where you really do see a very distinct
7 change in p-wave amplitude after a couple of months.

8 DR. CURTIS: So at least a month after the
9 procedure. You would have to wait or blank it out before
10 you could make an assessment about the long-term success
11 rate of it.

12 The issue comes in--we said black and white, if
13 you never have any more A-fib, that is just wonderful. But
14 what about the patients who have some and what is an
15 improvement. Certainly, if you wind up having to put the
16 patient back on an antiarrhythmic drug, that tells you
17 something.

18 Putting them back on an antiarrhythmic drug is
19 either a failure or a partial success depending, I suppose,
20 on what they do after that. That would be one thing that we
21 would have to consider.

22 The issue came up before about regression to the
23 mean, too. If you have somebody who has got a lot of
24 frequent episodes and if you could, somehow, do a sham
25 procedure, some of them are not going to have a lot of

1 episodes afterwards either, even if you didn't do anything.
2 So you have to be careful.

3 It may be a little bit like counting PBCs. We
4 know that, in patients who have a lot of PBCs, if you want
5 to assume or know that a drug is effective, you have to
6 really knock them down to a very low rate in order to be
7 sure that the drug is having the effect and that it is not
8 just random variation.

9 There may be something to that here, too. Again,
10 picking numbers and saying what percent decrease over what
11 period of time is going to be good enough is, I think, very
12 hard to say.

13 DR. SIMMONS: There are certainly no data. You
14 are just going to be making a judgment.

15 DR. CURTIS: It is just a plan that you are
16 making. I think if you have to resume antiarrhythmic drugs,
17 I guess you either have a complete success--you have a
18 patient have a recurrence but then you put them on
19 antiarrhythmic drugs and nothing else happens, that would be
20 a partial success because they are now controlled whereas
21 they weren't.

22 Or you put them on antiarrhythmic drugs and they
23 are still having episodes. You may be splitting hairs to
24 say whether that is a partial success because they are
25 having less than they used to or you just downright call it

1 a failure because you went through an ablation therapy and
2 you still have episodes.

3 I think it would be awfully hard to figure out how
4 you were going to finagle saying that, "Well, they had two
5 episodes in the three months before they started but they
6 only had one in six now on my drug and so, therefore, I have
7 got a partial success." I think that would be hard to say.

8 DR. TRACY: Some of the literature is reporting
9 that as partial success. I agree. It is another one of the
10 ambiguities of this whole thing, when does it slide from a
11 partial success to a failure.

12 DR. PORTNOY: If a patient is having fairly
13 frequent symptoms so we have some good data, which number
14 would you be more comfortable with for c., for example, a 50
15 percent decrease in frequency or a 75 percent decrease in
16 frequency, just to give us sense for what do you think is
17 clinically relevant.

18 DR. TRACY: At least 75 percent, I would say. You
19 have to demonstrate a very significant decrease.

20 DR. CURTIS: Probably something like that.

21 DR. SIMMONS: I would go for 75, too.

22 DR. VETROVEC: I have some trouble with b.,
23 though, increased time to first recurrence of atrial fib.
24 Since we are not going to have very good baseline data no
25 matter how hard we try, that number is going to be a very

1 funny number.

2 DR. CURTIS: I don't like that either. I don't
3 think that should be an endpoint.

4 I think that gives you some ballpark as to how we
5 are thinking about this.

6 No. 12. "To what extent would the risk/benefit
7 analysis and labeling claims be affected by the choice of
8 endpoints as defined above? If a patient acts as his own
9 control, what is the percent reduction in frequency of
10 symptomatic episodes that is clinically relevant?"

11 I think we just answered that.

12 No. 13. "What is an appropriate follow-up period
13 for evaluating recurrences of arrhythmias to be used in
14 assessing the chronic performance of the investigational
15 ablation system; three months, six months, one year or
16 something else?"

17 Minimum, six months?

18 DR. TRACY: Longer.

19 DR. SIMMONS: Longer, I think.

20 DR. TRACY: A year. After the blanking period.
21 Twenty years.

22 DR. CURTIS: Then it won't come before the panel
23 while we are on it. There is the thought about making it
24 longer than we were talking about for flutter.

25 DR. WHARTON: I just want to say one thing about

1 this blanking period. I don't argue at all about the
2 blanking period but just, again, for clarification, I would
3 still argue I think as we develop newer technologies for
4 atrial ablation that we record data during that.

5 When you say blanking period, to me, that sounds
6 too much like a pacemaker. That means we just close our
7 eyes and don't see what happens to the patient during that
8 period. But I would still be obtaining data in terms of A-
9 fib recurrences because newer technologies may have less of
10 a blanking period or not cause all this edema and swelling.

