

1 went back on Coumadin or did not go back on Coumadin
2 in terms of the efficacy of WATCHMAN versus the
3 control group.

4 DR. SOMBERG: But I have to see that data.

5 DR. HOLMES: Patients went back on warfarin
6 for a variety of clinical reasons. Do we have that
7 slide? We're just getting that. Because I agree.
8 That's a critical condition. So this would be the
9 patients who have on-treatment analysis versus
10 excluding all implants in the time from implant date.
11 Let's focus our attention on the bottom line, on-
12 treatment analysis of the WATCHMAN patients, 2.6,
13 control events would be 5.2. The relative risk is
14 .52.

15 It didn't matter whether they were put back
16 on it or taken off of it. All patients were taken
17 off of it at 45 days. As you will remember a small
18 number of patients were put back on sometimes up to
19 several months later for another condition. That
20 putting them back on several months later for another
21 condition did not impact on the results.

22 DR. SOMBERG: I hear that, but there was
23 this little conundrum about if, you know, if you take
24 them out of the efficacy point, then they may end
25 up -- this may be a toxicity. So I want this

1 efficacy balanced against your accession of toxicity
2 events for the on-treatment analysis of that specific
3 group where the people went back on Coumadin are
4 counted as toxicities but not as efficacy, if I'm
5 making myself clear.

6 DR. MAISEL: So maybe I'll interrupt for a
7 second. So, John, it sounds like what you're
8 interested in is knowing how the device off of
9 Coumadin, after 45 days, compares to patients who
10 were treated with warfarin in the control group.
11 That's sort of the on-treatment analysis, and I don't
12 agree with you, that someone going back on warfarin
13 on the devices is a "toxicity" necessarily. So --

14 DR. SOMBERG: No, I'm not saying that. And
15 they are presenting very clearly the relative risk in
16 favor of that, but remember, if you went back on
17 Coumadin, it may be that someone saw a thrombus and
18 that person is taken out of this database, and
19 therefore I want to see not just the efficacy, but I
20 want to see the toxicity. Did they have more --
21 because there would be a toxicity in the other area.
22 So I want them balance that.

23 DR. MAISEL: Yeah, I think that's a
24 reasonable request. I think, you know, we're dealing
25 with the vagaries of a randomized trial and then

1 trying to pick out nonrandomized subsets. So there's
2 a group that got put back on warfarin for some
3 reason. They may have a higher complication rate.
4 They may have, you know, different risk factors. So
5 to start carving out these little pieces is --

6 DR. SOMBERG: That is always dangerous and,
7 you know, I'm sitting next to the statistician. So
8 eventually I'm going to be chopped to pieces here
9 about on-treatment analysis with intent-to-treat, but
10 if the intention-to-treat goes in a positive
11 direction, if we accept all the definitions, then
12 we -- but the on-treatment analysis went in a very
13 different direction, it would cause a little
14 consternation.

15 If they can tell me that it shows efficacy
16 and it also shows now difference in toxicity accrual,
17 then I'd be very satisfied. I just don't know why
18 those two data, instead of having the FDA and the
19 Sponsor go back and forth and say it's included, it's
20 not included, that it can't be shown clearly with
21 that segregated out.

22 DR. MAISEL: Okay. My take would be that
23 that issue of whether it was included or not has been
24 resolved. It sounds like the patients were on
25 warfarin in that the patients who got re-added

1 warfarin were in that slide that was included.

2 The second point I'd make is that, keep in
3 mind the effectiveness includes ischemic stroke. And
4 so if we're looking at the patients who were not on
5 warfarin and truly the device was implanted and
6 warfarin was stopped after 45 days, if they started
7 having strokes left and right, that effectiveness
8 endpoint should get worse, not better.

9 DR. SOMBERG: Would it be counted as an
10 effectiveness endpoint or would it be on a toxicity?

11 DR. MAISEL: Well, ischemic stroke counted
12 was part of the effectiveness endpoint. But I'm
13 interested in hearing other people's thoughts. Fred.

14 DR. RESNIC: Just a question and maybe
15 Dr. Kelsey can help. All of these are derivatives of
16 the per-protocol analysis, which I think the FDA has
17 sort of warned us was a concern because there was
18 such censoring of the active treatment arm in the
19 per-protocol and all derivatives. So we basically,
20 we're throwing out all the adverse events in the
21 first 45 days, aren't we, from the -- in all these
22 derivatives of per-protocol. Is that correct?

23 UNIDENTIFIED SPEAKER: Yes.

24 DR. RESNIC: And so I'm concerned that as
25 we chop the per-protocol analysis up further and

1 further, we're getting -- it's fortunate that it's
2 not heading in a different direction because I think
3 it's going to get very confusing, and I would suggest
4 that the intention-to-treat is the only clean data
5 that we have unless you can, as a condition to be
6 discussed later, say that that would be important to
7 really spell out what are the subgroups that make the
8 difference for you.

9 DR. MAISEL: Dr. Kelsey.

10 DR. KELSEY: Yes, I would agree entirely.
11 The per-protocol is interesting. It might give some
12 hints about maybe what patients would not be suitable
13 for getting the device, but I think that we really
14 need to concentrate on the intention-to-treat.

15 DR. MAISEL: David.

16 DR. GOOD: Just a comment about ischemic
17 strokes. Remember that even patients with atrial
18 fibrillation that are treated have a relatively low
19 chance of stroke each year. It's what? Five or ten
20 percent. This study didn't go on very long. So in
21 terms of the stroke thing, you wouldn't expect a
22 sudden increase in stroke even if the device was
23 ineffective. So you really have to, again, I think
24 follow-up on a longer period of time to tell whether
25 this is really going to be effective or not.

1 DR. MAISEL: John.

2 DR. SOMBERG: I want to belabor the point.

3 DR. MAISEL: Yes, you do.

4 DR. SOMBERG: No, I'm not going to address
5 that, but I just want to comment on what you're
6 saying here, intention-to-treat is very important,
7 but in this situation when we're asked to recommend
8 or not recommend approval of the device, versus as an
9 alternative to Coumadin therapy, when in the
10 intention-to-treat group, a fifth of the patients, 22
11 percent, are still receiving Coumadin, that makes a
12 determination impossible. So that's why on-treatment
13 analysis becomes important.

14 DR. RESNIC: It's very confounded, I
15 understand.

16 DR. SOMBERG: And it's a quirk or
17 deficiency of the basic protocol, but we can't change
18 that. So that's why I'm forced to ask for that type
19 of data.

20 DR. MAISEL: Dr. Kelsey.

21 DR. KELSEY: But maybe 20 percent are still
22 on Coumadin, but 80 percent aren't, and that's a
23 benefit. It could be a benefit not to have to --

24 DR. LINDENFELD: This does have one other,
25 I think, implication in that this might be a device

1 for people who can't take warfarin, but on the other
2 hand, if there's still flow, at least the surgical
3 data suggests that when there's still flow in the
4 left atrial appendage that you partially occluded,
5 that the risk goes up.

6 So now we have potentially 20 percent of
7 patients where they still have flow and their risk of
8 stroke is greater and they can't be on Coumadin.
9 That is a partial concern. We can't speak to that
10 here, but it is a partial concern.

11 DR. MAISEL: Right.

12 DR. PETERS: I think that one of the
13 problems here is the number of events is relatively
14 small, and the more we chop it up, the less
15 meaningful it becomes. It's very difficult to judge
16 what's going on here. There just aren't that many
17 events in either group.

18 DR. MAISEL: So what I'd like to do at this
19 point is can we put the first FDA question up, the
20 effectiveness questions since we talked a lot about
21 that and just try to reach some consensus about that
22 issue.

23 So question 1 for effectiveness is, the key
24 primary effectiveness results for the updated 900
25 patient-year dataset are shown in Tables 1 and 2,

1 which are in your packet, the question packet. Do
2 these data, in addition to the original 600 patient-
3 year data, provide a reasonable assurance that the
4 WATCHMAN device can be used as an effective
5 alternative to standard warfarin treatment for
6 reduction of stroke, death, and systemic
7 embolization? Please discuss the confounding effect
8 of adjunctive antithrombotic drugs that were given to
9 patients in the device arm of the trial.

10 And before we go and answer the actual
11 question that's asked before us, I just want to try
12 to come to some consensus on a few of the points
13 we've been discussing. So is there anyone who still
14 has an outstanding issue on the endpoint
15 adjudication? Are you satisfied, or at least your
16 questions have been answered regarding the endpoint
17 adjudication? Are there people who do not think that
18 the intention-to-treat analysis is the correct
19 analysis that we should be focusing on? Obviously we
20 look at all the data, but we've heard from a couple
21 of people that intention-to-treat is the analysis.
22 We've heard from the FDA that that's the one we
23 should be looking at. Is there anyone who would like
24 to argue that that is not the main analysis we should
25 be looking at?

1 And, Dr. Somberg, we've heard from you.
2 You feel that's not the one we should be focusing on.

3 DR. SOMBERG: No, that's not it either. I
4 think I've made it clear. I think they're both
5 important. One cannot be looked at without the other
6 to reach --

7 DR. MAISEL: Can we hear from some other?
8 Norm, what do you think? Which? Intention-to-treat
9 or other analysis.

10 DR. KATO: I mean I guess I'm still kind of
11 tied up with -- I'm sorry. I was going to get back
12 to your first question before you went onto this one.
13 I'm sorry I didn't get my hand raised, but I guess
14 one issue about the, if I can bring this up, Bill,
15 I'm sorry, but -- so we just heard the adjudication
16 of these cases that the FDA claimed before they were
17 not privy to. Is that correct?

18 Dr. Swain, I'm curious. Before you
19 mentioned -- before our lunch break, you said
20 something about you were not aware -- you did not
21 have access to the criteria, you did not have access
22 to the data points or the patients who had these
23 complications, and so this has now been contradicted
24 by the Sponsor?

25 DR. SWAIN: No, no. We did not have access

1 to the CEC decision rules or the source data. All we
2 had are narratives prepared by the Sponsor which we
3 assumed were accurate. So that's all we could go on,
4 are one-page narratives of each event.

5 DR. KATO: So this is the first time you've
6 heard this.

7 DR. SWAIN: Yes.

8 DR. KATO: Thank you.

9 DR. MAISEL: Okay. So regarding the
10 intention-to-treat, John obviously has stated his
11 opinion. Is there anyone else who wants to argue for
12 something other than the intention-to-treat analysis?

13 (No response.)

14 DR. MAISEL: And then regarding the
15 statistical analysis that was performed on the data,
16 we haven't spent a lot of time talking about that
17 and, Sherry, maybe I'll ask you to comment first, but
18 there are obviously a number of issues there related
19 to the noninferiority plan, the specifics of that
20 plan, the constant hazard rate issue or the
21 assumption that wasn't really met, the credible
22 intervals, all of that. Can you just provide us your
23 take on the analysis?

24 DR. KELSEY: Sure. I congratulate the
25 Sponsor for using a Bayesian analysis. I keep

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1 predicting that it's going to take over, and it's
2 been very slow to take over, but I think it gives you
3 an outcome that is intuitively appealing. The idea
4 of a probability of something as opposed to a p-value
5 which people think is a probability but it really
6 isn't. It's more complicated. So I think that's a
7 good approach.

8 I did have a question, however, about the
9 hazard rate, and I think the FDA has provided good
10 evidence that it's not a constant hazard rate. This
11 is probably not unexpected with a device versus a
12 medical treatment because there's a hit at the
13 beginning with the device, and it's a more gradual
14 thing with the drug comparison.

15 So I guess my question for the Sponsor and,
16 Dr. Brown, is how this issue of the hazard rate
17 affects the analysis and the conclusions of the
18 analysis?

19 DR. BROWN: Thank you. Scott Brown again.
20 I appreciate the question. FDA, as you mentioned,
21 did show some data which suggests that we may have a
22 nonconstancy of the event rate particularly in the
23 treatment group.

24 We have a totally different analysis.
25 Honestly, the only difference between the two of them

1 that I think FDA cited a significant p-value in
2 talking about the nonconstancy. We get a slightly
3 different p-value. That's not the issue.

4 The issue is that if, in fact, those model
5 assumptions of constancy of event rates are violated,
6 what does it imply about the rigor? What does it
7 imply about perhaps the robustness of the analysis?
8 And for that purpose, I don't know if we can put it
9 up or not, but I had a slide during my presentation
10 this morning that talks about some of the other
11 analyses that were done.

12 So this was anticipated, that we may have
13 an issue with those model assumptions. Here it is.

14 So this was the slide I showed this
15 morning. The top row is, in fact, the Bayesian model
16 that we used as the primary analysis. This does
17 assume a constancy of event rates. This is what's
18 called a Poisson gamma model in the Bayesian
19 framework. It assumes a Poisson rate of events, that
20 is, a constant assumption. If we want to start
21 departing from that assumption, we try to look at a
22 couple of different ways we could depart, one being
23 simple proportional hazards but not constant rates,
24 and the other being a piecewise hazards model where
25 you're allowed to look at constancy of hazard only

1 over short periods of time, and then you essentially
2 amalgamate the effect and come up with an overall
3 effect size.

