1 arrhythmic trial, I can honestly say to that
2 patient, I do not know which approach is
3 better for you. You've never been on a
4 suppressive drug. It may work extremely well
5 for you, it may make you sick, it may be
6 ineffective. Equally, I don't know whether
7 ablation is the best for you.
8 As a clinician, I can honestly say
9 to that patient that it's a coin toss, and
10 hence, you are an excellent candidate to enter
11 into this randomized trial, and as a side
12 benefit to this randomization, you have access
13 to the new technology.
14 So I would respectfully request
15 that the panel strongly consider that the
16 criteria for study entry include patients who
17 have not necessarily yet failed a suppressive
18 drug. I think that that will help enrollment.
19 I think that that will be better for patient
20 care.
21 It is consistent with the most
22 recent guidelines document led by Hugh Calkins

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and HRS. And most importantly, it's consistent with my care -- my best care of my patient.

Second point: With some of the new circumferential pulmonary vein ablation technologies, we have the ability to create, with one energy delivery, a large lesion that, hopefully, will isolate the vein.

Due to anatomical variability among patients, and geometrical considerations of the catheter technology, often a balloon-based catheter technology, being used, we can often achieve 90 percent circumferential ablation, but just a small segment of the vein remains conductive.

If we continue to press forward with the investigational tool, we risk increasing collateral injury, and the reason for that is that catheters need to be angled, catheters need to be pushed deeper in the vein than we choose to, and there are several compromises that we make to get that last 10

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1 percent.

2 That's a small segment that we

3 know, with a conventional catheter, we could

4 go in, and probably in five minutes, finish

5 the ablation line.

6 The FDA has endorsed the tool kit

7 approach toward ablation, and I think that's

8 a good thing, so that you can use the new

9 technology, and then supplement the ablation

10 with more traditional steerable catheter

11 technology.

12 And yet some of the companies do

13 not have -- do not manufacture conventional

14 ablation catheters. That brings into

15 discussion the use of non-approved, non --

16 alternative manufacturer ablation catheters

17 for the touch-up lesions.

18 This obviously creates

19 difficulties in the final analysis, because

20 you're using two tools from two different

21 sources. But again, because of patient

22 welfare issues, in terms of efficiency,

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reducing collateral injury, I would like the panel to consider a possibility of allowing, as a tool kit, using an off-label catheter in conjunction with the investigational device to complete the lesion. Thank you.

DR. YANCY: Thank you very much.

We appreciate the comments during this open public hearing session. Having no other persons who have stepped forward to make comments, we'll close that session, and open this up for deliberation by the panel, with queries primarily directed to those who just spoke.

Let me once again begin by just acknowledging that we heard your concerns about changing the patient population, looking at a primary indication, that is, for persons who have atrial fibrillation, and haven't failed therapy.

We heard your sensitivities about crossover issues. We certainly respect the necessity to accurately diagnose atrial

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1 fibrillation if we are to have an appropriate
2 adjudication of these issues. And we continue
3 to hear stories about the awkwardness because
4 of the absence of FDA-approved devices that
5 already exist.
6 There is one question, though,
7 that I'd like to have someone address that
8 hasn't been addressed all day, because we've
9 consistently heard anecdotes and qualitative
10 statements that patients refuse to go into
11 these studies because they don't want to be
12 exposed to drug therapies, and they want the
13 catheter-based therapy. And some of that, I
14 think, reflects physician bias, and not really
15 patient preference.
16 But, apart from that, in the
17 privileged documents that we received, one
18 company actually took the time to quantitate
19 how many people opted out of a study because
20 they did not want to be exposed to drugs, and
21 rather than use that as our sole metric, are
22 there any of the sponsors who would like to

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volunteer, quantitatively, what percent of those patients who fail screen fail screen because they did not want to be randomized to drug -- not qualitative, but quantitative?

As a comparator, I will tell you that, wearing a different hat as a clinical trial investigator, we certainly anticipate, at best, eight to 10 percent of the people that we screen going into drug-based clinical trials.

So if we're dealing with a two to three percent metric for devices that involve a certain inherent risk, we may not be that far from expectations. So having numbers would be very helpful here.

Is there a sponsor who would wish to address this quantitatively?

MS. AKER: Yes, I'd like to address that. My name is Brenda Aker. I am employed by Biosense Webster as a clinical director.

As Dr. Waldo showed you in some of

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1 our slides, our randomization -- or our
2 screening data actually showed that we had a
3 pretty high level of patients that did not
4 want to be in the trial because of the
5 randomization issue.
6 And he presented that there were
7 62 percent that failed because of protocol
8 exclusion, but what we typically found with
9 our sites is that -- and our screening
10 information only collected one reason for
11 failure, for the screen failure.
12 So typically, what the sites did
13 is they would look at the patient chart. If
14 they were on amiodarone, then they were
15 excluded for that reason. So it was only the
16 additional 38 percent of patients that were
17 maybe even approached about the study.
18 Out of that 38 percent of the
19 patients that were approached after the
20 preliminary screen was done, about one in four
21 elected not to participate, because they did
22 not want to be randomized to drugs.