11 So, again, just a point of clarification.

12 DR. CURTIS: Excellent point.

13 DR. SIMMONS: I think you could actually make a
14 case to say that these people really ought to all be
15 provided with loop monitors. They go home with him. All
16 these people are going to have PACs and palpitations and
17 indigestion--not a Holter where they have to keep it on all
18 the time but some sort of a loop monitor.

19 DR. CURTIS: Does either of you want to support
20 the one-year--

21 DR. SIMMONS: Oh, yes; I support a year.

22 DR. CURTIS: Do you want to give some reasons for
23 it or justification?

24 DR. SIMMONS: Actually, you are talking about a
25 long-term cure. As we said before, these things go up and

1 down. You may see patients who have flurries of atrial fib
2 just like you see people who have flurries of VT. So I
3 think following them for a year, at a minimum, is
4 reasonable.

5 DR. WHARTON: Can I bring up another issue, and
6 this is a tougher issue and it is more just food for
7 thought. The other thing that has to be considered here--we
8 are talking about symptomatic episodes and we are talking
9 about event monitoring, recording, trying to determine
10 arrhythmia density pre- and post-procedure.

11 But one of the things these procedures have a
12 great capability for doing is basically slowing the rate so
13 that the patient doesn't know when they are in A-fib. I
14 think it is a big issue because all of us are looking at
15 this as a potential way to cure A-fib and hopefully get
16 people off Coumadin in the long term, stuff like that.

17 But the problem is if we are making them have
18 asymptomatic A-fib, you maybe make them feel better, improve
19 the quality of life, but the risk of stroke may not be
20 reduced. So we talk about event monitoring, but I think we
21 are going to have to impose in there somewhere along the
22 line monitoring for asymptomatic arrhythmia. So there is
23 going to be some degree of Holter monitoring during this
24 one-year period of follow up.

25 DR. TRACY: I think that is a good point. As the

1 study designs are considered, it might be reasonable for the
2 patients all to have trans-telephonic monitors that they go
3 home with and, for the first twelve weeks, they transmit at
4 least two strips daily or one strip daily.

5 I think that is very reasonable since we really
6 don't know how this is going to turn out, to really try to
7 get as much information about what is going on as you
8 possibly can. I think, in terms of justifying the one year,
9 again, it is a bit of a moving target even as V-tach is a
10 moving target.

11 The milieu changes. The substrate changes. What
12 are we doing? I think we just need to follow it for as long
13 as is practical. I know it is a burden on industry but that
14 is too bad because, again, we are doing something to treat
15 symptoms and we are not doing something to make people live
16 longer and we want to be sure that we are not making silent
17 A-fib that is going to cause strokes and harm people.

18 So we have to satisfy ourselves to the community
19 very carefully that we are doing the right thing here.

20 DR. SIMMONS: As long as you are up there, Marcus,
21 what do you think?

22 DR. WHARTON: About?

23 DR. SIMMONS: Long-term follow up. Six months? A
24 year? Two years?

25 DR. WHARTON: I think long-term follow up always

1 kind of rests upon the density of the patient population you
2 include. So if you do a Pritchett-type patient where they
3 are having high density in a month is defined two to four
4 episodes in a month, then the follow up is shorter.

5 If you take people who have one episode every six
6 months, then the follow up is longer. So follow up is
7 somewhat dependent upon what your initial patient population
8 is. But at least six months for high-density arrhythmias
9 and, if it is a lower density, then a year, minimum.

10 DR. CURTIS: I like that approach because that
11 gets back to what we were talking about earlier about what
12 kinds of patients you elect to put into the study. If you
13 deliberately go after patients on very high-density A-fib, I
14 think you can make an assessment in less than a year whether
15 or not you have had an impact on that.

16 DR. WHARTON: I think particularly the high-
17 density arrhythmias--I don't think we have good data, or we
18 have less well-studied data, for the lower density. But Ed
19 Pritchett's model of A-fib, which is kind of a standard now
20 for the pharmaceutical industry, is two episodes of A-fib in
21 a month. And there is good control data in terms of what
22 the recurrence rates are for that patient population, again
23 a relatively healthy people population.

24 So if you use that type of model, I think, again,
25 you can shorten down your follow-up period and have a pretty

1 good previous control population to show that you should
2 have picked up most of those patients who are going to have
3 recurrences if they had gone untreated.

4 DR. SIMMONS: Since you brought it up, and it is a
5 little off the topic, but in the follow-up period, are we
6 going to want these people to have TEEs? Just because we
7 don't see atrial fib, have we actually increased or
8 decreased their propensity to intramural thrombi. Should
9 they have a TEE at some point in time to make sure that we
10 haven't actually increased their risk of thrombotic events?