4 And I think the point that's most important
5 is that all of these analyses are largely consistent
6 with one another. In every case, it's called a
7 hazard ratio. In the case of the primary model, it's
8 actually a relative risk. But in every case, the
9 effect size favors the WATCHMAN group over control,
10 and in every case, the upper bound of the credible
11 intervals are similar to one another and all well
12 below the number of 2 that is that magic
13 noninferiority cutoff.

14 So I think that's the best answer that I
15 have as far as the robustness of that endpoint.

16 DR. MAISEL: Okay. Thank you. Any other
17 comments about the statistical analysis and some of
18 the issues we've been talking about? JoAnn.

19 DR. LINDENFELD: This is just a very
20 simplistic question, and maybe Dr. Kelsey can answer
21 that. It doesn't really have to do with statistics
22 except that we're making a decision here based on a
23 difference of five endpoints. And we have a very
24 powerful number, but maybe you can just help me feel
25 more comfortable making a decision on the basis of a

1 difference of five endpoints. There are 31 in this
2 600-patient analyses, and very often we've seen
3 studies that have been wrong with 50 deaths to
4 analyze. So when you look at a difference of five
5 endpoints, it seems surprising that we can -- I don't
6 argue with the statistics, but just help me.

7 DR. KELSEY: Okay. Well, one of the
8 things, too, is that there's twice as many people in
9 these device group, so that --

10 DR. LINDENFELD: Right.

11 DR. KELSEY: -- there's an absolute
12 difference.

13 DR. LINDENFELD: So there's a five endpoint
14 difference in the two groups. So it might be eight
15 or nine if you doubled.

16 DR. KELSEY: Yes.

17 DR. LINDENFELD: It's a very small
18 difference to make a very big -- I'm just asking for
19 some comfort here about some -- it's a very small
20 number of endpoints.

21 DR. KELSEY: Yes. Well, good for the
22 patients, they don't have a lot of the endpoints, but
23 a little bit harder for the statisticians to find a
24 credible difference, but I feel -- I think the
25 analysis is appropriate, and I feel confident in the

1 results of that difference.

2 DR. MAISEL: John.

3 DR. SOMBERG: The other side of the coin is
4 you could say that the device is not producing, you
5 know, it's not such an inferior device. It's not
6 such an inferior action that it's causing so many
7 events. So while you can say the small numbers, it's
8 hard to be assured of noninferiority, certainly of
9 superiority, but still the device is not acting so
10 disruptive of the biologic situation that it's giving
11 you. So it had that opportunity to show itself, and
12 I feel personally reassured that I don't see an
13 inordinate number of adversities on the device.

14 DR. LINDENFELD: But we haven't gone
15 through the safety events in detail.

16 DR. SOMBERG: I understand, but I'm just
17 giving you the balance there.

18 DR. MAISEL: How do people feel about the
19 noninferiority design of the study and the two times
20 threshold that was considered acceptable? So we're
21 using words like noninferior, but it could be
22 theoretically up to two times or not quite two times
23 as bad. The upper credible interval was 1.4. Are
24 people comfortable with the range of confidence we
25 have in the point estimate?

1 DR. RESNIC: I think the FDA Panel did a
2 great job in justifying the impact on the sample size
3 requirements had the noninferiority boundary been
4 reduced down to 20 to 50 percent as opposed to what
5 is really 100 percent at doubling. I think it's
6 fortunate that the 95 percent credible interval is
7 pretty far away. So that gives some relief to the
8 concern that two times is too high for really
9 considering something noninferior.

10 DR. MAISEL: Norm.

11 DR. KATO: You know, I have to disagree. I
12 don't tend to be an expert on statistics, and I've
13 been to a number of these Panels before, and I'm
14 probably even more confused now than I ever have
15 been.

16 I guess one of the problems is that by not
17 having a rigorous trial, we spend a lot of time
18 trying to figure out, you know, is the statistics
19 right, you know, and how are the different ways we
20 can slice and dice this thing? Do we add all the
21 adverse events together? Do we keep them separate?

22 And, you know, the disease process that
23 we're looking here is not one of 1,000 patients or
24 2,000, you know; it's not even half a million
25 patients. We're talking, at least according to the

1 American Heart Association, something like 2.5
2 million patients in the United States alone.

3 So to have a study done this way where the
4 potential application could be huge makes me very
5 nervous that we are basically agreeing to a false
6 positive, and when other Panel members have been
7 saying, well, gee, it's only 2 points or 3 points,
8 and you look at the 900 patient-year dataset, and in
9 the device section there are 20 adverse events, and
10 on the Coumadin side, there are 16 adverse events,
11 well, to me, just being a simple surgeon, it looks
12 like it's safer being in the control group.

13 So you -- what's that?

14 UNIDENTIFIED SPEAKER: --

15 DR. KATO: No, I understand that. I
16 understand that.

17 But again, it bothers me that we had to
18 compromise on the trial, that it had to be
19 noninferiority because again the times when we've had
20 to deal with noninferiority versus a randomized
21 prospective trial, we always get into this issue and
22 it muddies up the answer that we have to provide, and
23 then it's just a guess by almost every Panel member.

24 DR. MAISEL: Dr. Peters, did you have
25 something to say?

1 DR. PETERS: Yeah, it's my feeling that
2 with the number of events here, I don't know that --
3 it's been said by some of the, you know, senior
4 clinicians that if you really need statistics to
5 figure out the difference between groups, you really
6 don't have much of a difference. And that's the case
7 here. I just don't think we need to spend a lot of
8 time worrying about the difference. They're not that
9 big.

10 More importantly, I think we have to
11 concentrate -- I mean I personally can accept the
12 data that was presented here. I just don't know what
13 to do with it. I mean that's more important. I mean
14 who does this apply to? How do we train them? That
15 is what I think we should be spending our time on,
16 but I'm not sure given the number of events that
17 there's that much difference with the statistical
18 methods that we use. You can look at see, yeah,
19 they're pretty much the same.

20 Now, maybe that's simplistic, but that's
21 sort of the way I would look at this.

22 DR. MAISEL: So can we talk a little bit
23 about the antithrombotic medications and the
24 adjunctive therapy for patients who get this device.
25 Certainly we're aware of the data for atrial

1 fibrillation patients with regard to those
2 medications, and we've heard from the Sponsor that
3 it's aspirin for life and clopidogrel for at least
4 six months as recommended. But what do people think
5 about the antithrombotic issue, and does that make it
6 difficult to interpret the effectiveness, et cetera?

7 Dr. Kelly.

8 DR. KELLY: I have a question for the
9 Sponsor. And again we're getting back to chopping
10 things up, and I apologize, but do we have numbers
11 for how many patient-years of patients with the
12 device and aspirin, no Plavix, we have?

13 DR. MAISEL: Okay. So while they're
14 working on that, any other comments? John.

15 DR. SOMBERG: Well, I thought it was very
16 reasonable, the approach that was taken for keeping
17 people on the warfarin for a certain period of time
18 periprocedurally and then afterwards then adding dual
19 antiplatelet therapy and then stopping the
20 clopidogrel at a certain period of time. It makes
21 sense. I don't think the animal data countervails
22 that, and I think that should be in the
23 recommendations when we see approval.

24 What I am concerned about is, and I think
25 we have to discuss this, both in terms of the

1 pharmaceutical therapy and in terms of long-term is
2 I've reached a comfort level with the dataset that is
3 presented for recommendation, but follow-up data is
4 very critical, and the ends that are discussed are
5 woefully inadequate. So I think we need to have much
6 more information, and that information will impact on
7 how people -- we had that with stents as well. When
8 we get more data, we might find out that there is a
9 very small percentage that need dual antiplatelet
10 therapy for a year or two years, and that might need
11 to be reconsidered. But now after six months, you
12 have very small. You didn't give a number after six
13 months of clopidogrel. How many people are on
14 aspirin? And it's going to dwindle down here.

15 So therefore we really need much more
16 information before we reach a comfort level with
17 these other considerations.

18 DR. MAISEL: Dr. Reddy, did you want to --

19 DR. REDDY: I was just going to answer
20 Dr. Kelsey's question. So the device patients, 20
21 percent of the time on average, they're on Coumadin,
22 50 percent of the time they're on Plavix. The 30
23 percent was the residual time when they were solely
24 on aspirin. Again, for the reason that you stated,
25 because we starting to parse this data out incredibly

1 thinly, we did not do further analyses on those
2 patients.

3 DR. KELSEY: Okay. Thank you.

4 DR. MAISEL: Okay. The other -- yes, Mike.

5 DR. DOMANSKI: The one question I'd like to
6 just throw out and see what people think is I guess
7 I'm sort of impressed with the complication rate in
8 the control arm and, you know, I guess the argument
9 would be that that's what it's like out in the real
10 world and stuff, but it does seem like a high rate.
11 You wonder whether a little more effective patient
12 follow-up on the control side might have
13 substantially changed things. I mean are the results
14 really that bad out there, and can we really decide
15 that, you know, that the control group really got the
16 standard of care treatment. I think probably the
17 answer is yes, but I'm sort of interested in what
18 people think about it, on the Panel, that is.

19 DR. KELSEY: Yeah, I'm sort of surprised to
20 hear that because usually in clinical trials, they
21 get better than what's out there in the community,
22 and it's sounding like maybe from some of the
23 other --

24 DR. DOMANSKI: That's a pretty high rate
25 of --

1 DR. KELSEY: -- clinical people. So what's
2 the explanation here?

3 DR. MAISEL: John.

4 DR. SOMBERG: I think the Sponsor said 65
5 percent of the patients, which was on the previous
6 studies had the adequate anticoagulation as defined
7 by INR. So I mean you can speculate that if you saw
8 them every three weeks, that you got more INRs, you
9 might get that up, but would that change from the
10 population?

11 DR. DOMANSKI: But it looked like the
12 people who bled really hadn't been properly followed
13 up, at least some of them.

14 DR. SOMBERG: It certainly is a
15 possibility, and the closer the control, but then you
16 can argue that if more people were on higher INRs,
17 you might have more bleeding also with therapeutic
18 INRs. You might have decreased the high ones, but
19 you might have also increased the low to the middle
20 range, and that might make the middle people bleed.
21 So it's all speculation. What's comforting is that
22 they weren't statistically, in fact, they were dead
23 on in terms of numbers as previous studies have
24 reported, the incidence of, you know, prothrombin
25 times.

1 DR. ABRAMS: I want to comment. I mean it
2 may not be a complication per se of the Coumadin use,
3 but, and again I don't want to get back to this
4 falling thing, but this is the group that falls the
5 most in this country, and falls are, like everybody
6 knows, is a major health problem, and when you're
7 anticoagulating relatively elderly people, this will
8 turn out to be, you need to probably expect problems
9 like that.

10 Could I ask another question?

11 DR. MAISEL: Yes.

12 DR. ABRAMS: This is a question for the
13 Sponsor about this issue with aspirin. If you don't
14 tolerate aspirin, that means a contraindication to
15 using this device? In other words, this is a device
16 plus aspirin treatment.

17 DR. REDDY: Yes. One of the exclusion
18 criteria, that I don't remember if we went over, was
19 that you had to be able to take aspirin in order to
20 be included in the study. So patients who could not
21 take aspirin would not be allowed in the study. And
22 just to -- if I may, in terms of the adequacy of
23 follow-up in terms of the Coumadin arm, just two
24 quick points. One is 95 percent of the patients did
25 have their INRs checked, and the median time between

1 successive INR checks was 15 days. Those are the two
2 pieces of data that we have.

3 DR. MAISEL: So one other thing I wanted to
4 address while we're on this effectiveness topic,
5 we'll get to it a little bit later with the
6 indications for use, but it seems relative while
7 we're deciding about effectiveness, is the actual
8 effectiveness in what way because the statement is
9 that its indications for use is that it's designed to
10 prevent embolism of thrombi that may form in the left
11 atrial appendage, thereby preventing the occurrence
12 of ischemic stroke and systemic thromboembolism. I
13 would point out that there's a 50 percent increase in
14 ischemic stroke in the treatment group, in the device
15 group, and so we seem to have a little bit of a
16 disconnect. Obviously that statement, ultimately,
17 when we get there is going to need to incorporate all
18 of the risks, if you will. So while we're talking
19 about this effectiveness endpoint, we're going to go
20 around, I want to hear from everyone about how you
21 feel about the effectiveness balance, think of the
22 whole treatment strategy, not necessarily just that
23 ischemic stroke piece. David.

24 DR. GOOD: One thing, you know, whether or
25 not this is really an alternative to warfarin

1 therapy, I think, still is up for grabs because if
2 you look at the strokes that occurred, most of them
3 were when the person was always off warfarin,
4 ischemic strokes. And so is this really an
5 alternative or not when the INR was low. I think we
6 saw a slide on that earlier.

7 I think the other comment about efficacy, I
8 think you have to look at each one of the efficacy
9 measures. I think they're all important. I mean
10 death is quite different than stroke, and there
11 weren't many other thromboembolic events anyway.
12 Just two retinal events, and so that really isn't
13 useful. I think looking at death and ischemic stroke
14 separately are also important.