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1 So in our trial, which was several
2 thousands of patients that were screened, I
3 think, you know, it showed very clearly that
4 a high percentage of the patients did not want
5 to be in the trial because of the
6 randomization.
7 DR. YANCY: Would you permit me to
8 read the numbers that were provided on this
9 document from Biosense? If not, I'll --
10 MS. AKER: Percentage-wise, or --
11 we'd prefer to keep to percentages, if that's
12 okay.
13 DR. YANCY: Percentage-wise, is
14 that permissible?
15 MS. AKER: Yes. Sure.
16 DR. YANCY: Well, perhaps I'll do
17 this, to be fair. I'll just refer the panel
18 to the document you have before you, which is
19 a privileged document, and have you look,
20 under enrollment challenges, top reasons for
21 enrollment failures, and you can see the line
22 item that represents those patients who were

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1 unwilling to be randomized to drugs.
2 Thank you. Thank you very much.
3 Other questions from the panel to
4 the persons who just presented?
5 Dr. Zuckerman?
6 DR. ZUCKERMAN: Well, maybe Dr.
7 Milan wants to go first, but I'd like to
8 eventually ask a question.
9 DR. MILAN: This question is for
10 Dr. Haines. I heard your statement quite
11 clearly that you're in relative equipoise as
12 to the efficacy of atrial fibrillation
13 ablation versus anti-arrhythmic drug for
14 patients who have never been treated for
15 atrial fibrillation before.
16 But what about safety? Do you
17 have similar feelings about that?
18 DR. HAINES: I look at safety data
19 -- the main, I think, best trial that
20 addressed safety with long-term use of anti-
21 arrhythmic drugs in a mixed A.F. population
22 was the AFFIRM trial, randomized between

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suppressive drugs and rate controlling agents.

And there was, where the P equals 0.5-something, increase in mortality associated with the anti-arrhythmic drugs. Interestingly, when they did the death analysis, they were non-cardiovascular mortality, with a preponderance of pulmonary and cancer deaths.

And since cancer has a long lead time, the discussion is that adding anti-arrhythmic drugs in the mix in a sick patient just makes them a little bit sicker a little bit faster.

So I do not view anti-arrhythmic drugs as being benign. I think that the risk of death from pulmonary vein isolation procedures is very low. 0.1, 0.2 percent is the sense that I get from the literature.

And so I think that -- that ablation, if you look at the mortality statistics, is a very reasonable alternative to suppressive drug therapy.

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DR. YANCY: Dr. Somberg?

DR. SOMBERG: Well, I've been very heartened to hear that randomized trials are ongoing, and that their accession of patients, while difficult, has been able to be maintained.

But I wanted to ask the industry representatives, especially in this last session, who were distraught about the difficulties, have they considered an alternative trial design that hasn't been mentioned today?

And I'll preface that by saying the portal, to use sort of a computer term here, has been the electrophysiologist, and his take on atrial fibrillation. To my understanding, is most atrial fibrillation is not treated by electrophysiologists. They don't see most of it, et cetera. It's internists and general cardiologists who take care of it.

And have they tried, if they have

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1 failed on a randomized comparison, a non-
2 randomized comparison, where the same detailed
3 follow-up is provided to both a drug therapy
4 arm that is favored by the people who provide
5 that sort of care, versus the interventional
6 care given by the electrophysiologists, where
7 they get the same run-ins, baselines, et
8 cetera?
9 And there are going to be problems
10 of comparability of the patient population per
11 se, but that is one way to approach it, as
12 opposed to advocating a single-arm study and
13 a performance goal based on very little data.
14 MS. BRODERICK: This is Julie
15 Broderick from Bard E.P. Since I was one of
16 the most recent industry speakers, I'll
17 address that question, if I may.
18 Bard did evaluate a different
19 study design, not a single-arm study design,
20 but the trial B design that was described by
21 FDA this morning. As I mentioned in my
22 statement, we did have discussions with the

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FDA about a study design randomizing patients between our ablation catheter, and standard of care ablation.

And we were presented with this kind of three-arm design using a performance goal. And we felt that the drawbacks of that study design outweighed any advantages that it might have in terms of being able to enroll the study faster.

I think, from our perspective, we have not looked at single-arm study designs, because there has been such a strong message from the FDA, and such a history with other sponsors of the ablation versus AAD study, and we felt that going to FDA with a single-arm design was going to be an exercise in futility.

DR. YANCY: Dr. Zuckerman was next.

DR. ZUCKERMAN: Yes. This question is posed to both Dr. Haines and Dr. Neaton. And I would refer back to Slide 70

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1 from the FDA.
2 Dr. Neaton, this morning I don't
3 think we fully answered your question
4 regarding design A, which is the randomization
5 of -- after failure of one anti-arrhythmic
6 drug, randomization to ablation or another
7 anti-arrhythmic drug.
8 And you posed the very logical
9 question, why, in the medical arm, given the
10 reluctance of patients to go into the medical
11 arm, couldn't you have early crossover to
12 ablation. And I think you were thinking about
13 more of a treatment strategy approach where,
14 in one arm, you would get immediate ablation,
15 and in the other arm, you would get medical
16 treatment, and, if a failure, be offered
17 ablation.
18 From a clinical trial standpoint,
19 the clinician might be more comfortable with
20 that design, although it would be interesting
21 to hear from Dr. Haines.
22 From your vantage point, although

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1 you would answer a key clinical question
2 regarding timing of ablation therapy, do you
3 have any suggestions how you could also cull
4 out the requisite device information that we
5 would need?
6 Because, you know, your primary
7 analysis would be a treatment strategy
8 approach.
9 DR. NEATON: Yes. Let me just
10 kind of preface my response to that, in part,
11 by saying one thought I had with the earlier
12 presentations. I believe it was by, the Bard
13 presentation, and in talking about the plan
14 crossover.
15 If you're going to do that, you'd
16 better increase your sample size to preserve
17 power. This does not come for nothing. And
18 so, I think that, if you were to pursue a
19 strategy along those lines, I think you want
20 to do it by design, and not just have people
21 kind of crossing over kind of at whim.
22 And so there would be kind of

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criteria that would be pre-specified in the protocol, where you -- they would cross over, or have the option of crossing over, and hopefully, you would have a potential period of time that would be long enough to preserve the kind of drug versus device -- the ablation comparison, preserve that part of the randomization.