11 DR. WHARTON: I don't feel strongly about that for
12 right-sided only procedures. But as we start getting to
13 left atrial procedures, and this is something that has also
14 not come up today, we are going to have to come to some, I
15 think, relatively good criteria of how we are assessing
16 left-atrial transport function because there is no data that
17 is any good, at least in the literature in the present time,
18 that says what left-atrial transport is, be it after a
19 surgical MAZE procedure or a catheter MAZE procedure.

20 That is another big issue in terms of the
21 stroke. We may be rendering all these people in sinus
22 rhythm but if the left atrium is non-functional, their
23 embolic risk may still be unchanged in the long term, so I
24 am not sure we are serving any function or purpose in that
25 situation.

1 So TEEs, if we assume that is the best way to
2 assess left-atrial transport function, which, from what I
3 understand probably is at this point in time, may be an
4 important portion of the assessment in the long-term follow
5 up on these patients.

6 I know there is some data which will be coming out
7 of Australia looking at left-atrial transport after MAZE
8 procedures done by catheter techniques but in the operating
9 room. It is going to show that left-atrial transport is
10 probably reduced about 50 percent.

11 DR. SIMMONS: There is a real small study using
12 MRI which was published--

13 DR. WHARTON: Where was that?

14 DR. SIMMONS: Oh, boy. My name is even on it.

15 DR. WHARTON: Anyway, it is just another issue to
16 address.

17 DR. DeCARLO: I would like to make a comment
18 regarding the stroke issue in silent atrial fibrillation. I
19 would like us to keep in mind that everything is critically
20 dependent upon why you are doing the procedure in the first
21 place. If the patient is being brought to us for
22 symptomatic atrial fibrillation, the primary endpoint really
23 needs to be whether there is a recurrence of symptomatic
24 atrial fibrillation.

25 The patient will not have come to us, necessarily,

1 with a large amount of information regarding asymptomatic
2 atrial fibrillation, and the goal of the procedure is not to
3 reduce stroke risk, it is to reduce symptoms related to
4 atrial fibrillation.

5 If we want to make a claim for stroke risk, that,
6 to me, is a separate endpoint that needs to be considered.
7 Otherwise, it is simply a complication that, understandably,
8 needs to be followed.

9 DR. WHARTON: The thing about that is if we render
10 a person noninducible, the assumption is going to be made by
11 the practicing physician that they can stop Coumadin. That
12 is one of the big issues about this whole thing about
13 symptomatic A-fib anyway. We can render most people
14 asymptomatic of drugs or HIS ablation, if you want to make
15 them asymptomatic.

16 The bigger issue is, can I do something that would
17 allow me to take Coumadin off with all of the sort of
18 associated morbidity with that and the cost of monitoring
19 anticoagulation. So I think that, as we look at these
20 procedures, as we start looking at these procedures as
21 curative procedures and not palliative procedures, we are
22 going to have to look very closely at what we are doing to
23 atrial-transport function and emboli risk.

24 DR. TRACY: I couldn't agree more. We really have
25 to understand why we are doing this in the first place.

1 Right now, there is such an unknown thing to me--I am a real
2 skeptic. I don't know why we are talking about this whole
3 thing in the first place, anyway. Still, you are talking
4 about an entity where the prognosis is defined by the
5 underlying cardiac condition so anything we have been doing
6 so far for patients with atrial fibrillation has been to
7 make them symptom free.

8 We are opening up the question now of are we going
9 to make them better--are we going to reduce their risk of
10 stroke further by doing an ablation or a MAZE procedure than
11 we would reduce the risk of stroke by adequately and
12 appropriately anticoagulating patients at risk for stroke in
13 the first place.

14 We would have to go a long way before I would be
15 convinced that we are achieving better than what we can do
16 with Coumadin therapy. So why are we doing this in the
17 first place? I don't know, but I sure know that I don't
18 want this to be done and to have anybody made worse, to
19 increase their risk of stroke by not knowing about the
20 silent episodes of atrial fibrillation that are occurring,
21 by not realizing that atrial transport still is depressed,
22 by inappropriately discontinuing Coumadin therapy sooner
23 than it should be done.

24 So I think there are still just, to me, a lot
25 unknown about what exactly it is that we hope to accomplish.

1 I think it is not unreasonable to provide a patient with a
2 palliative procedure but, at this point, we really have
3 nothing more--we can't claim anything more than we probably
4 are going to palliate them at this point. We can't.

5 DR. WHARTON: If we palliate them, make them
6 asymptomatic, but they still have the same risk of stroke,
7 that is no different than just doing a HIS ablation which is
8 a lot simpler and not going to the associated with the
9 procedural morbidity that is going to be associated with
10 left-sided procedures.