15 DR. MAISEL: So what I'd like to do now is
16 just very quickly go around the table. This is not a
17 formal vote. I just want to make sure we understand
18 how everyone's feeling about the effectiveness
19 pieces. It doesn't concern safety. You can still
20 have your safety concerns or you can think that the
21 device is extremely safe. This is just about
22 effectiveness. Does the device do what it claims to
23 do with regard to an alternative to warfarin,
24 understanding what that means, 45 days of treatment
25 and then you can stop the warfarin. And I'm going to

1 start with Dr. Kelly and go around the table.

2 DR. KELLY: Well, I think if we use the
3 intention-to-treat analysis, that data would suggest
4 that the device plus aspirin and Plavix is effective.
5 I'm not convinced we have data from the device and
6 aspirin alone.

7 DR. MAISEL: John.

8 DR. SOMBERG: I'm comfortable with the
9 assertion that the device, given implanted and given
10 with the conjunctive therapies for the time limits
11 specified, is effective and that the sum total, and I
12 think that's the important thing, the sum total of
13 adversity due to stroke which is both hemorrhagic and
14 ischemic is comparable. I wouldn't say superior. I
15 think that should be cut out from all discussion, but
16 I think it is comparable, is the word, to long-term
17 warfarin therapy.

18 DR. MAISEL: Sherry.

19 DR. KELSEY: Yes, I agree that it has been
20 demonstrated to be effective in that while it's not
21 superior, it's certainly no worse.

22 DR. MAISEL: Tom.

23 DR. VASSILIADES: I think it's effective.

24 DR. MAISEL: Dr. Peters.

25 DR. PETERS: I think it's effective in a

1 population that was studied here. Unfortunately, I
2 don't know what that means in terms of how this is
3 going to be used, but I think that what we've seen
4 here, I think they've demonstrated equal
5 effectiveness.

6 DR. MAISEL: Okay. Norm.

7 DR. KATO: I would have to agree with the
8 very careful wording that it is equally effective to
9 Coumadin. It is not better, you know, with all the
10 side effects of warfarin therapy, it's as good as
11 that is.

12 DR. MAISEL: Dr. Good.

13 DR. GOOD: Well, I would agree that within
14 the limits of the study, that it's not inferior. I'm
15 concerned about the timeframe, since it's a
16 relatively small timeframe, and I'm also concerned
17 about the small number of outcome events and making
18 judgments on that.

19 DR. MAISEL: JoAnn.

20 DR. LINDENFELD: Well, I'm still a little
21 bit uncomfortable. I agree that the analysis of the
22 primary endpoint was positive, but I have two major
23 concerns. One is ischemic stroke clearly isn't
24 different, and a big difference here is in
25 hemorrhagic stroke, and the incidence in this study

1 of hemorrhagic stroke in the control group was way
2 higher than other atrial fibrillation trials on
3 Coumadin by a factor of 4 or 5.

4 So with this very small number of
5 endpoints, I would say, yes, but I am not very
6 confident.

7 DR. MAISEL: Gary.

8 DR. ABRAMS: Well, I'm uncomfortable. I
9 understand the whole issue with the CEC, but there
10 are just a number of issues about that that make me
11 feel that a lot of the events that are counted here
12 as strokes, to me I'm just skeptical about them being
13 strokes. So while I don't know whether -- I guess at
14 this particular point, I'm not sure if it's
15 effective.

16 The second thing I'm concerned about is
17 whether, I think it may be an alternative to
18 Coumadin, but I don't know whether we clearly know
19 that it's working because it's definitely preventing
20 stroke by preventing thrombus in the left atrium, and
21 I have a question with that particular interpretation
22 of this, although it may well be an alternative to
23 Coumadin if I look aside of those issues of how you
24 interpret those events.

25 DR. MAISEL: Dr. Brinker.

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1 DR. BRINKER: So I would say that the true
2 measurement of effectiveness should be pretty much
3 based on ischemic stroke differences because I
4 believe that most of the hemorrhagic issues are
5 really complications of Coumadin therapy for better
6 or worse. And that's part of the problem in our
7 understanding of this. This is sort of mix and match
8 between effectiveness and safety.

9 So given the proviso, the provisional
10 answer I got from the Sponsor that the CHADS group 1,
11 which made up a third of the cases and would be
12 adequately treated by the antiplatelet arm of your
13 regimen, without the actual device itself, given your
14 answer to me that you have data that shows it makes
15 no difference of the incidence of ischemic events in
16 the above CHADS₁ group, was at least no greater in
17 your device arm than the control arm, I would be
18 happy to say that it is not inferior to Coumadin in
19 preventing ischemic stroke, and I would rest my
20 recommendation on the other side, which is what I
21 would consider a safety issue. I think it's probably
22 safe.

23 DR. MAISEL: Mike.

24 DR. DOMANSKI: Yeah, I guess I'm
25 uncomfortable, too. I think the analysis is what it

1 is and it looks like the reason it's not, you know,
2 we know that it's not more than two times inferior,
3 if you will, is based on the fact that it apparently
4 kept Coumadin out of the hands of their investigators
5 who were in the control arm. It's certainly not the
6 strongest demonstration of efficacy, but I think
7 within the bounds that we've defined it, I think
8 you'd have to say that it was effective.

9 DR. MAISEL: Fred.

10 DR. RESNIC: Yeah, I thought about this
11 earlier, and I think it is comparable in terms of
12 effectiveness in reducing the composite event and
13 reducing the complications associated with long-term
14 warfarin therapy, but I can't tease apart the
15 efficacy from the safety because, in fact, it was the
16 safety that's driving the difference. So I think
17 it's just effective because it reduces the
18 complications associated with long-term warfarin
19 therapy.

20 DR. MAISEL: Mike, any comments on
21 effectiveness?

22 DR. FLEMING: Well, from what I've heard
23 today and what I've read here, I am confident that
24 its effectiveness is there. Obviously my concern
25 would be longer term, which we'll address later in a

1 postmarket environment, but no, I think the device is
2 certainly not inferior to warfarin.

3 DR. MAISEL: Mike, do you want to comment
4 on the effectiveness discussion?

5 MR. HALPIN: From an industry perspective,
6 this is the first of a kind device where we're
7 comparing it to a therapeutic. I think that the
8 study was designed very well to evaluate the
9 effectiveness in terms of noninferiority to warfarin
10 or Coumadin. I think if you look at the actual data
11 in terms of the whole time course, it actually shows
12 a slightly absolutely lower rate, and the confidence
13 limits appear to look very well compared to what
14 their actual theoretical boundary of 2 was. So
15 they're not approaching until they're actually well
16 underneath that.

17 So I think that from an effectiveness point
18 of view, it looks to be effective. When comparing a
19 device to a therapeutic, you always have this
20 interesting difference where you're intervening and
21 looking at procedural issues as we are crossing the
22 septum and other things of that nature. So I think
23 you have to weigh those out in terms of how you think
24 about the product, but they will be different, but I
25 think they did actually demonstrate effectiveness and

1 comparability to warfarin.

2 DR. MAISEL: Okay. I thank everyone for
3 their comments on effectiveness.

4 We're going to move onto the safety
5 discussion.

6 DR. ZUCKERMAN: Okay. Dr. Maisel, that was
7 a good introductory discussion, but for the purpose
8 of the FDA, we haven't put question number 1 to rest,
9 and if I can explain why. Let me indicate what
10 additional questions the FDA has.

11 Number one, I'd like the Panel members to
12 look at FDA's slide 65, which shows the Kaplan-Meier
13 curve and the amount of follow-up at different time
14 points. It would be quite helpful if we better
15 define effectiveness. Are we talking about acute
16 effectiveness, midterm effectiveness, chronic
17 effectiveness?

18 The second point is that the question asks
19 us to drill down on the composite effectiveness
20 endpoint. This morning, the Agency presented some
21 data regarding systemic embolization occurrence, and
22 we would like a discussion about whether perhaps we
23 have missed some embolic events and whether that
24 might change our interpretation of effectiveness
25 here.

1 DR. MAISEL: John.

2 DR. SOMBERG: Well, I'd like to address
3 your first point, and that is that I think we're
4 talking about short-term effectiveness. I think this
5 is a good start to the study, but like most of the
6 studies we've seen, the follow-up long-term is never
7 adequate, and we need more information, and your
8 slide 65 emphasizes that, you know, 2 years, 52
9 versus 92, 12 versus 22, at 3 years, you know, really
10 very small numbers.

11 So that has to be certainly rectified, and
12 I also want to say is whatever my personal
13 recommendations are, so I mean that's all they are is
14 recommendations to the regulatory body, and you're
15 charged congressionally with the responsibility of
16 the public health here. So I mean the question is do
17 you want to approve a drug or a device, I'm sorry,
18 but do you want to approve a device that's based on
19 short-term follow-up, or do you want to wait for
20 another few years to get more data.

21 So my comment initially about 25 minutes
22 ago about effectiveness or comparability was short-
23 term, and I must say I don't see anything diverging,
24 you know, the differences in this Kaplan-Meier line,
25 but I think that's very small numbers. I don't see

1 anything diverging in the wrong direction that would
2 raise eyebrows, but I would hope we would rectify
3 this in a postmarketing, if this is recommended and
4 receives approval, postmarketing study.

5 DR. MAISEL: David.

6 DR. GOOD: Well, if you look at these
7 Kaplan-Meier curves, I mean the numbers are very
8 small in terms of numbers of patients, but it's
9 almost as if the lines become almost more parallel
10 towards three years, but it's too small a number of
11 patients to really judge. But, you know, that's my
12 concern, too. If it's long-term, I'm not sure we
13 really have the answer.

14 DR. MAISEL: Mike.

15 DR. DOMANSKI: The thing that I think is,
16 you know, in effect is a flaw in the design relative
17 to ascertainment of endpoints here is the fact that
18 you don't have scans on these people down the pike,
19 that you just have the clinical events of stroke. I
20 don't know what would happen if these people had been
21 studied, how much silent embolism there is or how
22 much embolism that's not recognized there is, and I
23 think the, you know, I don't know what the right way
24 to put this is, the risk to the Agency of, you know,
25 of putting this out on the street is having somebody

1 come back later and find out that there are a lot of
2 strokes that just didn't get recognized in this very
3 small trial with probably less than optimal approach
4 to ascertaining the stroke endpoint.

5 DR. MAISEL: But the truth is that this was
6 the study design that was agreed upon.

7 DR. DOMANSKI: Well, that's a formalism. I
8 mean I'm giving you what I think is a reasonable
9 scientific thing, and then they can, you know, deal
10 with the regulatory side as they wish.

11 DR. MAISEL: Right, but there's also -- is
12 there reason to believe that -- we don't know, right?
13 I mean we don't know if they're asymptomatic --

14 DR. DOMANSKI: Well, I think there's a flaw
15 in the design.

16 DR. MAISEL: -- and we just don't know.

17 DR. DOMANSKI: I think there's a flaw in
18 the design. Let me put it differently. I think that
19 a better design study would have looked for emboli
20 that were not clinically apparent, and I think if you
21 were designing this study as a scientific study, you
22 know, I think that that would be a significant
23 criticism when you go to publish it.

24 DR. MAISEL: Other comments regarding
25 Dr. Zuckerman's points about effectiveness duration

1 or composite effectiveness?

2 DR. SOMBERG: What was the second point?
3 You had another point that I didn't address.

4 DR. ZUCKERMAN: Okay. The first point was
5 to look at slide 65 to better describe what you mean
6 by effectiveness duration.

7 The second point was to look at Table 2 to
8 drill down on each component and the one component
9 that wasn't discussed in detail until Dr. Domanski's
10 points, was systemic embolism. Are there more that
11 just weren't picked up with the way the trial was
12 performed?

13 DR. MAISEL: David.

14 DR. GOOD: We know that a number of strokes
15 occur with implanting this device. It's clear. So
16 the question is, I think, whether more than one
17 stroke could be occurring or subclinical. You might
18 find a show of emboli if you did a CT scan or MRI
19 scan. We don't know. And I agree, it would be
20 somewhat embarrassing to approve the device and find
21 out later in post-approval trials that, in fact -- of
22 emboli were occurring with implantation. We don't
23 know. It would have been nice to have imaging
24 studies, but we don't have them.

25 DR. MAISEL: John.

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1 DR. SOMBERG: But the clinical outcome is
2 what is most important from the patient's point of
3 view, and I think also the physician following it.
4 These nonclinical strokes, let's say we scanned
5 everybody, we did MRIs on everybody. It might be
6 very interesting information, and we know it goes up.
7 I mean there are studies on atrial fibrillation, all
8 these nonclinical, but the real question is, what's
9 happening, and I must say I do give the Sponsor a lot
10 of credit for their initial discussion of what
11 happens with strokes because in some of the ischemic
12 strokes, they were mild. In the hemorrhagic ones,
13 you're dead. So I do agree with my colleague who
14 said that, you know, maybe this is referring to, you
15 know, get rid of Coumadin, that's the major benefit
16 here, but that is a benefit, and therefore I'm most
17 satisfied with the clinical outcome. So I wouldn't
18 think looking at that.

19 But I would say is that the 45-day period
20 that's blank for toxicity, I think that has to be
21 emphasized especially when someone talks to a patient
22 that the initial implanter who doesn't have that much
23 experience is going to have a lot of toxicity, and
24 that's going to be upfront, and you have to take that
25 into consideration. So someone has to balance, well,

1 I might have two years later a hemorrhagic stroke and
2 die, but I could have an air embolism and die during
3 the procedure, and do I want an extra two years or
4 not.