DR. ZUCKERMAN: Again, this is hypothetical, but there would be, presumably, a large crossover on the order of, perhaps, 50 percent. Even with that type of magnitude, is it possible to prospectively think about this?

DR. NEATON: I think it would depend upon if the crossover occurred after a reasonable period of time, which would allow you to understand the effects of ablation versus drug therapy, say, over a six-to nine-month period, say. Then I think that would still be feasible.

But you probably, for the longer-term outcomes, would have to inflate your

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sample size by a substantial amount if it was that high.

DR. YANCY: Dr. Haines?

DR. HAINES: I've always had great difficulty with comparison of drug versus device with regard to adverse events. You're front-loading your adverse events with the procedure and the device arm, and we know that, in the drug arm, the adverse events are slowly accumulating over time.

It's one of the most obvious apples and oranges types of comparisons that I've come across, and in my discussions in terms of designing trials, it's the issue that we always struggle with. And the best solution that we've come up with is to propose, for the primary end point of safety, to really depend more on an OPC, or some equivalent, that is derived from other ablation trials.

I think that -- and if we do that, then the disadvantage of the early crossover

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goes away, because all you're looking -- all you're really using that information for is the efficacy end point, and then you can compare efficacies.

But comparing safety between drug and device -- it's a daunting task, and I think, at the end, it's going to be almost uninterpretable. That's one man's opinion.

DR. YANCY: Dr. Neaton?

DR. NEATON: I guess I would offer a different opinion on that, because I think actually what you want to know are -- you want to understand those risks to balance them the best you can to the risk of drug therapy, so the obvious solution to the problem is a longer follow-up study.

And so that, if you follow patients longer, perhaps to kind of give you more opportunity to observe some of the long-term risks of the drug, that would be kind of a way of kind of reaching to your issue.

I don't think ignoring the safety

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outcomes, or using a non-randomized comparison or OPC criteria, which we've already heard are pretty difficult to come by, is the solution. I think that you have to establish that, by some grounds of evidence, that that early risk of that procedure doesn't outweigh what -- if you do a short-term study, what are perceived to be the long-term risks of the drug.

DR. HAINES: I disagree in terms of availability of OPC information regarding drug risk. We have thousands and thousands of patients in the drug literature, with drug versus placebo in the treatment of atrial fibrillation.

And if you look at those trials, those trials that enrolled paroxysmal atrial fibrillation patients had a fairly similar population to those patients who are now being referred for catheter ablation.

So we have, you know, one-year, two-year, longtime follow-up. We have AFFIRM, which has long-term follow-up. I think there

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is ample -- there is ample, well controlled, well monitored safety data in the literature regarding drug therapy.

DR. YANCY: Dr. Page?

DR. PAGE: I'm trying to reconcile, as we've heard today, the difference in experience with enrollment into randomized trials.

And I think, in part, where we heard one completion -- and congratulations on completion of the CryoCor -- that may have -- part of it may have been the fact that it was a novel therapy as compared to what standard of care is in many institutions, and that's radio frequency-based.

But along that line, if I can understand -- if that had a drug versus ablation -- but did I hear right that patients could continue the drug they were already on and that they -- say if they were on amiodarone already, presumably they failed amiodarone, or they wouldn't be enrolling in

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the trial.

So your medicine arm was continuing a failed drug, and comparing that to ablation? And in that case, what was your crossover from ablation -- are you able to share with us preliminary data in terms of how many of your patients crossed over from drug to ablation?

DR. BAROLD: I don't know if I understand the first part of your question, but let me see if I can try to answer it anyway.

So the way the study works for medical therapy patients, you have to have failed a medication at a particular dose. When -- if you randomize to medical therapy, you have three months, during the blanking period, for the investigator to optimize your therapy.

So they can put you on another anti-arrhythmic, they can increase the dose, they can switch it three or four times, they

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1 can get you as good as they think they're
2 going to get you on medical therapy, all
3 right?
4 We request that, if you're on
5 amiodarone, that you stay on amiodarone. Now,
6 you can add things to amio. You can add
7 calcium channel blockers, beta blockers. You
8 know, you can add other things. And we
9 request that you stay on amiodarone.
10 We have had a number of patients
11 that have had to come off of amiodarone
12 because of side effects, but you can also
13 change the dose of amiodarone to optimize
14 their medical therapy.
15 At the end of three months, which
16 is the blanking period for the study, the
17 ablation arm -- we request that the
18 investigators stop the anti-arrhythmic
19 therapy, and we then evaluate the patients off
20 of anti-arrhythmic therapy.
21 There are cases where they can't,
22 and they end up going back on it, or they

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decrease it slowly, or it doesn't happen exactly at three months, or the patient doesn't want to come off it because now they feel good. So you know, we're going to see a variety of scenarios in the study.

I cannot share with you right now our crossover rate, because we haven't finished, so I can't tell you for sure what it is. But it's a significant crossover rate, as I think all of the trials are going to see, but I can't give you a number. Okay? Does that answer it?

DR. PAGE: Yes, I think so. So just to confirm, if someone's already on amiodarone, obviously has failed, or they wouldn't be coming to their doctor for novel therapy, but the medicine arm included patients on the same drug that had already failed, and the comparison was between continuing failed therapy with the ablation.

DR. BAROLD: Yes. Okay. But --

DR. PAGE: Thanks.