11 DR. TRACY: Right. But there are the rare
12 patients whom we have done HIS ablations on who still remain
13 symptomatic from loss of atrial synchrony who do go on to a
14 MAZE procedure. So a lot still is unknown about this whole
15 area.k

16 DR. DeCARLO: I am going to respectfully disagree
17 about the stroke issue. The purpose of the procedure is to
18 resolve and relieve symptoms related to atrial fibrillation.
19 The patient came to you with symptoms, not with a stroke.
20 Yes; atrial fibrillation does represent a stroke risk.
21 However, the claim is that this procedure is going to
22 prevent your symptoms, palpitations, shortness of breath,
23 syncope, whatever it may be, related to your atrial
24 fibrillation.

25 There is no intent to make a claim by doing an

1 ablation procedure that somehow that procedure has, in fact,
2 modified your stroke risk anymore than it may have modified
3 the natural history of whatever structural heart disease you
4 may have if you don't have idiopathic atrial fibrillation.

5 I would encourage the panel and the FDA to
6 consider carefully whether or not linking between resolving
7 symptoms, which is what brought the patient to the ablation
8 procedure, and modification of stroke risk, which has got
9 medications and other considerations involved, really should
10 be tied together or kept as two separate issues,
11 understandably important but, nonetheless, two separate
12 issues.

13 DR. CURTIS: I don't that is what anybody is
14 saying. Nobody is saying that ablating atrial fibrillation
15 has to reduce the risk of stroke. I think what Dr. Tracy
16 was saying is we don't want to get a false sense of security
17 or assume that we have reduced risk of stroke by doing an
18 ablation procedure.

19 That has nothing to do with the study trial
20 design, outcomes, anything like that. It means the primary-
21 care doctor saying, "Oh, whoopee; I don't have to use
22 Coumadin."

23 DR. DeCARLO: I think we agree on that. I am
24 trying to carefully delineate there is a big clinical
25 question looming here that is separate from the science of

1 the procedure.

2 DR. CURTIS: Yes; there certainly is.

3 DR. SIMMONS: And you are going to be comfortable
4 coming back here three years from now and having your
5 indications being this catheter is intended only for the
6 relief of symptoms and has no proof of efficacy for
7 prevention of stroke--

8 DR. DeCARLO: For stroke risk.

9 DR. SIMMONS: That patients have to be maintained
10 in Coumadin--

11 DR. DeCARLO: Absolutely. Why would I want to
12 claim that without data?

13 DR. SIMMONS: Why wouldn't you want to? You are
14 going to be very angry when, two years from now, we put all
15 these restrictions on your catheter and there is going to be
16 a different guy here. You are going to want much more than
17 what you are getting.

18 DR. DeCARLO: To tell you the truth, I think you
19 are assuming more on my part than you may want to assume.
20 Frankly, I would be very happy to come to you and say, "I
21 have a procedure which will relieve symptoms of atrial
22 fibrillation." Stroke is a different medical, clinical
23 issue that has to be described, defined and cared for by
24 clinicians. That is not my intent.

25 DR. TRACY: But patients who have had the MAZE

1 procedure do not chronically remain on anticoagulants. The
2 statement has been made. That is how it is done. So we
3 need to know what happens with these patients as well. We
4 need to know.

5 DR. SIMMONS: I would think that is true, too. I
6 would be very reluctant to proceed ahead with a procedure
7 where you didn't know what the outcome of the patient was
8 going to be.

9 DR. VETROVEC: I think you could paint it in its
10 worst scenario that you get rid of the symptoms and you
11 increase the stroke risk. So I think if you want to be a
12 real cynic about it--I think you need to know something
13 about the stroke risk. Whether you claim it or not, we need
14 to know how to label the product or what the public needs to
15 know about their risk if they have this procedure done.

16 DR. CURTIS: One of things we will to know in
17 follow up is how many strokes occur in these patients,
18 whether or not they are on anticoagulant--we assume that we
19 want to keep them on anticoagulants but whether they are
20 taking them--probably data about their INRs.

21 And then the issue about echocardiography, we are
22 getting now right-sided versus left-sided ablations and
23 whether the issue of transesophageal echocardiography is
24 essential only for left-sided ablations or both. I don't
25 know.

1 Let's go to No. 14. "Is it appropriate to begin
2 an A-fib study in the right heart only in order to
3 characterize the safety of the device in a lower-risk
4 environment or can patients be treated in the left heart
5 with a new ablation system without any right heart
6 experience?"