5 So the data has to be presented or be
6 presentable or be there for the person who's going to
7 be discussing it with the patient to be able to
8 present because that's going to be very important.

9 DR. MAISEL: Okay. So we'll obviously be
10 revisiting some of these points again as we go
11 through the rest of the questions, but let's move
12 onto safety at this point.

13 Question 2, safety. Do the data provided
14 from the PROTECT AF study provide a reasonable
15 assurance of safety? In your discussion, please
16 specifically comment on the incidence and
17 significance of the pericardial effusions associated
18 with the use of the device. Please also comment on
19 the incidence of device embolization and thrombus
20 present on the device.

21 So this question basically covers all the
22 big ticket items that we discussed and heard about
23 with the pericardial effusions, some requiring
24 surgery, some episodes of thrombus and device
25 embolization, other surgical complications, et

1 cetera. So other thoughts regarding the safety.

2 Tom.

3 DR. VASSILIADES: I'm most concerned about
4 the thrombus, and I think something that JoAnn said
5 earlier about if it's not completely occluded, then
6 you create a worse situation.

7 So I think it really underscores the fact
8 that you're not going to know which patients are
9 going to have to come off of Coumadin and who are
10 going to have to stay on it when you put the device
11 in.

12 You're just going to have to limit the use
13 of it to people who can continue to take warfarin. I
14 think that it's going to be absolutely -- I mean we
15 don't really know the answer of whether or not
16 patients can come off of Coumadin long-term because
17 you don't know which one of those patients
18 necessarily who can't take Coumadin initially then
19 will have to be on it because you've created a
20 situation where now they're even more likely to have
21 a stroke.

22 DR. MAISEL: John.

23 DR. SOMBERG: I sort of disagree with that,
24 and I think more people in this study came off
25 Coumadin than had to return to it. It was a small

1 number. It was like 8 percent, 9 percent of
2 patients. So I think we can safely say that people
3 can come off Coumadin and do comparably to the group
4 that continues Coumadin.

5 I think what we can't say, and this is my
6 great concern, is that this substitutes for warfarin
7 therapy and you give it to people who can't ever take
8 warfarin. That has to be studied because to get into
9 this program, you have to be able to take aspirin,
10 you have to be able to take clopidogrel, and you have
11 to be able to take warfarin. And if you can't take
12 those three, you can't get the device on day one. So
13 that's critical.

14 Now, maybe there's another study I heard
15 was mentioned, to study, you know, in Europe first,
16 that uses the device without any Coumadin. That
17 would be interesting. I have my doubts, but right
18 now I think the majority of people came off Coumadin
19 and we didn't see a major blip in adversity. And the
20 idea that if you're only partially occluded, it gets
21 worse, that's based on a very, very few patients.

22 DR. LINDENFELD: But it's based on a fair
23 amount of surgical data, not a huge number, but a
24 fair number of patients where a clot clearly
25 increases when you partially occlude the appendage

1 from the stapling trials.

2 I want to just come back for a second
3 because I think this is both what Bram brought up,
4 and then safety, too, is that I do think -- at first
5 I wasn't worried about not doing any sort of standard
6 imaging to look for emboli because I figure, well,
7 it's the same in both groups, but it's actually not
8 the same in both groups as I think about it more.
9 Because when you look really early on, a device,
10 there was a higher incidence of events early on, and
11 with the control group, it was sort of a steady
12 progression, but that means we missed -- if we had
13 done imaging and we just sort of, a lot of events are
14 asymptomatic, by not doing routine imaging, we may
15 have missed more early on associated with the
16 procedure. So it's not a big deal, but I do think us
17 not doing imaging especially early on after the
18 procedure might bias for the device rather than
19 against.

20 DR. MAISEL: Jeff.

21 DR. BRINKER: I think that what John was
22 saying, I could live with very happily if the
23 assumption is that the TEE guidance as done in the
24 study were mandated for clinical care, which is a big
25 load of TEEs over the course of the time, but

1 otherwise I think that the concern about not doing
2 that and therefore not recognizing something and not
3 treating it, even 20 percent with Coumadin, could up
4 the event rate by 10 or 20 percent. So I would agree
5 with that.

6 DR. VASSILIADES: So what you said was, I
7 mean we're already looking at a fairly low number
8 comparatively speaking of people who are therapeutic
9 on Coumadin, and if we have that low rate of success
10 out there in the community, I mean it's 60, 65
11 percent in the clinical trial and maybe lower in the
12 community, now you're expecting at least that for
13 TEEs. I think you're expecting a lot in terms of
14 compliance with that.

15 So what I'm saying is that it's hard --
16 we're not doing such a good job in keeping people
17 therapeutic on their Coumadin, and now we're going to
18 have to try to make sure that they get in for their
19 regular TEEs, and you do a good exam and you're able
20 to adequately visualize the device and adequately
21 determine whether or not there's flow around it or
22 whether there's thrombus on the face side of it. I'm
23 not so sure that that's -- that to me would probably
24 be even more of a difficult thing to do than maintain
25 people on Coumadin.

1 DR. BRINKER: Well, if you're going to
2 maintain people on Coumadin, then there's no real
3 rationale for the device in the first place, but I
4 think it's not so hard actually from my own clinical
5 experience. Patients with atrial fibrillation, they
6 get a lot of cardioversions. They get a lot of TEEs.
7 Sometimes they're not on Coumadin or they're off it
8 for a little bit and then they get this.

9 And by the way, one of the questions that
10 should address this, patients who get cardioversion
11 who have the device and they're not on Coumadin, I
12 would wonder whether they should be TEE'd before they
13 get cardioverted. That wasn't addressed, but that's
14 some other issue that you'll have to --

15 DR. VASSILIADES: Can they even be
16 cardioverted? I guess they must.

17 DR. BRINKER: I don't know.

18 DR. VASSILIADES: Well, I mean I guess
19 after a certain period of time, the device is well
20 integrated into the tissue.

21 DR. LINDENFELD: Somewhere doesn't it say
22 at least not for 30 days? There's some
23 recommendation in the booklet that says people
24 shouldn't be cardioverted within 30 days of the
25 procedure. There wasn't any data for why that

1 recommendation --

2 DR. REDDY: It was exactly 30 days. So
3 there's no intervention or cardioversion allowed
4 within 30 days of the procedure. So indeed patients
5 did have cardioversions but beyond the 30-day time
6 point after the implantation.

7 DR. MAISEL: So are you suggesting that the
8 AHA guidelines for anticoagulation around patients
9 with atrial fibrillation and cardioversion don't
10 apply once you get this device?

11 DR. REDDY: Well, what we've done in the
12 study is that after the 30 days, after the patient's
13 appendage has been treated, they were allowed to have
14 cardioversions at that point with whatever therapy
15 they've had, whether aspirin or aspirin plus Plavix.

16 UNIDENTIFIED SPEAKER: Without TEE.

17 DR. REDDY: Without TEE, that's right. But
18 again that's what was done in the study. I don't
19 think we're making any claims one way or the other in
20 this presentation.

21 DR. MAISEL: David?

22 MR. GOOD: Just getting back to the primary
23 question here, the evaluation of safety in more of a
24 global sense, you know, when you look at some of the
25 graphs that we've seen some of the tables, for

1 example, slide 82 of the FDA, and page 70 of 95 on
2 the material we have on the -- I think this is on the
3 Sponsor's summary, you know, you're talking a
4 percentage here. When I add them up, I think 10.3
5 percent of randomized patients had a safety event
6 under the device, 5.4 under control and, you know,
7 that's also reflected on slide 82. And these are
8 not -- many of these devices are fairly significant.

9 DR. BRINKER: But most of those, the device
10 were implant related --

11 DR. GOOD: Right.

12 DR. BRINKER: -- and I think we can believe
13 that they're going to go down with experience like
14 every other device we've ever used.

15 And the second thing, my feeling is that
16 eventually you all will be putting them in in
17 Coumadinized patients anyway because there's an
18 increase in confidence that you can do TEEs, you can
19 do afib ablation, and you can probably put this in a
20 patient that continues to be on Coumadin.

21 DR. MAISEL: So I actually think that's a
22 good table. If everyone on the Panel could turn to
23 page 70 of 95 in their packet, it's the Sponsor's
24 Executive Summary. It's Table 1023, and it lists the
25 primary safety events by type and intention-to-treat,

1 because I think it really summarizes the balance very
2 nicely.

3 DR. SOMBERG: Can you just give us a moment
4 to find that?

5 DR. MAISEL: Sure. That's page 70 of 95.
6 It's the third tab in your packet I believe. It
7 might be -- it's the fourth tab. Fourth tab, and
8 then page 70 of 95. So it's Table 1023, and as David
9 was pointing out, I mean basically it shows you the
10 cost of the device from a safety standpoint. There's
11 22 serious pericardial effusions or 4.8 percent, as
12 well as some acute ischemic strokes that are balanced
13 by the 2.5 percent hemorrhagic strokes which are the
14 safety on the other side.

15 So we basically need to decide whether it's
16 worth those events to save those hemorrhagic strokes.

17 DR. BRINKER: So once again, you have to
18 believe that this, as their preliminary data show,
19 and as every other procedure we've ever done shows,
20 that this is now approaching a 1 percent -- or
21 serious pericardial effusion.

22 So I know that this is true, this exists,
23 but I'd be willing to even accept 1 to 5 percent
24 incidence which we get in atrial fibrillation
25 ablation procedures, 1 to 5 -- for some benefit. In

1 this case, I'd rather have that than hemorrhagic
2 stroke on Coumadin.

3 DR. MAISEL: So I would just take issue
4 that it tends to get better. I think it gets worse
5 before it gets better. When it goes out to the real
6 world, and --

7 DR. BRINKER: And then it gets better.

8 DR. MAISEL: And then it gets better. I
9 agree with that.

10 DR. DOMANSKI: You know, it's hard to
11 operate on that kind of promise though, you know, it
12 really is. That I don't think is really a data
13 driven decision. You know, the data that are
14 presented here actually do show a lot of
15 complications of this procedure, and they're serious
16 complications. So I'm not sure that I'd be willing
17 to set them aside by just saying, well, it's going to
18 get better, you know. Maybe it will, but prove it.

19 DR. MAISEL: Other comments on safety?
20 Norm.

21 DR. KATO: I would have to agree with Mike.
22 You know, we've had that experience in cardiac
23 surgery. You know, years ago we'd try to go into
24 minimally invasive and do all this fancy stuff with,
25 you know, try to make it more catheter driven, and

1 all we did was just make it more complicated,
2 outcomes were worse, and everybody, you know, they've
3 pretty much gone away, gone back to the standard
4 tried and true open heart surgery. So I have to
5 agree with Mike.

6 DR. MAISEL: Other safety comments? Fred.

7 DR. RESNIC: I think that, you know,
8 there's clearly over-exuberant adoption of technology
9 if it were to be approved. I think history, at least
10 interventional cardiology and also in
11 electrophysiology for complex procedures that are
12 performed that do go through profound learning curve
13 effects, I think that there's data actually out of
14 NCDR looking at interventional cardiology procedures.
15 The decision shouldn't pivot on this point, but
16 undoubtedly complication rates do go down in
17 experienced centers over time. You can look at the
18 outcomes of traditional cardiac surgery over time,
19 the tremendous reduction in bleeding risks and
20 adverse outcomes in hospital, long-term outcomes,
21 same thing in interventional cardiology, device
22 implants, ICD implants. I think it's universal.

23 So I don't think that it is necessarily
24 important to predict what that benefit will be, but
25 it's unlikely to be worse over time. In fact, all

1 history points to being better, but it takes communal
2 experience to get there.

3 DR. MAISEL: Other specific safety comments
4 or observations?

5 So I'd again just like to go around the
6 table and just hear individually your thoughts on
7 safety, whether you think -- obviously it's hard to
8 do safety in isolation without balancing the benefit
9 you get. I'm going to start this time on this end,
10 Mike, and hear your thoughts.

11 MR. HALPIN: Okay. So I'll leave most of
12 the discussion to the medical folks. The only thing
13 that I wanted to bring up was that if you look at the
14 category, the largest one in the device group seems
15 to be pericardial effusion, and I was just wondering
16 from your perspective, is that just the cost of doing
17 interventional business and how you actually get
18 there versus a very device related one, and obviously
19 it's an issue, but it seems to be something that may
20 be very standard for that type of procedure versus
21 very specific to this device.

22 DR. ZUCKERMAN: Okay. If I could interrupt
23 just before the other M.D.'s try to answer this
24 question. In addition to the overall gestalt of
25 composite safety, how does it compare to the control

1 group? We're specifically asking you to hone in on
2 three safety problems. One is pericardial effusions.
3 You know, to elaborate on some of the comments that
4 Dr. Brinker was making, do you think that with this
5 device, that's still a significant safety problem or
6 not, so that there are acute safety problems. And
7 then there were chronic safety problems that were
8 elaborated on this morning, the most prominent one
9 being thrombus at varying time points.

10 So if one could give us a general gestalt
11 as well as to hone in on effusions, thrombus, and
12 device embolization problems. Thank you.