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1 DR. BAROLD: Well, yes, but you
2 have to understand that those patients are
3 going to be randomized to both sides, too, and
4 so they'll have -- they'll be on that therapy
5 for -- you know, there should be an equal
6 weight between the medical arm and the
7 ablation arm for the number of patients that
8 are on amio. And you're allowed to change the
9 dose.
10 DR. PAGE: Thank you.
11 DR. BAROLD: So -- okay.
12 DR. YANCY: Dr. Morrison?
13 DR. MORRISON: I'd like to begin
14 with the perspective that the two most
15 important things I was hoping to arrive at at
16 the end of the day were randomized trial, and
17 against medical therapy.
18 Now, with that in mind, I'd like
19 to suggest playing off Dr. Neaton and Dr.
20 Haines' conundrum against another conundrum
21 that was raised earlier in the day. It seems
22 to me that Dr. Haines' point about early

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versus late complications would apply if the drug therapy were amiodarone or 1C=s, but it would not apply to beta blockers or calcium blockers.

And earlier in the day, people said, could we not propose to have the randomized trial medical therapy for first takers, or for people who failed beta blockers and calcium blockers.

It seems to me considering that option also may be more in line with the results of the AFFIRM trial, and I'm saying that only because, as a non-E.P. person, I can't help but believe that we are here primarily not because industry wants to approach a few thousand people with paroxysmal atrial fibrillation in their 50s who have good hearts, but that, rather, there's an awful lot of look toward the 10 million people over 70 years of age, and so forth.

So I would like to suggest that that conundrum of medical therapy versus, you

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1 know, early and late complications -- I would
2 agree that long-term follow-up is probably
3 another great principle, but it may not be as
4 necessary if the drugs that people are
5 required to fail are beta blockers and calcium
6 blockers.
7 And that would, from what every
8 industry person has suggested here this
9 morning, imply that you would be enhancing the
10 pool of people who would be willing to
11 consider randomization, and your operators
12 would be more willing to portray equipoise if
13 that were the comparator.
14 DR. YANCY: Is there any response
15 from industry? I know several of you spoke to
16 the notion of a primary A.F. drug versus
17 ablation trial. Any other comment on Dr.
18 Morrison's query?
19 Dr. Yaross?
20 DR. YAROSS: Yes, I think that's
21 one of the potential designs that would be
22 helpful. I think one of the other points that

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1 was made this morning, and into the afternoon,
2 is the idea that a variety of different trials
3 should be possible.
4 I think one of the things that
5 Drs. Packer and Calkins and some of the others
6 talked about, was a hierarchy of types of
7 evidence. And certainly, you know, there are
8 trial designs, and this whole issue about
9 asymptomatic versus symptomatic, you know, is
10 highly relevant if you're talking about
11 elimination of all A.F. claims of cure, et
12 cetera.
13 But I think sponsors need to be
14 able to tailor the study to what is the claim
15 that they want to make, and certainly, if they
16 want to talk about being able to deal with a
17 specific population, such as those that are
18 just resistant to A.V. nodal blockers, things
19 of that sort, you know, that's certainly one
20 option.
21 But we need to be able to have a
22 variety of ways of tailoring the study designs

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to the specific population. And I think your point is well taken that we're designing trials right now by trying to align with this guidance document that are just focusing on a very narrow band of the population.

DR. YANCY: I think Dr. Neaton has a direct response, or at least a somewhat --

DR. NEATON: Well, I mean, I think that's still -- I agree with you. I think that's an idea that sounds like, from the discussion this morning, that should be pursued a little bit more.

I'm not sure that it gets away from the problem that -- in the ablation arm. There's probably going to be a higher risk, early on, of safety kind of outcomes compared to the drug arm. That's still going to be there.

I do think, just more generally, that if one moves into the population where you're studying ablation as a first-line therapy, the -- what's the right word? -- the

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rigor, or the design, both in terms of follow-up and end points, may have to be a little bit stronger, in my mind, than in the study designs that we started talking about this morning.

And I would definitely want to see longer follow-up in those studies, and perhaps -- perhaps with a different end point than we've discussed so far. But I think it's -- some stronger evidence is required in that -- in that target population, I would say.

DR. YANCY: Dr. Schoenfeld, and then Dr. Tracy, and Dr. Kato, and then we will begin to really hone our attention towards the FDA questions.

DR. SCHOENFELD: I'm sorry, but I'm going to have to, unfortunately, leave shortly, but to emphasize the C in the RCT aspect of things, like the three types of models that have been here discussed, are either de novo anti-arrhythmic versus ablation, if you want to presume that this

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1 isn't a firm type of patient who has failed
2 calcium channel blockers or A.V. nodal
3 blockers; essentially, rate control. That's
4 one model that's been proposed by Dr.
5 Morrison, for example.
6 Another is the typical type A type
7 of program strategy that's been proposed by
8 the FDA, which is somebody who's already
9 failed one more cardiospecific anti-arrhythmic
10 drug, and that's against the ablative
11 strategy.
12 And the problem that has been
13 raised there is that, if you fail one, doesn't
14 that increase the likelihood that you will
15 fail another. And, for enrollment purposes,
16 you're less likely to garner up enough
17 patients who are willing to do that.
18 Or the third strategy, which is to
19 compare one type of ablative tool versus
20 another ablative tool, so-called standard of
21 therapy, recognizing there is no gold
22 standard.