7 I don't know that doing it in the right heart, by
8 itself, is going to tell me something about--if it is
9 100 percent safe in the right heart and nothing ever happens
10 there, it still doesn't tell me I am not going to have a
11 stroke when I do it on the left side. So I don't think that
12 is the reason why we would thinking of it.

13 The reasons why investigators have thought about
14 right-sided-only versus right-and-left is it is easier,
15 shorter. If you can get an adequate success rate on the
16 right side, you avoid having to go on the left side which we
17 think is likely to have a higher complication rate.

18 So I don't think the way the question, as posed--I
19 am not sure that is the right question to ask.

20 DR. SIMMONS: I agree. It implies you are doing a
21 lesser procedure just to find out what the risks are.

22 DR. CURTIS: Yes.

23 DR. WHARTON: Can I make one other comment that I
24 think goes unnoticed with regard to this subject? There is
25 a huge learning curve with the investigator with any new

1 catheter. I think, in terms of safety, it is probably
2 better for them to learn in the right atrium where there is
3 less they can hurt before we start sticking--

4 DR. TRACY: Would it maybe be more appropriate for
5 any company that is serious about having their product out
6 there to take the investigator and have them work in an
7 animal laboratory for a period of time?

8 DR. WHARTON: The problem about these types of
9 catheters in animals is there is no good animal that
10 represents a human atrium. So whatever you learn, it is
11 somewhat reasonable to do, I think, in terms of handling
12 human catheter characteristics. But it still not the same
13 as putting it in in a person, trying to figure how it
14 displays and how it rotates and what the limitations and the
15 good points of the catheter are.

16 DR. TRACY: I appreciate what you are saying but
17 if it is not likely to be--if the success is not likely to
18 be very high with right-sided lesions only, then it doesn't
19 make sense to limit a study to right-sided lesions only.

20 DR. WHARTON: Can't argue that.

21 DR. CURTIS: Then you are using the patient to get
22 your learning curve in without--

23 DR. WHARTON: What I would argue is if you go to
24 the left side, you are still using the patient to get your
25 learning curve in, but at some risk to the patient.

1 DR. CURTIS: As I said, I wouldn't really think of
2 this in terms of characterizing the safety of the device
3 because I think the risks on the right and left side are
4 inherently different, no matter what you do. So if you
5 ablate on the right side only, and you don't have a lot of
6 strokes, that doesn't really help me because I think I am
7 going to be more likely to do one on the left.

8 So that wouldn't be very helpful.

9 DR. PORTNOY: One of the things that we have
10 looked for is is there any obvious evidence of thrombus
11 formation on the catheter to suggest that there may be a
12 greater thrombogenic potential before the investigators go
13 the left side. So we are trying to assess, as much as
14 possible, about whether this might result in stroke or not,
15 whether this particular ablation system--

16 DR. CURTIS: Okay.

17 DR. PORTNOY: But I understand what you are saying
18 and a bunch of issues were just raised which are also very
19 helpful in thinking about this right versus left.

20 DR. CURTIS: How would that be assessed?

21 DR. PORTNOY: In the clinical setting, it is
22 probably just by observing, looking at the catheter, and
23 seeing if there is more thrombus on the catheter than you
24 are used to seeing, something like that.

25 DR. TRACY: You shouldn't see any thrombus on any

1 catheter. I think that the thrombus I would be worried
2 about is the one that I couldn't see, the ones that are
3 forming inside the heart that you are not going to be
4 pulling out on the catheter.

5 So if you see thrombus formation on the catheter,
6 yes; that is a bad thing. But if you don't see it, that is
7 not necessarily reassuring that there isn't thrombus some
8 other place that you are not seeing.

9 DR. CURTIS: That may be something that is
10 answered better in animal studies because you can see the
11 pathology. If the catheter had an awful lot of thrombus
12 formation, you would probably be concerned about using it in
13 humans because I don't know what you would assess if you did
14 a right-sided ablation in a human, in terms of knowing that.

15 DR. SCHWARTZMAN: We are focussing on stroke, and
16 I appreciate that. Obviously, that is one of the main
17 issues. But having had the experience of doing extensive
18 animal work to develop a protocol which I have since taken
19 into humans, I can tell you that the human situation is far
20 different.

21 First of all, as Marcus said, the geometric issues
22 in animals are far different but also the rheologic issues
23 are far different. The fact that you are given a new
24 catheter is the first step. Then you have to couple it to a
25 power source and understand how to titrate which is far from

1 straightforward with the various systems that are out there.

2 So I would at least encourage the panel to
3 recommend a right-sided feasibility stage to any new
4 technology. The issues of learning curve for the involved
5 physicians, I think, is also incredibly important. That is
6 not as important, though, as understanding how to achieve
7 the result one sets out to achieve.