13 DR. MAISEL: So just to follow-up with your
14 question, I mean for similar left atrial procedures
15 like an ablation, the pericardial effusion rate would
16 be or perforation rate would be expected to be around
17 one percent. Dr. Fleming, do you want to comment on
18 the safety issue?

19 DR. FLEMING: Well, I believe that it looks
20 to me like the device is safe relative to the use of
21 warfarin. I personally, as a potential consumer of a
22 device like that, would prefer a device over
23 Coumadin, but from the data that I've seen, the
24 device appears to be safe for its intended use.

25 DR. MAISEL: Fred.

1 DR. RESNIC: I think it is safe in the
2 context of the comparison to which the analysis was
3 performed with regard to the three considerations. I
4 think one has to differentiate procedural pericardial
5 effusion due to catheter perforation at the time of
6 transseptal puncture as well as device manipulation
7 in the very, very thin wall, left atrial appendage
8 structure, separate that from the later effusions
9 that were documented, which I believe were thought to
10 be due to relative oversizing, stretching of the left
11 atrial appendage, and small tears in the structure
12 itself. Separating the two causes of pericardial
13 effusion, I think the first is addressable through
14 very strict recommendations regarding the training
15 and experience if this were to roll out as an
16 approved device. And that I think has to be a
17 critical component of the consideration for the
18 discussion.

19 I believe that the device specific
20 effusions as evidenced by the FDA and the
21 manufacturer seems to be well within the acceptable
22 range in my opinion. The two other complications or
23 two other safety effects were device embolization. I
24 think the rates are actually quite low given the
25 complexity of the procedure, and thrombus on the

1 device I don't know has really been definitively
2 associated with any clinical endpoint. So I would
3 say that in all those regards, safety seems
4 adequately demonstrated given the small sample size
5 and always in reference to the comparative group.

6 DR. MAISEL: Mike.

7 DR. DOMANSKI: You know, it's a little bit
8 hard to parse, to really completely separate the
9 things, but you're certainly not taking about
10 something that's more effective than the Coumadin,
11 and in looking at the pericardial effusion that it's
12 generating, I mean it's pretty hard to look at these
13 data and say that that demonstrates safety at least
14 in my view.

15 I think with respect to the other, the
16 device embolization, I guess, you know, three is a
17 pretty small number. There were a lot of implants.
18 One could certainly see that happening, I guess. So
19 it's a very qualitative thing, but it seems like a
20 small number. But I would be concerned about a
21 safety of a thing, particularly when the device is
22 not better than the Coumadin, of accepting this kind
23 of a complication rate with pericardial effusion.

24 DR. MAISEL: Jeff.

25 DR. BRINKER: So first I'd like to

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1 compliment the electrophysiologist in Boston for
2 getting over the learning curve of atrial
3 fibrillation ablation so quickly because most places
4 had a 1 to 5 percent perforation rate with the higher
5 number during the first year or so of their
6 adaptation of this technology. And I think you have
7 to accept it.

8 The second thing is that you can't judge
9 safety for this device by adding up the total number
10 of adverse events for the device and the total number
11 of adverse events for the drug, in coming to an
12 analysis in that way, because the device will lose
13 clear away. It's two things. One is the impact of
14 the adverse events that occur, and an intracranial
15 hemorrhage is huge. We all know it. Coumadin has a
16 long and semi-distinguished career in treating a wide
17 variety of different disease processes and implant
18 processes, and there's always this forever risk of
19 something happening, and here you have the five or so
20 intracranial hemorrhages, I think it was five, in the
21 Coumadin group over this period of observation versus
22 a large number of adverse events. They are of
23 concern, but they're unassociated with death.

24 So I think if you take that route, I don't
25 think there's a patient, especially as they get

1 older, around that would not accept the rate of
2 pericardial effusion and potential surgery to fix it
3 than the possibility of having to take Coumadin for
4 the rest of their life, and if they fall, which
5 eventually most will on occasion, or if they have
6 hypertension or any other predisposing fact to an
7 intracranial hemorrhage, we'll have that.

8 So that said, a small group of patients,
9 we're dealing with small numbers of adverse events in
10 both groups. I know that the numbers will get better
11 with the device, and they're not going to get better
12 with the Coumadin.

13 DR. MAISEL: Gary.

14 DR. ABRAMS: I'd like to view it the same
15 way in terms of safety impact. I think that the
16 safety impact, if you take a look at it like that,
17 the device I think wins out in that particular
18 analysis because of the devastating effects of the
19 Coumadin, which I think would occur if you follow
20 this out long-term, you're just going to have more
21 bleeds from more accidents, falls, whatever, over the
22 years.

23 From the same perspective that I question
24 the efficacy, whether the efficacy is as good, I do
25 think though that if the efficacy were as good, the

1 safety would be a major positive factor here.

2 The question with thrombus, I don't know
3 whether we can say what the long-term implications
4 are of thrombus formation. I just don't think
5 there's anything here to -- we don't know enough
6 about the incidence of thrombus formation and what
7 the incidence of later embolism. So I'm not sure we
8 can comment on that at all.

9 DR. MAISEL: JoAnn.

10 DR. LINDENFELD: I think I agree with most
11 of these comments. I'm not too worried about the
12 pericardial effusions. No one likes to have surgery
13 to have that relieved, but they seem to be relieved
14 safely. And the device embolization is bad, but it's
15 a small number.

16 But I am concerned about two issues in
17 safety. The first is that although it appears safe
18 because hemorrhagic strokes are a problem, once again
19 I come back to this issue of these are very small
20 numbers, and this is a much higher incidence, 1.7
21 percent of hemorrhagic events than we've seen in any
22 other atrial fib study. And there are clearly more
23 ischemic strokes with the devices.

24 So if this is just a matter of small
25 numbers and we have overestimated the hemorrhagic

1 strokes in the control group, and we only had seen
2 one in this, then this wouldn't be a safe device.
3 We'd have far more ischemic strokes. So it's hard to
4 say. The numbers are what they are. This was a
5 randomized trial, but this is probably, you know,
6 close to a fivefold increase in hemorrhagic strokes
7 than we would expect to see.

8 In terms of thrombus on device, I think
9 it's a small number, but they need to be continued on
10 warfarin, and I'm not comfortable that we know really
11 that these patients are going to get TEEs, you know,
12 as Tom mentioned, and that at the very least we're
13 going to have to mandate some kind of protocol for
14 that to be sure.

15 DR. MAISEL: David.

16 DR. GOOD: Well, first of all, regarding
17 the pericardial effusions, as a noncardiologist, I'm
18 really not in a position to judge this. If it's
19 relatively easy to correct it, I certainly can live
20 with that. Superficially, it seems bothersome to me.
21 It's not my area, so I'm going to back off on that
22 one.

23 The second thing, device embolization seems
24 rare. To me it seems at least one case that there
25 was valvular damage was a problem, but it's a very

1 rare complication. So I'm not particularly concerned
2 about that.

3 Thrombus, it's hard to tell. There's not
4 enough data, I think, to really to say.

5 There's one other thing that hasn't been
6 mentioned yet that I'm a little bit concerned about,
7 and that's the multiple attempts it takes to place
8 this in some people. Sometimes it's impossible to
9 place it at all. It seems to be a little bit
10 bothersome to me that it might take three or four
11 attempts to place, and I think a couple of strokes
12 actually occurred during that, and I don't know if
13 that's a significant risk or not, but we haven't
14 really addressed that. I guess it's kind of buried
15 in the total number of periprocedural strokes. So
16 that's all I would say.

17 DR. MAISEL: Norm.

18 DR. KATO: I guess bottom line is I would
19 have to join JoAnn. I'm still very nervous about the
20 small numbers, and again it all comes back to study
21 design, you know. I mean even the issue about is
22 this really the mechanism to treat this problem or is
23 this just another device looking for a disease
24 process. But the small numbers make me very
25 apprehensive about making a conclusion about safety

1 and efficacy.

2 DR. MAISEL: Dr. Peters.

3 DR. PETERS: Small numbers notwithstanding,
4 I think that the safety profile is acceptable in the
5 way this was used in the population that was studied.
6 But I wouldn't go beyond that.

7 DR. MAISEL: Tom.

8 DR. VASSILIADES: Again, I think I'm most
9 concerned with thrombus because that's not so much a
10 function of the line curve as the other two
11 complications are, but more inherent in the device or
12 the process. And I just have concerns about that
13 still.

14 DR. MAISEL: Dr. Kelsey.

15 DR. KELSEY: Based on the data that I've
16 seen, I would say that yes, it's acceptably safe.

17 DR. MAISEL: John.

18 DR. SOMBERG: A lot's been said, and I
19 don't want to repeat it, but my additional thoughts,
20 especially to what my agreements with Dr. Brinker
21 were, number one, Dr. Lindenfeld, you said the small
22 numbers, but if there were larger numbers, maybe the
23 hemorrhagic stroke would diminish, but maybe also the
24 ischemic stroke on the device side would diminish as
25 well in regression to the mean. So I have a hunch

1 that we would tend to find similar results more
2 likely than anything else, but, you know, the larger
3 the study, sometimes you're surprised, and that's why
4 it's always good to address new things.

5 The second point is the thrombus. I think
6 thrombus is one of the most critical issues on the
7 device because we have such small data afterwards,
8 and therefore I think it's very critical to mandate a
9 postmarketing study looking at that and getting a
10 handle, but until we have more information on that,
11 we must mandate the use of dual antiplatelet therapy.

12 And that comes to my last point. Where I
13 think the greatest benefit of this device is, it's
14 not that everyone should immediately stop Coumadin
15 therapy and go onto this device, but there is in my
16 practice, and I think others' as well, there are many
17 patients who have atrial fibrillation, have a strong
18 indication for anticoagulation and need to stop it
19 for a host of reasons. And maybe they have
20 Parkinson's disease and are falling. Maybe they need
21 an arthroplasty or something of that nature, and
22 while surgeons yell and scream, or orthopedic surgeon
23 or other procedures, yell and scream about doing
24 things on dual antiplatelet therapy, it can possibly
25 be done, but it certainly can't be done on Coumadin

1 therapy. And, therefore, I think that's going to be
2 a major use of the device and I think a justifiable
3 use where people can stop Coumadin and go on to
4 having this device in place for something elective or
5 some other procedure. There was no point that I
6 blacked out on. Okay. I'm sorry.

7 DR. MAISEL: Dr. Kelly.

8 DR. KELLY: I don't think I have anything
9 tremendously different to say. You know, the Kaplan-
10 Meier curves, you know, the AEs aren't weighted and
11 it's difficult to weight them. I think everybody
12 would agree a pericardial effusion is not as bad as a
13 hemorrhagic stroke. Still at three years, the curves
14 don't meet, you know. The argument's been there's a
15 lot of upfront risk and then it will even out. And
16 at three years, with very, very small numbers, they
17 don't meet. So I'm not convinced we've demonstrated
18 safety.

19 As with most other people, I don't think we
20 have enough information about the thrombus, and
21 device embolization is rare enough I don't think it's
22 a huge issue.

23 DR. MAISEL: Okay. Dr. Zuckerman, any last
24 safety questions or issues before I move on?

25 DR. ZUCKERMAN: Well, I did hear a

1 divergence of opinion. So why don't you try to
2 summarize what you heard the Panel say for the
3 record.

4 DR. MAISEL: My summary would be there's a
5 divergence of opinion and that the precise balance
6 for individuals with regard to effectiveness, we'll
7 find out in a few minutes or in a little while with
8 our vote, I think you've summarized it. It's clear
9 that some people have lingering concerns and some
10 people feel that there's enough data to suggest that
11 it's safe.

12 So we'll drill down on those points a
13 little bit more, but I think we'll move on and see
14 what the balance is in a little while.

15 So for question 3, which is the training
16 program, the pivotal trial demonstrated that
17 qualified physicians need to carefully place this
18 device in order to minimize acute procedural
19 complications. Is the applicant's proposed training
20 program adequate for training a new set of physicians
21 in this procedure?

22 As best I could tell is the applicant's
23 proposed training program slide 101 that was
24 presented earlier, I didn't -- I don't know that I
25 was able to find a specific proposed training program

1 other than a -- is slide 101? So slide 101 in the
2 presentation this morning shows proposed simulation,
3 case observation, online case review, and testing.
4 Specifically lacking from the training program was
5 proctoring, an actual device implant with a physician
6 who's implanted one before. Specifically absent was
7 a specific mention of an industry person there to
8 support the implant. I don't know how we feel about
9 that issue. I'd be interested in hearing about that.
10 We didn't hear anything about certification or those
11 type of things. If we truly have major issues about
12 the acute procedural implantation, we can talk about
13 some of these issues.

14 So training, what should it be? Fred.

15 DR. RESNIC: I'm particularly concerned
16 about this issue. I think that the results that were
17 admirably achieved with the trial will not be likely
18 reflected if adopted by less exceptional centers, and
19 therefore, you would pay an enormous price in terms
20 of safety if we do not recommend an increased level
21 of training than what has been recommended by this
22 single slide.

23 So I think that one ought to consider or I
24 would recommend that there be some level of
25 certification and that there ought to be live

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1 proctoring.