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1 And I think that that's really
2 what it comes down to, really, at this point.
3 And I think the idea of a control, and also
4 the concept of crossover is just so important,
5 because it's so reminiscent of previous
6 discussions that we've had with regard to
7 neurocardiogenic syncope, when we thought
8 pacemakers were the be-all and end-all.
9 But the controls that we were
10 looking at -- it was either a beta bocker
11 versus a pacemaker or, it wasn't until a
12 pacemaker was inserted into everybody and it
13 was turned on or off that we saw that maybe it
14 didn't make any difference.
15 And the same thing we're seeing
16 for the crossover trials for defibrillators,
17 with cardiac resynchronization therapy.
18 Patients got the device, they felt better, and
19 then we told them, some time later, that their
20 device was off, and they no longer felt
21 better.
22 And I don't think we can

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1 underestimate the placebo effect of an
2 intervention. And I think that I just want to
3 get back to that whole issue of crossover and
4 control, because I think it is important.
5 But what I'm hearing is that there
6 are three different things that have been
7 projected -- the advantage of the de novo, or
8 the patient who is the rate control failure
9 for these devices. You'll get definitely much
10 more recruitment. It may be something that's
11 long overdue, and CABANA may be addressing
12 that anyway, but now may be the time that is
13 ripe, and it will definitely ensure
14 enrollment.
15 The problem with the current type
16 A program that FDA is proposing is that you're
17 already having problems enrolling as it is,
18 but it has to be fully acknowledged that, if
19 you're comparing one ablative tool with
20 another ablative tool, they're still getting
21 an interventional type of device, and who's to
22 say what the gold standard is. And that is

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1 the challenge, nonetheless.
2 But if you're looking at safety,
3 then probably that's a very good way of
4 evaluating the safety.
5 DR. YANCY: Dr. Tracy?
6 DR. TRACY: Obviously, afib is not
7 a single disease. I mean, there's such a
8 different patient population, and the
9 different studies are kind of reflecting that.
10 It strikes me that CryoCor is the
11 one company so far that's been able to go
12 through the enrollment successfully, have
13 completed enrollment at least, at this point.
14 And one of the major differences here, even
15 though they comment in their presentation that
16 they'd had difficulty enrolling patients,
17 amiodarone was permitted to be in the study,
18 as opposed to some of the other studies where
19 it was not permitted.
20 I'm curious. It seems, if we
21 broaden what the drug inclusions permittable
22 in the studies, it certainly would help, but

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I'm curious about any comments you might have, how -- what actually were your difficulties in enrollment.

DR. BAROLD: I think we've had the same difficulties that all the other companies have had. One is, you know, CryoCor is a very small company, 38 employees, so, as opposed to some of the larger companies, we don't have the resources to, you know, get out constantly and, you know, meet with the investigators to try to enroll.

So we didn't have that part, but we did -- we have a novel device, okay? So there are certain selling points that the investigators can use to sell the study or, sell the study, which is not a good term, but, you know, cryoablation may have specific advantages over R.F. So that is a way to sell the study.

We do allow a crossover. You have to have episodes after the blanking period. I mean, there are strict criteria. But that

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is an incentive to the patient, also.

And also, we started the study early. We were one of the very first companies, so we did get in early. And I think, like I said, we have a very motivated group of investigators that just want to finish the study, and they want to see what the data is.

I think everybody's really interested in, you know, what is the true effectiveness of ablation, and what is -- what's really going on with the medical management group. So I think, if you present it that way to investigators -- you know, we really want to answer these types of questions -- they seem to be more willing to enroll, and that's what we found.

We also -- you know, we have 24 sites. That's a lot of sites, and we found that, initially, the enrollment was very, very good, and then it plateaued out. I think what happened was that people got sick of

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enrolling. They said, you know, and also the nurse coordinators, I mean, this is a really hard study for them.

And so if you get a, you know, 10, 12 patients at your site, and you've got to follow them for one to three years, depending on how many things, they may say, okay, you know, you've got to stop enrolling at this site, because we've had enough.

So what we did is that we had -- we added additional sites later, and that seemed to infuse sort of some new excitement into the study, and that's really when we finished, so that's what we found.

DR. YANCY: Dr. Kato?

This will be the last query directed towards the earlier speakers, and then we'll go into our FDA questions, unless someone on the panel has a concern.

I know we haven't heard from our consumer representative yet, and we haven't heard from surgery yet, so I do want to yield

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to you if you have questions.

But, Dr. Kato, please.

DR. KATO: Tell you what, after that last comment, I'm going to save my comment for our general discussion.

DR. YANCY: Any questions from our consumer representative?

MS. MOTTLE: Not specifically for these people. I have some questions dealing with some of our more chronic afibbers, and being excluded in these trials where we're using -- we're not getting the data to treat them by using a different population. But I'd like to address that with the panel.

DR. YANCY: From Dr. Jeevanandam or Dr. Blackstone, if you've got any additional perspectives?

DR. JEEVANANDAM: One -- I think he left, but he posed the -- a concept of three different types of studies, and one of the studies was to try to use a device de novo for people who have failed beta blocker or

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calcium channel blockers.

Now, that actually is attractive to me because, if consensus papers say that the devices we have now can be used with failed medical therapy, then, if we're going to be testing new devices that are theoretically better for treating atrial fibrillation, then it's a different -- it's a different kind of market. It's a different patient population, where you're now comparing device directly to medication, before they get started on amiodarone.

So basically, you're going to be comparing that to amiodarone, a first membrane drug.