8 That gets into an issue we really haven't talked
9 about. We have been focussing more on clinical outcomes
10 rather than anatomical outcomes, even though most of the
11 companies that are submitting IDEs here are conceptualizing
12 an anatomical solution to this.

13 So, again, just to reiterate what Marcus said but
14 also, maybe, to segue into endpoints that are not related to
15 the clinical outcome of the procedure.

16 DR. CURTIS: There may be a lot of value to that
17 anyway because if you are talking about new catheters and
18 you are learning how to use them and all the rest of that,
19 to have to go to a right- and left-sided ablation at one
20 setting is going to be an incredibly long and difficult
21 procedure.

22 There probably is a lot of value to saying the
23 first X number of patients, we are going to do on the right
24 side only. That doesn't stop you from going back to the
25 left side later on if you are not controlling the

1 arrhythmia.

2 I think there is some reason to think--there is
3 certainly data in the literature that suggests that right-
4 sided lesions alone just don't work out as well as also
5 approaching the left side. So I think that is probably,
6 ultimately, going to be necessary unless some new techniques
7 get developed.

8 But that probably would be reasonable to at least
9 start on the right side with new catheters.

10 DR. VETROVEC: Point of information. Are patients
11 with paroxysmal arrhythmias more likely to respond to just
12 right-only compared to people with more chronic arrhythmia
13 where they have more dilated atria, or does that make any
14 difference?

15 DR. TRACY: There is a little bit of information
16 on that but, again, there is not enough information--and I
17 think some of the studies are in the packet that we
18 received. I don't think that we know that well enough. I
19 don't think we have characterized things well enough to
20 state that with any degree of certainty.

21 DR. VETROVEC: If that were true, then it would be
22 to recommend that the first ones be done on the paroxysmal
23 arrhythmias to get experience on the right side. You could
24 always go back, if you had to, but you wouldn't be
25 jeopardizing the patient maybe to the same degree you would

1 if you know, in chronic, you have to do both sides.

2 DR. CURTIS: Aside from the small subset of focal
3 A-fibs that are in the pulmonary veins, I don't think we
4 know for sure that anybody can just be done on the right
5 side.

6 Let's do 15 because I think it is still getting
7 into these right- versus left-sided issues. "Is there a
8 clinically appropriate way to conduct a staged anatomical
9 approach for treating A-fib patients? For example, could
10 patients be treated only in the right atrium and then, if
11 symptoms persist one month post-ablation, a left-sided A-fib
12 ablation could be performed?"

13 "Is it appropriate to conduct a study in the right
14 heart only for A-fib ablation or does the literature suggest
15 that A-fib ablation should be performed in both the right
16 and left hearts?"

17 We were talking about these catheters and their
18 initial use and using it in the right side only to get some
19 experience with it, and that would probably be a good way to
20 have a small feasibility study. Let's say you did that and
21 you didn't see any particular problem. You were able to
22 maneuver the catheter and the device worked in your system
23 and all that.

24 Then you are talking about the clinical-trial
25 design of the various ways to do it; right-sided ablations

1 in all patients; go to the left if they fail. You might
2 want to have a trial where some patients get right-and-left-
3 side right up front versus a right-sided only. That would
4 be another way to do it.

5 DR. TRACY: I agree. Otherwise, you are talking
6 about something that gets pretty complex. If you say, okay,
7 when you first do this, you can only do this on the right
8 side and then, since you can't really be sure what is going
9 on for the first X number of weeks, then X number of weeks
10 go by and you are pretty sure, after watching them for
11 another month or two, that it really didn't work, and then
12 you go back on the left side.

13 So you are getting pretty boxed in at that point.
14 You have got a lot of time going by here. So, again, I
15 think to limit it only to the right side is not necessarily
16 the right thing. I think maybe comparison. I think it is
17 going to depend on the catheter design what seems to be
18 appropriate for that particular device.

19 DR. PORTNOY: So we are talking about multicenter
20 study now, the study that is going to support the PMA;
21 right? That is what we are talking about now?

22 DR. TRACY: Yes.

23 DR. CURTIS: I think that, after an initial
24 feasibility study, to know that a catheter was safe and you
25 could work with it, say, on the right side, your clinical-

1 trial design could be right-and-left-sided ablation, period.
2 I don't think it has to be compared to something else if
3 that is the way the company wants to design it.

4 So I think there are some data that suggest if you
5 don't hit the left side, it is not going to work. I think,
6 certainly, to say that you have got to do a full trial with
7 right-sided ablations only and then go on to do something
8 else may be wasting time.

9 It may be necessary to do both--it probably is
10 necessary to do both sides. It might be the best way for a
11 company to do the study is just to design the protocol that
12 way. They go in on the right-and-left sides and create
13 these lesions and then see what happens.