2 DR. MAISEL: Certification by whom?

3 DR. RESNIC: Well, I think we would have to
4 leave the FDA to have the Sponsor, Atritech, make a
5 recommendation regarding certification and that
6 Atritech would maintain that certification, but the
7 certification should include both transseptal
8 puncture expertise as well as device implant
9 expertise. You'd have to qualify for both in my
10 opinion, and that one should be proctored, whether
11 for one or two number of cases, by someone who's done
12 more than one or two before.

13 DR. ZUCKERMAN: Dr. Resnic, could I ask you
14 to elaborate on that? From what we've heard, around
15 the table so far, ideally a fully qualified physician
16 should have an acute procedure success rate with this
17 device greater than 90 percent, and a pericardial
18 effusion rate of around 1 percent. How do you get a
19 new physician there?

20 DR. RESNIC: Well, I think that actually
21 what the Sponsor has laid out is an excellent start.
22 I think it's primarily didactic. There's some
23 simulation training, which I think is wonderful, you
24 know, augmenting the didactic, but I think by the
25 nature of the recruitment of centers into a trial of

1 a novel device, for which there's really very limited
2 predicate experience, that is even the
3 electrophysiologists who are the most experienced at
4 manipulations of catheters in the left atrium aren't
5 spending a lot of time in the left atrial appendage,
6 which is the thinnest wall structure.

7 So I would say that how do you get upon
8 launch? We should recommend a standard of experience
9 by qualified physicians by which I would
10 unfortunately burden the Sponsor, the manufacturer,
11 to certify all physicians who are going to be
12 implanting these devices to have all the
13 qualifications of training plus for their first X
14 number of successful implants, be proctored by an
15 experienced person. They have 59 centers, 55 of
16 which are in the United States. They have reasonable
17 geographic distribution. I think it's a burden, but
18 a burden worth imposing upon the Sponsor if this were
19 to be approved, that the rollout be as safe as
20 possible.

21 And I'm really concerned that if you don't
22 require those hurdles, that because of the
23 attractiveness to the patient population, the pull
24 through demand will be large, and there will be an
25 interest in providing for this device for patients

1 who simply don't want to be bothered with Coumadin
2 and INR checks, and I think that will encourage less
3 than experienced physicians to attempt this when they
4 should not be doing so without proper training.

5 DR. MAISEL: So other comments from people?
6 We've heard about some ideas. Jeff.

7 DR. BRINKER: There are a lot of things
8 that need to and should be done, and I think it's
9 hard to know how much the Sponsor has in mind since
10 the slide doesn't represent it, but I think choosing
11 the right anatomy, atrial appendage anatomy and the
12 right device, both in terms of delivery and size, is
13 key, and both the echocardiographer and the
14 interventional electrophysiologist or cardiologist
15 should be well trained in some of these nonphysical
16 things before they get to the physical manipulation
17 of the device.

18 Now, I think that the company, if not by
19 ethics, by mandate, should be responsible for
20 tracking for X number of time or procedures. The
21 performance of people they train, they shouldn't over
22 commit, if the device is approved and on market, over
23 commit to a large number of people all at once to
24 train them and end up doing less than a credible job
25 in doing that.

1 I think this is a little bit different than
2 most of the other devices that we see, but no
3 terribly different. I'm sure that interventional
4 cardiologists that have done ASD and PFO closures,
5 have been in the left atrium a lot and know how to
6 unscrew a cable from a deployable device. Those EP
7 guys that have ablated all the veins in the left side
8 of the heart probably have been in the left atrial
9 appendage more times than they'd like to. They all
10 have a head start, but they just need to have the
11 specifics, the concerns that pertain to this device
12 in particular.

13 Again, a lot in terms of anatomy and ways
14 to get around anatomy. Who is not a good candidate,
15 what complications they run into, and be prepared to
16 demonstrate knowledge in how to overcome or get
17 around or treat those complications acutely should
18 they occur. I think that should all be part of the
19 process, and it's not something that's terribly
20 burdening if the Sponsor takes the right view of
21 this.

22 DR. MAISEL: So can we drill down a little
23 bit and be more specific? So, first of all, is there
24 a consensus that there should be proctoring of actual
25 implantation standing next to a person who has done

1 the device before, or do some people think that's not
2 necessary? Do some people think animal or simulation
3 is enough and you can stand there by yourself alone
4 and do your first one?

5 DR. BRINKER: I think there needs to be
6 somebody there personally.

7 DR. MAISEL: Does everyone agree with that?
8 I see everyone shaking their heads.

9 So how many times does someone need to be
10 there? Give me a number.

11 DR. BRINKER: So I would say some of it
12 depends on the experience of transseptal and device
13 use of the particular operator, but I would say at
14 least three.

15 DR. MAISEL: So let's assume proficiency at
16 transseptal in general, maybe not with these big
17 sheaths, but let's presume the operator is proficient
18 in transseptals. How many? So we have three. Is
19 that about the right number?

20 DR. BRINKER: That --

21 DR. MAISEL: Okay. So the things I wrote
22 down were the concept that the training program
23 should include demonstration of proficiency at
24 transseptal catheterization. I mean that can be
25 defined by somebody who's done a whole bunch of them

1 or in some other fashion. A didactic training
2 program and passing the test that's been proposed by
3 the Sponsor. That would include issues like patient
4 selection, device selection, and management of
5 complications. And then actual proctoring of device
6 implants, the number to be determined but somewhere
7 it sounds like in the 2 to 3 or 2 to 4 range is kind
8 of what the sense is.

9 I would also comment that I think there
10 should be training for echo readers and certification
11 of echo readers as well in. That could potentially
12 just be an online thing or some other program for
13 people to read echos, and that obviously should
14 include both the operators but also anyone who's
15 going to officially read a TEE or perform a TEE.

16 DR. BRINKER: So knowing what I know of
17 most operators, I think that the echo attending or
18 person who's responsible for the TEE at the time of
19 the procedure should be there and understand the ins
20 and outs of the device procedure well enough to help
21 the operator.

22 DR. MAISEL: Tom.

23 DR. VASSILIADES: Another idea would be to
24 have online presentation of the cases and in a
25 certain amount for each center. So basically show

1 the echo clinical data and have experienced centers
2 review and discuss and see whether these people are
3 appropriate to begin with. So I think that patient
4 selection is just as important as having somebody
5 there to help you do the procedure.

6 DR. MAISEL: Yeah, and the Sponsor did
7 include that as part of their proposed training
8 program.

9 DR. ZUCKERMAN: Could you elaborate on how
10 you've picked three as the number for training a new
11 investigator when it took the whole trial really to
12 train perhaps the best investigators in the U.S.?

13 DR. BRINKER: So, first of all, the trial
14 helped establish best practice. So once you have
15 these people go through this, I think there's a
16 better understanding, I mean the original group,
17 there's a better understanding of the right ways to
18 do something, the little pearls and hints and stuff
19 that help get the right size device in the right
20 place, the best echo planes to imaging, when the
21 echo's not perfect, and we're not taking -- again,
22 this is for somebody with skill in transseptal.
23 We're not taking somebody, a fellowship, who has
24 never done a transseptal and say, well, do three
25 cases of this and then you can do it. I think the

1 three cases coupled with all the background material
2 that are proctored should be a minimum. If the
3 proctor doesn't think that the operator is capable of
4 operating independently, he should make that decision
5 that he should have more proctored cases. It's
6 iterative. I just put a minimum at three because
7 some people may be very good, do the first in flying
8 colors, and the company or the proctor says, oh,
9 you're good, go ahead and do them. I don't think
10 that's the case. I think three is a true minimum.

11 DR. MAISEL: I would also note that in the
12 Sponsor's packet on page 79 of 95, it's Table 1030,
13 shows a pericardial effusion by site experience, and
14 they break it up into early patients, 1 through 3,
15 and late patients, 4 and more. And there's a
16 difference, and the complication rate is lower for
17 the 4 plus for any serious pericardial effusion goes
18 from 7.1 percent to 4.4 percent. So that would
19 provide some data and rationale for that number.

20 DR. PETERS: I think the number three comes
21 from the see one, do one, show.

22 DR. MAISEL: Are there any other comments
23 about the training program? Yes, Gary.

24 DR. ABRAMS: At first look at this,
25 qualified physicians that qualifies at a minimum has

1 to be a cardiologist with transseptal or
2 cardiothoracic surgeon, or what is the definition of
3 a qualified physician?

4 DR. MAISEL: I mean I think if we start
5 with proficient at transseptal catheterization,
6 that's the qualified.

7 DR. ABRAMS: Okay.

8 DR. MAISEL: Okay. Let's move onto --

9 DR. RESNIC: Can I ask just one more
10 question?

11 DR. MAISEL: Yes, Fred. Sorry.

12 DR. RESNIC: If there is a formal
13 certification process that's recommended, it's sort
14 of self-evident, but the certification shouldn't
15 occur until after the proctor signs off, that is, you
16 don't get certified, then get proctored, and then
17 have free rein to disregard the proctor's concern
18 that you need more than three. So Dr. Brinker's
19 comments that a three is minimum, but the proctor
20 ought to have some independent oversight over the
21 recommendation to proceed to further training or not
22 further certification.

23 DR. MAISEL: Right. I mean it's not just
24 complete three. It's complete three successfully
25 maybe or those details can be worked out, but your

1 point is well taken.

2 Let's move onto the indications for use,
3 question 4. Please comment whether the proposed
4 indications for use statement appropriately
5 identifies the patient population evaluated in this
6 study.

7 The indications for use can be found in the
8 draft SSED, which is I believe about the fifth tab on
9 page 2 of 34. I think we've already decided that it
10 doesn't quite fit what we're looking for.

11 Right now it reads, "The WATCHMAN Left
12 Atrial Appendage Closure Technology is intended as an
13 alternative to warfarin therapy for patients with
14 nonvalvular atrial fibrillation. The WATCHMAN LAA
15 Closure Technology is designed to prevent
16 embolization of thrombi that may form in the left
17 atrial appendage, thereby preventing the occurrence
18 of ischemic stroke and systemic thromboembolism."

19 As we have discussed, it turns out that the
20 rate of that stuff is actually higher in the device
21 group. So we need to craft an indication statement
22 that fits what we've discussed today.

23 I have a start based on what Fred had said
24 earlier. So let me put something out there, and then
25 we can work on it. It's not quite right yet, but I

1 have something like indicated in warfarin-eligible
2 patients with nonvalvular atrial fibrillation as an
3 alternative and comparable treatment to warfarin for
4 reducing the composite risk of ischemic or
5 hemorrhagic stroke unexplained or cardiovascular
6 death or systemic embolization. It needs some work,
7 but it's basically incorporating that primary
8 endpoint into the indication statement.

9 DR. GOOD: I think that's good. I'd take
10 off the systemic embolization because it really don't
11 happen with atrial fibrillation, but that's a minor
12 point.

13 DR. MAISEL: Other comments? Does everyone
14 agree that the way it's written in the SSED is not
15 quite right?

16 DR. LINDENFELD: I think yours was very
17 good. It just needs to be reworded.

18 DR. SOMBERG: Do you have say it is
19 indicated or can you say that it can be considered as
20 an alternative to long-term Coumadin therapy?

21 DR. MAISEL: I was trying to avoid
22 alternative to long-term Coumadin therapy.

23 DR. SOMBERG: Why?

24 DR. MAISEL: Because many of the device
25 patients get Coumadin therapy both for 45 days and

1 many of them end up on warfarin therapy. So I was
2 trying to word it such that we didn't explicitly
3 say --

4 DR. SOMBERG: But it is the alternative to
5 long -- I mean 45 days is not long-term Coumadin
6 therapy. I know people on it for, you know, 20, 30
7 years. So gee whiz. This is the alternative.

8 DR. MAISEL: What do people think about the
9 concept of as an alternative to long-term warfarin
10 therapy?

11 DR. DOMANSKI: Yeah, I really agree with
12 that. That's why you're -- that presumably is why
13 one would consider it at all. So, yes, I think
14 that's correct. Also instead of comparable, you
15 might want to use the term noninferior since that's
16 what we've been saying all day.

17 DR. MAISEL: Yeah, to me that -- I mean we
18 can hear what other people think. That's also a
19 slippery slope because of the definition of
20 noninferior.

21 DR. DOMANSKI: Well, definition of
22 comparable. I mean, you know.

23 DR. BRINKER: I like this also, but I would
24 put in when you get to the risk section that one risk
25 is that you may require Coumadin therapy, prolonged

1 or lifelong Coumadin therapy with this device as a
2 potential risk.

3 DR. KATO: One thing that might help if
4 maybe we could have somebody type this as you're --
5 up on the screen.

6 DR. MAISEL: Be my guest. Is there someone
7 who wants to help?

8 DR. ZUCKERMAN: What would be helpful to
9 the FDA is if you just give us really the grand
10 strokes. The actual minute wordsmithing we can
11 handle.

12 DR. MAISEL: So it sounds like we want,
13 indicated as an alternative to long-term warfarin
14 therapy in warfarin-eligible patients with
15 nonvalvular atrial fibrillation for reducing the
16 composite risk of ischemic and hemorrhagic stroke
17 unexplained or cardiovascular death. Systemic
18 embolism is either in or not in there. And obviously
19 the wording needs to be spruced up a little bit.