Now, I guess my question to industry is, are you guys willing to do that, right? So you're now going to compare the device to a patient who's failed a beta blocker, and that would mean that your effectiveness is going to be different compared to medical therapy, so your power's

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1 going to have to be adjusted appropriately,
2 and you're going to probably have to do more
3 patients to show a difference to drug therapy.
4 So, how does industry feel about
5 doing patients like that de novo, straight
6 off, if they're -- failed beta blocker or
7 calcium channel blocker?
8 DR. CALKINS: Hugh Calkins. The
9 only comment I want to make is the three --
10 there have been those four randomized studies
11 that were cited earlier that were patients who
12 have never been on an anti-arrhythmic drug,
13 and the drug response rate in those studies
14 was maybe 30, 40 percent, and the catheter
15 ablation response was 70, 80 percent.
16 I mean, there was -- they were all
17 positive studies, so I agree that you may have
18 to -- there may be a slight increase in sample
19 size, but I think, fundamentally, you know, I
20 think the strongest evidence is that catheter
21 ablation is better than anti-arrhythmic drug
22 therapy.

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1 As long as you look with equal
2 metrics for symptomatic and asymptomatic afib
3 in the two populations, I think you'll see the
4 same difference based on those four studies
5 that have been done in identically this
6 patient population.
7 One was published in JAMA, you
8 know, good journals, and this is exactly the
9 study that we're thinking of expanding to that
10 group.
11 DR. YANCY: We can take one more
12 comment. Yes.
13 MR. BARRETT: Yes, Burke Barrett
14 from CardioFocus. I can tell you -- I can't
15 speak for industry, but I can tell you, for
16 our company, that our study is powered based
17 on a safety analysis. And if you look at our
18 feasibility ablation study results, and our
19 expectations from any anti-arrhythmic drug
20 therapy, we probably wouldn't need increased
21 sample size.
22 The risk in this design for us, as

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you=ve heard from others, continues to be that we may not be adequately powered for safety because of the early crossover in the drug arm.

DR. YANCY: I think that we've entertained all of the queries from the panel.

We need to take just about five minutes to get focused on our FDA questions, so use this to perhaps go to the restroom or return calls. But it will only be about five minutes, just to get our questions posted. Thank you.

(Whereupon, the meeting went off the record at 2:37 p.m. and resumed at 2:43 p.m.)

DR. YANCY: We need to resume our meeting, and I'd like to do that immediately. Please have your seats so that we can resume our meeting immediately. Once again, please return to your seat or move your conversation outside.

There has been one speaker who has

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been inadvertently overlooked, and we want to entertain all comments.

Dr. Saxena, if you would identify your affiliation and conflicts, we'll begin with your statement. Thank you. And thank you for your patience.

DR. SAXENA: Thank you, Dr. Yancy.

I'm Sanjay Saxena. I'm a cardiac electrophysiologist in New Jersey. I'm on the faculty of Robert Wood Johnson Medical School. And I'm medical director of a nonprofit foundation and research foundation.

The foundation conducts clinical trials for a variety of sponsors and has contractual relationships with both device, ablation and drug sponsors of clinical trials. So that's my disclosure.

I've been -- I also wear another hat -- is that I'm an editor of -- one of the two editors in this room for a journal in electrophysiology, so this interests -- the reporting standards issue has been important

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to us.

There are two points that I -- the discussions today have gone a long way towards bringing information to the table. The longest period of time some of you will know that our center has been involved with device-based monitoring of atrial fibrillation and device-based hybrid therapy of atrial fibrillation, devices and ablation, devices and drugs, ablation and drugs.

So we have about a 10-year to 15-year experience with device-based monitoring of atrial fibrillation. We've also conducted some clinical trials for sponsors in that area.

And one of the key things that we reported of several years ago in some of these trials was that while randomization in clinical trials is generally accepted to balance the risks and variables in two different groups, that unfortunately clinical randomization, as we clinically do it, does

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not balance atrial fibrillation burden.

In fact, in one of the -- couple of these trials, the difference in atrial fibrillation burden in randomized patients, both randomized to -- to an active treatment arm an on-and-off design, could be as different as a factor of 10 to the power of three.

So when you introduce asymptomatic atrial fibrillation burden into the equation of the end point, it's important to realize that your asymptomatic burden is not balanced.

And that information -- we've conducted two natural history studies on the basis of symptoms and A.F. burden, and there's one coming out now in the American Heart Journal which is a combination of the aspect study and the natural history of A.F. study which will be published, I think, in a month or so, which shows the progression, the natural progression, of atrial fibrillation burden.

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1 What that data shows is that we do
2 not by randomization make the burden on both
3 sides of the arm equal. So I think that's
4 very important variable.
5 We've always been a proponent of
6 judging asymptomatic atrial fibrillation as a
7 risk and a recurrence to atrial fibrillation,
8 but I'm getting concerned that the pendulum is
9 going too far the other way.
10 You know, medical students with
11 Holter monitors show asymptomatic atrial
12 fibrillation for years and years of their
13 life, lasting 30 seconds or a minute. So we
14 should never forget that when we get concerned
15 about atrial fibrillation is when the
16 substrate changes. We start getting sustained
17 atrial fibrillation lasting long periods of
18 time.
19 So when you look at secondary end
20 points as the HRS consensus document suggests,
21 I think you have to use the heart failure
22 analogy -- clinically relevant asymptomatic

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1 atrial fibrillation.
2 So in our reports that we are --
3 that we are reporting on the long-term outcome
4 of our device-based patients, we look at
5 hospitalizations based -- where atrial
6 fibrillation drives the hospitalization,
7 cardioversions, enhancement of heart failure,
8 situations where a clinically relevant event
9 occurs.
10 So if atrial fibrillation lasts
11 longer than 24 hours, most of us trigger on
12 anticoagulation. So if asymptomatic A.F.
13 lasts more than 24 hours, perhaps that is a
14 reasonable point to think about in that
15 composite end point.
16 So I think it's important to take
17 the next step from asymptomatic atrial
18 fibrillation to when does it become clinically
19 relevant asymptomatic atrial fibrillation.
20 And that should be -- I would say to you that
21 the first people that for 30 seconds are --
22 that is A.F. as an end point for the current

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was actually ours back in the mid 1990s based a device.