14 DR. WHARTON: I think, though, we have to be
15 careful when we talk about right and left sides what we
16 define as the endpoint of the study. I think there is--and
17 you can argue whether it is good or not--but there is a fair
18 amount of data to suggest that arrhythmia frequency can be
19 changed in at least a proportion of the patients by a right-
20 sided-only procedure.

21 So if the endpoint is just decreasing arrhythmia
22 density, not cure, then a right-sided procedure may work in
23 some proportion of patients. If you are looking for cure of
24 most people, I agree that it is a right-and-left-sided
25 procedure. This is where those sorts of definitions of

1 endpoints of what you are really looking for become very
2 important.

3 While you are just trying to palliate, a right-
4 sided procedure maybe a conservative approach in some
5 patients.

6 DR. CURTIS: And that would be a different kind of
7 trial design. If my endpoint is to reduce the frequency by
8 75 percent, I am going to do right-sided ablations only and
9 then I am going to follow my patients. If my goal is I want
10 everybody cured, I have got to do both sides. And that is
11 how I am going to do it from the very beginning.

12 DR. SIMMONS: But you still probably have to do a
13 feasibility study of the right side before they could start.

14 DR. CURTIS: Yes.

15 DR. VETROVEC: There have been a number of trials
16 in all kinds of things where the first three procedures done
17 in each investigator's institution are done a specific way.
18 In this case, it would right-only. Then, after that was
19 demonstrated to have no complications and given that the
20 data coming in at that point showed that the centers were
21 all having a high incidence of recurrence, then it would
22 allow all the investigators to go forward and do right and
23 left at the same time.

24 I think you could stage the entry. And that has
25 been done before for other studies.

1 DR. TRACY: I think that would be a very good way
2 of approaching it.

3 DR. ROSS: My name is Michael Ross. I am from
4 industry, a company called Atrionics, working specifically
5 in catheter ablation of atrial arrhythmias. I remain a
6 little confused on this right-sided, left-sided, debate.
7 The reasons are as follows.

8 If you look at the results of right-sided
9 lesioning over the past couple of years, at best, I think
10 the companies that have released their results are operating
11 at the margins and, at worst, I would say that the data that
12 I am seeing from these studies would probably never pass FDA
13 scrutiny.

14 I am wondering as we move from the question which
15 is, will right-sided lesions work, to, are they needed at
16 all, and they probably are--but the more important statement
17 is that left-sided lesions are almost certainly indicated to
18 cure this disease.

19 So it begs the question. How do you consent a
20 patient for a right-sided-only procedure and is it ethical
21 do to? If we are trying to cure this disease and not change
22 the results with drug therapy, how do we go to these
23 patients and tell them we are going to do a procedure on the
24 right side, it is probably not going to work but we just
25 need to get this data.

1 So I remain somewhat confused and I would be more
2 inclined to argue for the ability to do left-sided
3 procedures given a set of safety data from animal studies.

4 DR. CURTIS: That could be one approach is having
5 some animal data that shows that you didn't have some
6 particular risk of thrombogenicity, or something like that,
7 and having the trial design as a right-and-left-sided
8 ablation from the very beginning.

9 I think that could be a way to go.

10 DR. SIMMONS: That data is not at all clear.

11 DR. CURTIS: That's right.

12 DR. SIMMONS: And a company comes and says, "I am
13 going to do a right-and-left-sided ablation, that is my only
14 goal," I think you are right. To submit a patient to a
15 right-sided ablation just to get practice is not going to
16 happen. It is not going to happen.

17 DR. CURTIS: The other thing, too, though, is that
18 with the initial patients, we know it is not going to be a
19 30-minute procedure. You are talking about a very long,
20 drawn-out thing. If you say, "You are one of the first
21 people we are doing this on. It is new thing. We are
22 excited. We think we may be able to cure A-fib," and they
23 know that you are collecting that information and that they
24 can go back to the left side later, it is a two-part
25 procedure. But, again, each part of it is half the length

1 of what the entire procedure could have been up front.

2 DR. TRACY: I think we have already pretty much
3 agreed that you are not going to restrict somebody from
4 coming back and doing something on the left side. It is
5 just that it does become somewhat cumbersome if you only
6 restrict it--I like the idea of saying the first three
7 patients, you will start by just doing right-sided energy
8 deliveries, and then you have got, whatever, five centers
9 that are just doing that.

10 Then, a few months later, you know that the right-
11 sided lesions, the recurrence rate is 75 percent or
12 whatever. And then you can proceed from that point forward
13 and maybe have different criteria for when you can go back,
14 maybe not have to define them by going through the entrance
15 criteria again of failing drugs and so on and so forth, but,
16 at that point, immediately can move them back into the
17 labeling.