20 Yes, Patricia.

21 DR. KELLY: I think we maybe need to
22 include something about they have to be able to take
23 aspirin or Plavix.

24 DR. MAISEL: Yeah, I mean there will be
25 indications, specific indications and exclusions down

1 below. So this is supposed to be just a succinct
2 overview of who the device would be indicated for.
3 So we're saying they need to be warfarin eligible.
4 It's an alternative to long-term warfarin therapy,
5 and it's for reducing the risk of those endpoints we
6 discussed. John.

7 DR. SOMBERG: I'm not comfortable with
8 exactly the way you worded it, and the reason is that
9 it sounds like people would interpret that this
10 device might be better at that composite endpoint,
11 and I want to underscore that, you know, I think
12 everyone is saying here, well, it's small numbers but
13 it looks pretty comparable to the two, and if you do
14 want to stop this, this might be equal to. So you
15 have to de-emphasize because if you put it, you know,
16 the device is comparable to that, and then, by the
17 way, it reduces stroke, people say, oh, it reduces
18 strokes. So it's superior. And that's not what you
19 mean, I know, but that's how people misinterpret
20 stuff.

21 DR. MAISEL: Yeah. So the alternative, I
22 mean when we say reducing those things, I mean we're
23 saying reducing it compared to no treatment. And we
24 don't actually have that study --

25 DR. SOMBERG: Well, the way to say it is

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1 that Coumadin and this device in Coumadin-eligible
2 patients may be equivalent or this device may be
3 noninferior or you can say it is comparable. I like
4 the word comparable in terms of a composite endpoint
5 of blank, blank, and blank, just what they had shown.

6 DR. MAISEL: One last try, and then I think
7 we're going to --

8 DR. ABRAMS: Are we allowed to say possibly
9 comparable.

10 DR. MAISEL: So here, let me try this. I
11 have indicated as noninferior treatment to long-term
12 warfarin therapy in warfarin-eligible patients with
13 nonvalvular atrial fibrillation for the reduction or
14 for the treatment of the composite risk of those
15 three things. Bram, do you have enough?

16 DR. ZUCKERMAN: That's fine.

17 DR. MAISEL: Okay. So let's move on from
18 the indications and onto labeling which is question
19 5. Please comment on the contraindications section
20 as to whether there are conditions under which the
21 device should not be used because the risk of use
22 clearly outweighs any possible benefit.

23 And please comment on the warnings and
24 precautions section as to whether it adequate
25 describes how the device should be used to maximize

1 benefits and minimize adverse events.

2 So the contraindications is typically
3 described as something you should never do, and the
4 warnings and precautions are things you should do
5 very carefully or with much thought and probably
6 should not do.

7 The contraindications, warnings and
8 precautions start on page 5. Right now the listed
9 contraindications are intracardiac thrombus
10 visualized by TEE, atrial septal repair or closure
11 device is present, left atrial appendage anatomy will
12 not accommodate a device, and "all the customary
13 contraindications for other percutaneous catheter
14 interventions," e.g. patient size or condition such
15 as too small for TEE probe, bleeding disorder, et
16 cetera.

17 Any other things that should be considered?

18 DR. VASSILIADES: How about inability to
19 take warfarin?

20 DR. SOMBERG: Well, actually the inability
21 to stop warfarin for the procedure.

22 DR. VASSILIADES: Well, then if you've got
23 continued flow there and you're not on it now, you
24 may have to go on it later.

25 DR. SOMBERG: I mean the inability to have

1 to stop it because, correct me if I'm wrong, to do a
2 transseptal, you need to stop.

3 DR. VASSILIADES: No.

4 DR. MAISEL: Not necessarily. I mean in
5 this trial it was stopped. There are afib ablations
6 that are performed on therapeutic INRs now, although
7 on this trial it was stopped.

8 DR. VASSILIADES: You have to be on
9 Coumadin for a certain period of time if everything
10 goes well. So the inability to be able to be on that
11 short-term amount of Coumadin is a contraindication,
12 right?

13 DR. RESNIC: I think it would be
14 appropriate to say that the patients who are unable
15 to take Coumadin have not been studied and therefore
16 safety cannot be assessed. I think it would be
17 somewhat wrong to consider that there aren't
18 exceptional patients who can no longer be on Coumadin
19 and whom we would say this is an absolute
20 contraindication. They had been on Coumadin but now
21 they have Parkinson's, they've fallen three times.
22 They can't be on Coumadin anymore. You're willing to
23 make the decision. It's not as the protocol. It's
24 not based on the evidence we saw today, but to carve
25 out such patients, I think, would be unnecessarily

1 withholding.

2 DR. VASSILIADES: So are you going to allow
3 the procedure to be put in and no perioperative
4 Coumadin be used?

5 DR. RESNIC: I think it should be a strong
6 warning, a very strong warning.

7 DR. BRINKER: But they should demonstrate
8 that first before, I think, before they had an
9 opportunity to and they have an opportunity in the
10 future to. Remember, and they could, as a future
11 study or something that could start very soon, they
12 could do a study of this device in patients that
13 can't be Coumadinized.

14 UNIDENTIFIED SPEAKER: I think that's
15 happening in Europe, right? That's --

16 DR. BRINKER: Well, and as soon as it's in,
17 I think that this labeling can be changed.

18 DR. MAISEL: So my personal take would be
19 that not taking warfarin is not quite a -- a
20 contraindication to me means there's data to suggest
21 that you will be harmed if you do that. I don't know
22 that we have data --

23 DR. VASSILIADES: But yet you have a
24 foreign body on the left side of the heart with no --

25 DR. MAISEL: I mean I think it's a -- I

1 understand what you're saying.

2 DR. VASSILIADES: So are you telling me
3 there's no data at all? I mean there's no data in
4 this trial, but I mean I guess I would disagree. I
5 would consider it a contraindication, not a strong
6 warning. I don't know if we're going to resolve it.

7 DR. MAISEL: Can we hear from other people
8 regarding that issue? So should inability to take
9 warfarin be a contraindication or a warning?

10 DR. SOMBERG: I think it should be a
11 recommendation, a strong recommendation, but as you
12 said, if you contraindicate it, to do that is to go
13 against, you know, what is -- I hate to use the word
14 malpractice or advisable practice or whatever you
15 want to say, it is very strong and maybe over-strong
16 in this thing because you could make the argument
17 that, you know, thrombus is there, et cetera. Later
18 on, dual antiplatelet therapy may be all you need to
19 cover this thing but we don't want to recommend it --
20 I don't think we want to chop off people's hands if
21 they do this.

22 DR. MAISEL: Mike.

23 DR. DOMANSKI: Yeah, I think you don't have
24 the data really to say it's contraindicated. I think
25 that is taking it too far. I agree with Dr. Somberg.

1 DR. MAISEL: JoAnn.

2 DR. LINDENFELD: Well, I don't know. I
3 don't think we have any idea what the risk of
4 thromboembolism is at day two or day three without
5 Coumadin. We just have none, but it might not be a
6 big deal, but what if it's large?

7 DR. MAISEL: So I think the message from
8 the Panel on that issue is we would like the FDA to
9 craft a label that accurately reflects the Panel's
10 significant concern about patients not on warfarin
11 therapy getting the device. And so we'll leave it to
12 you to find the right spot on the label, somewhere
13 between warnings and contraindication.

14 Other issues for the label? What do we
15 want to say about antiplatelet therapy?

16 DR. LINDENFELD: Are we still on
17 contraindications?

18 DR. MAISEL: Yeah, please if you have other
19 contraindications.

20 DR. LINDENFELD: Well, this may be included
21 in the nonvalvular atrial fib and indication, but do
22 we need to put in here mitral stenosis or prosthetic
23 mitral valves, where we know that a large percentage
24 of the clots are not -- at least half are not atrial
25 appendage clots. That may not rise to

1 contraindication. It may need to be something else.

2 DR. SOMBERG: It's only in nonvalvular
3 heart disease. It's indicated.

4 DR. LINDENFELD: Right. So maybe that
5 takes care of the --

6 DR. SOMBERG: No, I mean you have to be
7 sort of off to -- if it's indicated for that, not to
8 use it in something.

9 DR. LINDENFELD: Well, that may be. I just
10 don't know.

11 DR. BRINKER: Well, if the patient has
12 another reason to be on Coumadin, could you justify
13 putting this device in?

14 DR. SOMBERG: No.

15 DR. KATO: Well, because, you know, one of
16 the exclusion criteria is ejection fraction less than
17 30 percent.

18 DR. SOMBERG: But he's saying let's say
19 somebody had a pulmonary embolus --

20 DR. KATO: Okay.

21 DR. SOMBERG: -- and has an absolute need
22 to be on Coumadin, what's the purpose of this device?

23 DR. KATO: Right.

24 DR. MAISEL: Okay. Other --

25 DR. KATO: You have to have some reason for

1 being off even though you can take it.

2 DR. SOMBERG: That's right.

3 DR. MAISEL: Other contraindications?
4 Other specific patients that should not get it? So
5 now warnings and precautions, we have a bunch that
6 are listed in your book. I won't read through all of
7 them.

8 DR. SOMBERG: I have a quick question while
9 you're thinking about this, and I don't mean to cause
10 consternation, but there's going to be more than one
11 antiplatelet therapy. I understand the Advisory
12 Panel on the CDER side had recommended -- for
13 approval. That is certainly more potent. Are we
14 going to talk about the requirement for clopidogrel
15 and aspirin or are we going to talk about dual
16 antiplatelet therapy?

17 DR. MAISEL: So I'll give you my take and
18 then you can comment, but what we've done with other
19 labeling in the past is describe what was done in the
20 trial. So in this case, it's aspirin for life and
21 clopidogrel for six months, and data on other agents
22 is not available.

23 DR. SOMBERG: I agree.

24 DR. MAISEL: Other comments about the
25 antiplatelet issue? Other warnings or precautions?

1 Fred.

2 DR. RESNIC: I'm sure that this doesn't
3 fall under warning. Is it appropriate anywhere in
4 the instructions for use to indicate that according
5 to AHA/ACC guidelines, CHADS₁ patients may be
6 effectively treated with aspirin as opposed to the
7 Coumadin for which they may be looking for an
8 alternative? I mean there's a third alternative for
9 that population of patients. It was well studied,
10 the benefits in the subset, although there are
11 concerns about too fine a carving of the data, but I
12 think that by including what was 33 percent of the
13 population being CHADS₁, are we implicitly
14 recommending in some ways that they be either treated
15 with warfarin or this device when, in fact, there was
16 an untested third possibility, that is, has strong
17 recommendations from scientific advisory bodies?

18 DR. MAISEL: John.

19 DR. SOMBERG: Well, I mean I think we
20 should state what the protocol included someplace in
21 the label. It's not a contraindication, but it
22 should be pointed out that people with CHADS₁ score
23 may be treated with antiplatelet therapy alone and
24 that the physicians must individualize the need for
25 Coumadin because we're saying here, this is in a

1 population that Coumadin is indicated. That was the
2 indication. So they said or someone said there was
3 some intuitive knowledge here that was developed. I
4 wish you could quantify it and publish it. There was
5 some intuitive knowledge who would be at higher risk
6 in CHADS₁ population, but unless knowing how to
7 identify that, I think it should be only people who
8 the physician thinks needs Coumadin, and that should
9 be pointed out. So you have a very good point.

10 DR. MAISEL: It sounds like a reasonable
11 point. We typically describe the patient population
12 within the label, and I think it would be reasonable
13 to have a statement that CHADS₁ patients may also be
14 eligible for aspirin alone.

15 Other labeling issues. I didn't really see
16 a patient brochure. Maybe I missed it, but it seems
17 like this is a big deal, and there should be a really
18 well thought out patient brochure explaining atrial
19 fibrillation, strokes, clots, the procedure, the
20 relative risks and benefits, and those sorts of
21 issues. And there's a very nice one in the packet I
22 see.

23 DR. SOMBERG: Okay. Here's a --

24 DR. MAISEL: To follow-up on that thought,
25 a physician training video as I know you've put

1 together and those sorts of things, I think which
2 also come under the labeling are obviously very
3 important. Bram.

4 DR. ZUCKERMAN: Okay. The post-procedure
5 information for the implant is .20 on page 8. A
6 question for perhaps Dr. Brinker or Resnic, there's
7 no criteria for how many TEEs should be done in
8 follow-up. What would you recommend as a point C?

9 DR. SOMBERG: Your page is not the same as
10 our page 8.

11 DR. ZUCKERMAN: It's the label.

12 DR. SOMBERG: So this is Tab 6.

13 DR. ZUCKERMAN: It's the draft IFU and
14 patient label, page 8.

15 DR. SOMBERG: And you said that's .20.

16 DR. ZUCKERMAN: Yeah.

17 DR. SOMBERG: I'm not sure I have the right
18 page.

19 DR. MAISEL: What page are you on, Bram?
20 We have the tab. What page is it?

21 DR. ZUCKERMAN: It's page 8, .20.

22 DR. SOMBERG: It's in the IOPO. Post-
23 procedure.

24 DR. RESNIC: I'll take a stab. I think
25 that the protocol required patients to have the TEE

1 at 45 days, at which time there was the treatment
2 decision based on the findings as well as the
3 clinical input and that should be recommended. I
4 think that that was part of the safety demonstrated
5 by the trial. I think beyond that, one should
6 recommend only that it was four patients in whom
7 continued flow was demonstrated, that these patients
8 were treated, if possible, with continued
9 antithrombotic therapy with warfarin.