Now it's been adopted as a standard, but I am concerned that there's a long gap between 30 seconds and clinically relevant atrial fibrillation.

The last point that I'll make in the couple of minutes that I have is that as an editor of a journal we do set up reporting standards and we do try -- we have recently enforced things like gender and reporting of certain subgroups that have to be reported.

And certainly we will sensitize our reviewers to what the HRS standards are, but there will be a long time before you will get data that will -- has to be prospectively done this way.

So I think while it's -- while it's important to sensitize everybody that we want things reported that way, there will be a lag time and I think I spoke to that earlier.

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1 So I just wanted to raise these
2 issues with you. I think -- let's -- you
3 know, having been very critical of the way
4 A.F. studies have been reported -- and we
5 published in our journal about Hopkins=
6 experience with the low efficacy rates in --
7 for -- of these studies, we don't want the
8 pendulum to swing completely the other way;
9 that is, you know, you're measuring every 30-
10 second episode of atrial fibrillation and
11 calling it clinically relevant. Thank you
12 very much.
13 DR. YANCY: Thank you for your
14 comments, and we certainly will put that in
15 the context of the other statements we heard
16 about, the accuracy or lack of accuracy of
17 some of our metrics.
18 Is there a direct question in
19 response to what we just heard from any panel
20 member?
21 Yes, Dr. Peters?
22 DR. PETERS: Well, I was just

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curious about your comment that afib burden is not sort of handled by randomized clinical trials. It doesn't make a whole lot of sense. It's possible just that the standard deviation is so large that you just need a tremendous sample size, or --

DR. SAXENA: No, no.

DR. PETERS: -- do you have any other explanation for it?

DR. SAXENA: No, the explanation for it actually -- and you're at disadvantage because the -- some of the data that we have in the natural history study is not out in the -- is not published.

It is clear that atrial fibrillation burden, when you follow patients over years -- there's a group that it remains absolutely static and it does not increase, and it's usually the group without structural heart disease.

But if you have any form of structural heart disease, there's an

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1 inexorable progression which actually -- on
2 the regression line it was 14 seconds a day
3 over this period of time that it progresses.
4 Now, you don't match your patients
5 for who has heart failure, who has
6 hypertension, who has E.F.s of less than 30,
7 over 45. Your patients don't match in all
8 those groups. So the substrate changes are
9 clearly not matched.
10 And triggers, actually, over time
11 decline. What is interesting in this data is
12 the triggering premature groups that are
13 targeted actually decline, and it explains why
14 the progression of atrial fibrillation is a
15 function of both age and heart disease.
16 So you cannot -- unless you match
17 them for all these covariates, and we don't
18 even know all of them, the studies like the
19 Medtronic A.F. study, for example, showed very
20 clearly a huge difference in A.F. burden in
21 the different arms.
22 DR. PETERS: Well, perhaps it

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would be helped if we did at least do structural versus non-structural and stratify that way. Maybe that would help to equalize it.

DR. YANCY: There's a comment from Dr. Neaton.

DR. NEATON: I just would say, though, that on average randomization's going to balance that, and there may be chance imbalances in important factors, like you're talking about at the outset. If that's what the point is in a small study -- but the likelihood of something on the order that you talked about in a moderate-sized study is very, very low.

If it's an outcome -- I'm sorry, I misunderstood that -- it's a whole different matter, and so with randomization the advantage of it is it basically gives you balance on factors that you don't stratify on as well as those that you do.

DR. SAXENA: Dr. Neaton, that's --

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I think that's a very important comment, and I accept that. But I think what you have to see is the disparity and spread in A.F. burden between individual patients that look and present with the same two episodes of clinical A.F.

These are very high event rate situations. They're very -- if you look at, for example, the Hindricks article and some of those other articles that were shown here, is that in -- and there's a bunch of studies from Luigi Padeletti's group that show enormous variation week to week in the A.F. burden.

So this is not easily reproduced. I think the week that you randomize may not be always reproduceable while you're doing this over time. I just don't know the high variability model of fixed randomization, and I can only report on observations from the studies.

DR. YANCY: If there are no other questions, we'll begin our FDA questions.

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1 Did you have a follow-up comment,
2 Dr. Neaton? Okay.
3 Let me just remind the panel that
4 we have approximately 11 questions, and we
5 would like to have some tangible response to
6 the FDA from the majority of the panel on as
7 many of these as possible, and certainly by
8 5:00 p.m. we will begin to lose our critical
9 mass, so keep that in context as we're making
10 our commentary.
11 We actually believe we should
12 start with question number two, so if those of
13 you in the audience have a list of the
14 questions and are following along with us, we
15 will begin with question number two.
16 What trial designs are viable
17 options to develop valid scientific evidence
18 of the safety and effectiveness of a new
19 ablation catheter system? Please consider the
20 two example trial designs presented by FDA.
21 A, what is the appropriate control
22 for the study of the safety and effectiveness

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of ablation catheters for the indication and treatment of atrial fibrillation? Do the different types of atrial fibrillation need different control groups?

B, for what duration should safety of the ablation device be measured?

And C, for what duration should effectiveness of ablation device be measured?