18 What Anne says is very valid, that these are not
19 going to be short procedures and that it would not be
20 unreasonable to stage it anyway. There are cases, even,
21 with very standard thing that we might be doing things in
22 sort of a stage procedure.

23 You have a couple of accessory pathways and an AV
24 node to modify. You might end up just being too tired and
25 the patient too antsy to stay in there all day long and you

1 might come back a month later and finish the rest of
2 ablation.

3 So to think of this as a stage procedure might be
4 very reasonable as long as, once we have done the first
5 three sort of feasibility patients, if it turns out that it
6 isn't working, that we don't subject those patients to a
7 very long waiting period and subject them to going through
8 sort of the whole entry criteria once again, that we could
9 quickly move them in and then apply left-sided lesions.

10 DR. CURTIS: Let's go to No. 16. "Is there an
11 optimal lesion set for treatment of A-fib? If not, can an
12 multicentered study be conducted using more than one
13 prescribed lesion set or should a feasibility study be
14 conducted to optimize the prescribed lesion set prior to
15 multicenter expansion?"

16 I think one problem I could foresee that we should
17 think about is there is always a chance that one company
18 guesses better than the other one, and put one extra linear
19 lesion in the left side, or did something a little bit
20 different from another company and has some other different
21 outcome.

22 Is it their catheter? Or is it the lesion set?
23 If it is the lesion set, then anybody's catheter who can do
24 that, it ought to be effective for. You would hate to see
25 somebody have done a two- or three-year study with, whoops,

1 the wrong lesion set and you get the questions about
2 generalizability.

3 If this company's lesion set works and I have got
4 a catheter and I can do that kind of stuff, do I still have
5 to go back and do that study again in order to know that it
6 is going to have the same kind of outcome in order to get
7 the labeling indication.

8 DR. TRACY: We are struggling to figure out
9 exactly what it is that needs to be done. We don't even
10 know. So I think it makes designing a study very, very
11 difficult because we don't know very much about even what it
12 is that we are trying to accomplish.

13 DR. CURTIS: I would have to say I don't know what
14 the optimal lesion set right now is so you don't know that
15 answer. There is not one in the literature, the catheter-
16 based MAZE 3 is the way to go. Nobody knows that so you
17 can't say you have got an optimal lesion set right now.

18 Could you do more than one? It might well be
19 worthwhile for a company to have more than one to see if the
20 extra effort involved in putting two more lesions on the
21 left side makes enough of a difference that it is going to
22 affect what we consider the success of the procedure.

23 So I think having more than one lesion set
24 probably would be not a bad way to go.

25 A feasibility study to optimize the prescribed

1 lesion set--a feasibility study is going to be hard-pressed
2 to tell you the long-term outcomes with that sort of thing.
3 You might have some safety data from it and get some
4 information.

5 DR. SIMMONS: I agree. I disagree with one thing
6 you said. If a company comes and does a lesion set and then
7 someone else does a slightly different lesion set, it
8 doesn't mean that their catheter could actually be approved
9 because now they can do that second lesion set. It might be
10 a completely different problem with the catheter tip or the
11 material or the way--so, if they guess wrong, it is probably
12 too bad, isn't it? It is a shame, but that is the way it
13 will have to be.

14 But I agree.

15 DR. TRACY: It is the kind of situation where you
16 would hope that, ha ha, industry would be communicating so
17 that if somebody knew that lesions in such-and-such a
18 location never worked that they would tell everybody so that
19 nobody wastes anybody's time doing things that don't work.

20 We are subjecting people to lots and lots of
21 radiation, lots and lots of effort. I think this is really
22 calling on the scientific community as well as the industry
23 to really be forthright about what information they are
24 gathering so that people don't waste their time and expose
25 patients to unnecessary risk.

1 This is very, very important.

2 DR. CURTIS: Other comments? Any other issues
3 that we didn't discuss that you want to hear some comments
4 on? Then, I would have the motion to adjourn.

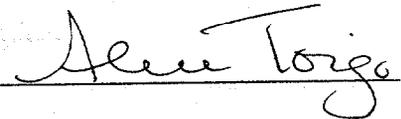
5 DR. SIMMONS: I reached this point the other day.
6 We don't have a quorum among the voting members so I guess
7 it is your power to adjourn us.

8 DR. CURTIS: Then let's adjourn. Thank you all
9 very much.

10 [Whereupon, at 12:40 p.m., the meeting was
11 adjourned.]

C E R T I F I C A T E

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script that reads "Alice Toigo". The signature is written above a horizontal line.

ALICE TOIGO