10 And I think that the point was that most of
11 those flows stopped at some point later. So I don't
12 know that you have to mandate this six month, one
13 year, and two year TEEs, but that Coumadin or
14 warfarin should not be discontinued without
15 demonstration of cessation of flow by transesophageal
16 echocardiogram.

17 DR. MAISEL: Anyone --

18 DR. BRINKER: I don't know if we have the
19 information as to -- I think one of these patients
20 had a clot on a late echo. And I don't know for sure
21 that that patient was demonstrated to have some flow
22 around the device on the echo prior to that.

23 I think that this is the way it was done,
24 and I would say that this is the recommendation.
25 It's hard for me to say you don't have to do the

1 things that were done because the late echos led to
2 10 or how many percent of the people remaining on
3 anticoagulation.

4 DR. MAISEL: So could we phrase it
5 something like before discontinuing warfarin, at 45
6 days or later, a TEE should be performed to
7 demonstrate, you know, complete occlusion of the
8 appendage?

9 DR. BRINKER: I guess what I would probably
10 say is this is what -- the trial performed echos at
11 these intervals and with the results. We've done
12 this before on instructions for use and with the
13 result that, whatever, 10 percent ended up on
14 anticoagulation, and it affected the treatment of
15 patients with prolonged anticoagulation in some 10
16 percent of the patients.

17 DR. MAISEL: So we have two camps. We have
18 the mandate the echo before discontinuation and we
19 have describe the data and what's been done in the
20 protocol. So how many people are in favor of the
21 mandate the TEE before warfarin discontinuation?

22 DR. BRINKER: I think we need data on how
23 many people with the 45-day or 6-month echo would
24 have stopped on later evaluation, would have that
25 reconsidered. In other words, they all had the later

1 echos, and I'm not sure how many of them would have
2 been stopped at 45 days if there were no later echos.
3 You know what I'm saying?

4 DR. MAISEL: Can we hear from other people
5 on the Panel? John.

6 DR. SOMBERG: Well, I would like to hear
7 from the Sponsor, or actually let me correct that.
8 I'd like to hear from the investigators who had
9 experience because it's my feeling that I think there
10 should be a mandated 45-day TEE. Then we should say
11 what was done based on the findings of that, if you
12 had flow, you instituted Coumadin. If you have
13 thrombus afterwards, and then after that, we should
14 say what was done in the study. They had a TEE at a
15 year and whatever else after that, and leave it up to
16 the judgment of the clinician to decide what they do
17 on the basis of that afterwards.

18 But it has to be somewhat informative
19 because I don't think anyone's going to go through
20 the study like we did.

21 DR. MAISEL: Tom, what are your thoughts?

22 DR. VASSILIADES: I would agree with what
23 John said.

24 DR. MAISEL: Okay. So I mean we know in
25 the study that patients got a TEE and were eligible

1 to have the warfarin discontinued at that TEE at 45
2 days if it looked okay, if there was no flow. So it
3 sounds like people want to describe --

4 DR. BRINKER: But they had reinstatement of
5 their Coumadin based on later TEEs, and that's what
6 bothering me. So if we're going to suggest the TEE
7 schedule, we really have to know how many -- whether
8 we can legitimately say is all you need is one at 45
9 days or 6 months and you never have to do another
10 one.

11 DR. MAISEL: What I was going to suggest
12 was describing very carefully what was done in the
13 study because I don't know that we can do more than
14 that. Mike, you're looking skeptical.

15 So is everyone okay with just describing
16 what was done in the study with the TEEs? Fred.

17 MR. RESNIC: Just one point is that the
18 current description under .20 doesn't actually say
19 that if you find flow. So it's inadequate as it
20 stands even if you were to describe the protocol
21 further. I don't think what is described here is
22 adequate.

23 DR. MAISEL: So we want the label to
24 reflect what happened, when the TEEs were performed
25 and what happened in the protocol in response to the

1 TEES.

2 DR. RESNIC: Right, and it's not just
3 adding an item C, D, and E. It's actually A is
4 incorrect.

5 DR. MAISEL: Other issues for the label
6 that we haven't already covered?

7 Okay. Let's move onto question 6 which is
8 the postmarket evaluation.

9 Let's go back to number 5, back to the
10 labeling for a second. Please comment on the
11 operator's instructions as to whether it adequately
12 describes how the device should be used to maximize
13 benefits and minimize adverse events.

14 I think we've talked a little bit about
15 that in the training program, and obviously there has
16 to be labeling to support that.

17 Please comment on the remainder of the
18 labeling, and I think we've done that.

19 Okay. Postmarket evaluation, and keep in
20 mind this doesn't mean we're approving the device.
21 It's just helpful discussion whether or not the Panel
22 votes for approval.

23 Please comment on the appropriateness of
24 the proposed post-approval studies to assess the
25 short-term and long-term safety and effectiveness of

1 the device in real world use. This should include a
2 discussion of the proposed endpoints, length of
3 follow-up, and choice of study population.

4 Please discuss if there is a need for a
5 post-approval study to evaluate the implanting
6 physician's experience and its effect on the
7 performance of the device.

8 There is a description. We heard from the
9 Sponsor about the post-approval studies. There's a
10 description in Tab 8. They have proposed two
11 studies. One is continued follow-up, a long-term
12 study of their study participants out to five years,
13 and the other is in an acute study of up to 300
14 patients that would be followed for several days
15 post-implant.

16 So given that, let's start from scratch,
17 and what are the post-approval issues, keeping in
18 mind that we can't ask questions that are required
19 for safety and effectiveness to support approval, but
20 assuming it were approved, what are the post-approval
21 issues and what kind of study design do we need to
22 answer them? John.

23 DR. SOMBERG: Well, I mean the questions
24 that I've heard here today and some of mine and some
25 of others, I don't mean to steal anyone's ideas, but

1 certainly transseptal on Coumadin, putting this
2 device in, I would be interested to know what
3 happened.

4 I would be interested also to know if this
5 device could be implanted without ever being on
6 Coumadin and be an alternative. Someone said the
7 study's ongoing, fine. And I think that that needs
8 to be run through the FDA if it's going to be used at
9 a later date for a label modification.

10 And the other thing that I'm very concerned
11 about, and I think the Sponsor continuing to follow
12 up these patients is a very good idea, and I think
13 the acute study they're talking about is a good idea
14 as well, but I also think there's needing to be a
15 much larger expansion of this study in registry form
16 with comparable groups. I would like to see who were
17 placed on Coumadin. I'd like to see a group placed
18 on this device. And I'd like to see several times
19 the number. So maybe we're talking about 2,000
20 patients who are followed for a couple of years. So
21 we would have an adequate number.

22 The beauty of that for the Sponsor is they,
23 I guess, get reimbursed. The benefit of that for
24 everyone else is that we're no longer talking about
25 small data and we can make confident future

1 recommendations to our patients.

2 DR. MAISEL: What are the endpoints of your
3 study? What are you studying?

4 DR. SOMBERG: I would kind of want to take
5 in similar endpoints, and I'd like to look at, you
6 know, intent-to-treat and on protocol analysis as it
7 was done here. So I would use stroke, maybe, you
8 know, some of the people who are more expert than I
9 on the Panel, neurologists who have said, well, maybe
10 it's not a stroke, maybe it is. They should take
11 that into account when they look at this data, but
12 the endpoints they were looking at, stroke, total
13 stroke, hemorrhagic stroke, ischemic stroke, death,
14 embolization, these are all things we are all
15 concerned about.

16 So I'd just like to see a larger study
17 because I don't think 400 patients is, as Norm Kato
18 said, going to be suffice for 2.5 to 4 million
19 patients with atrial fibrillations, and the total
20 universe is very large here.

21 And the second thing is, as Dr. Zuckerman
22 pointed out, I mean we're judging two years and three
23 year follow-up on the basis of terribly small
24 numbers. We need hundreds in that group, not 20
25 versus 30.

1 DR. MAISEL: Other comments?

2 DR. PETERS: Another thing that bothers me,
3 the population, I know what to do with the majority
4 of these patients which are CHADS score 1 and 2, but
5 how about a person with heart failure, diabetes,
6 hypertension? We have very, very few data on that,
7 and I think we need more information. I don't know.

8 DR. MAISEL: So let's get a little specific
9 about some of the studies. We heard 2,000 patients,
10 two years. Can I hear from other people regarding
11 size, duration, and endpoints? David.

12 DR. GOOD: You already have two studies
13 proposed, and you're proposing a third. It sounds
14 like the first thing would be the long-term study
15 that has already been proposed by the Sponsor,
16 looking at the cohort we already have, right? And
17 that's at least one thing that certainly should
18 occur.

19 DR. SOMBERG: I'm proposing a registry.

20 DR. GOOD: Okay. So that's really a
21 third --

22 DR. SOMBERG: Yes, absolutely. Because
23 what they're proposing to do is follow-up the number
24 of patients that were assessed now and see where they
25 go.

1 DR. GOOD: Right.

2 DR. SOMBERG: And even in the early times,
3 we had too small of numbers to -- and it made you
4 uncomfortable and others. So I'm saying in a
5 registry, we would accomplish a lot more and see,
6 that's why I mentioned, yes, 2,000 patients for two
7 years.

8 DR. GOOD: Okay. So there is merit in
9 that, but for the two things that have already been
10 proposed, the follow-up of the cohort is certainly
11 one thing that should be done, I would think, and
12 that's what they're proposing. The only problem is
13 that they're only following the subjects that were
14 implanted, and is that reasonable or do you think
15 that they should be following people that weren't
16 implanted, those in the warfarin group as well? You
17 know, I mean those patients are available.

18 DR. MAISEL: Well, this Device Panel has
19 pointed out many times that a registry or any follow-
20 up study without comparable, you know, something to
21 compare to is a disaster because whatever happens, it
22 was either too good to be true or so terrible as to
23 warrant, you know, execution. So don't do that
24 please.

25 DR. MAISEL: Fred.

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1 DR. RESNIC: So trying to incorporate I
2 think a good suggestion regarding a much broader
3 registry that you're suggesting. I think that that
4 actually is what I would place their continued --
5 well, there's two proposals that they've put forward,
6 right, that the Sponsor's put forward. One of them
7 is the long-term follow-up of the patients who got
8 the device. So the first recommendation is the
9 follow-up ought to include the patients who did not
10 get the device so that the 5-year outcomes could be
11 relayed to the Panel, to the FDA, and the numbers
12 would be 400, 200, all the way out to 5 years except
13 for deaths. And that would have at least some hint
14 of your long-term safety. That is not answered and
15 is not a condition really for approval at this stage
16 since the data doesn't exist under any means.

17 The question of whether a separate registry
18 of higher numbers containing both implant as well as
19 a control arm, it would have to be, you know, much
20 more of an observational study.

21 DR. KATO: But I think you're absolutely
22 right. It is an observational study, and that's why
23 I think, you know, you have to have a comparative
24 group. You have to have, you know, you have to look
25 at large numbers because this could potentially be

1 very widely applicable, and extrapolating the effect
2 of a device on, you know, just a handful of patients
3 relative to the total market, in very select centers
4 with very select physicians, I don't think is, you
5 know, you can't extrapolate too far beyond what we
6 know today.

7 So I mean I would agree with John, and
8 personally I don't know whether 2,000 is enough. You
9 know, maybe it's not enough. Maybe it needs to be a
10 larger number. Again, I don't think there's going to
11 be an absence of patients to not, you know, to not
12 include.

13 DR. RESNIC: One critical piece of this is
14 that as soon as this is approved, the investigators,
15 you recall the people that got standard therapy and
16 say this is approved now, and I don't think you'd be
17 able to have the cohorts of patients that you had in
18 this trial followed for five years. The other group
19 who are interested in being part of the trial
20 initially will have their interest even piqued now
21 that it's no longer a study. I don't think you're
22 going to have that comparison.

23 So I think that the only thing you're going
24 to have is a registry of people getting these
25 devices. I don't think it will be easy to do --

1 DR. MAISEL: I think that's an excellent
2 point. With that being said, I'm not sure we should
3 throw away this potential to monitor long-term as
4 well as we're ever going to get a change to monitor
5 patients. So I agree that we should monitor them
6 all. I don't think we can say you have to stay in
7 that treatment arm. I mean that's not ethical, but
8 if a lot of people crossover to the device, we've got
9 more information about the device and about the long-
10 term safety of the device.

11 What we do in registry, what is the control
12 arm of the registry? And I'll offer two
13 possibilities, and people can chime in with thirds.
14 We've heard a concurrent group of atrial fibrillation
15 patients. I think my concern there is they're not
16 going to be equal because some of them are going to
17 get put in a given arm for a given reason, although
18 that is a possibility.

19 Two would be the device arm of the trial so
20 that we would be assessing the real world performance
21 of the device and comparing it to the clinical trial
22 of the device. So I'm open to other suggestions, but
23 those are two I thought. Sherry.

24 DR. KELSEY: I would definitely agree that
25 there should be long-term follow-up of the patients