So we're focusing on trial design. This is a time period for discussion between panel members only, so there won't be any other commentary.

Dr. Somberg?

DR. SOMBERG: Thank you.

Briefly, I think all we've heard today does not undermine the need for randomized controlled clinical trials. They're ongoing. A number of them -- one has been successful -- completion. Some of them are closer to completion than not. And we're going forward on that. So I think that should be emphasized.

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1 Now, if you can't do a randomized
2 controlled trial -- and I think you can. But
3 if you can't do it, then sometimes at least a
4 controlled trial and maybe non-randomized
5 would give you the best information.
6 Single-arm studies or some
7 performance goal I think in this area is truly
8 inadequate. And there are a lot of
9 subcategories we can talk about -- end points,
10 et cetera. I'm not sure we're going to be
11 able to get into all of them today.
12 But one of the important things
13 here is that I think we have to be more
14 permissive to facilitate a randomized
15 controlled trial by relaxing things like
16 potentially frequency of occurrence, possibly
17 concomitant drug therapy, amiodarone -- which
18 is always problematic. I love the drug, but
19 it's a problematic agent, to say the least.
20 And these sort of things --
21 they're -- you know, the -- everything's in
22 the details. But overall, it should be

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emphasized -- and I think we heard today, at least in my opinion, and I think a number of other people on the panel have said this, that randomized controlled trials should be the standard we aim for today.

DR. YANCY: Thank you for very clear commentary.

Dr. Kato?

DR. KATO: I would -- I would have to agree with that. I think the -- there were compelling presentations from representatives of the Heart Rhythm Society as well as the American Heart Association which -- organizations advocated the need for randomized controlled studies.

I think, you know, historically we've seen other devices come before this panel, and we've really run into a lot of problems when the study wasn't a randomized controlled trial, when it was tried -- you know, people tried to do one-armed or whatever, but something less than a randomized

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1 controlled trial.
2 And I say -- I think I remember
3 several studies where even if end points had
4 to change, or there was a problem during the
5 trial when it was still a randomized
6 controlled trial and the sponsor was
7 forthright and transparent about their
8 problems during the trial, even though they
9 had to change end points or they had to change
10 the -- even the type of device that was used,
11 the panel was still fairly forgiving about --
12 you know, I mean, that's just the real world.
13 And the panel accepted that data,
14 I think, favorably. I think the -- so I would
15 caution the sponsors on the, you know, running
16 behind -- saying that randomized controlled
17 trials are too expensive, or they're too --
18 you know, we have to get too many patients
19 enrolled.
20 I think we've seen also an example
21 today of a small, nimble company doing exactly
22 that, and getting to market first, and that's

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exactly what -- that's exactly what the marketplace is supposed to do.

DR. YANCY: Do remember that Dr. Page identified some of the unique characteristics of that trial that facilitated its success. That may not be the same kind of trial that others are doing, but your comments are definitely well taken.

Did you need to continue, Norman?

DR. KATO: You know, in terms of the actual end points to be used, you know, I would leave that up to the sponsor or, you know, to the individual company itself, because I think that the -- you know, every company tries to use to their comparative advantage some type of comparison for saying my drug is better than this, or my device does this.

And I think that those end points, in order, you know, to make that comparison, have to be left up to the company. And that -- and that becomes their market advantage or

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disadvantage.

DR. YANCY: So so far I have two panel members that suggest trial A, if we can just put it in a rough bucket.

Who would like to speak next?

Dr. Tracy?

DR. TRACY: I also think if it's -- if feasible, the randomized controlled trial is optimal. The question then becomes what is the control group. And as it stands, you could either have another ablation technique, another ablation tool that's currently in clinical practice being used, or a medical group.

Both of those are fraught with their own special problems, both in terms of safety and efficacy, but the peculiar place that it puts the currently used ablation tools that we use clinically is that how in the world will they ever be approved for use in ablation therapy of atrial fibrillation.

There's nothing then that would

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1 make that company go back and get a four or
2 five French --
3 DR. ZUCKERMAN: Dr. Tracy, if I
4 could just interrupt a moment, we're not
5 saying that one size does not fit all. One
6 size does not fit all. I wouldn't worry about
7 one particular company. I would try to
8 address this question in a general context for
9 the wide variety of sponsors you've heard
10 from.
11 DR. TRACY: Yes.
12 DR. ZUCKERMAN: We are more than
13 willing to look at some unique problems post
14 this panel with specific device manufacturers.
15 DR. TRACY: Yes. I think that
16 would have to be done, because it does put the
17 current clinical practice, what we are all
18 doing, in a peculiar position. I think that's
19 an important point.
20 DR. YANCY: Dr. Page?
21 DR. PAGE: Yes. I'd just like at
22 the outset to say that I firmly believe in

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randomized controlled trials. Dr. Kato and I have sat at a number of these meetings wishing we had better data and always insisting on a high level of data.

On the other hand, at the outset of this meeting, I implied that I was skeptical about plan A or protocol A, and I remain skeptical in that if you go back to looking at how that was set up, it's insisting on patients who have failed one drug going onto another new drug, agreeing to participate, presumably mostly in radio frequency ablation studies, which are -- the patient's going to wonder why should I enroll in this if I could go ahead and get what is standard of care.

I think we saw data that there were 30,000 ablations done this year.

Now, a compromise might be to have a trial where we're randomizing people at the outset. This is contrary to the guidelines or the position paper from HRS, though HRS

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1 does have the wiggle room to have primary
2 therapy as ablation.
3 But for a patient who's just been
4 on nodal blocking drugs, I think you -- one
5 could make the argument to enroll -- randomize
6 between those two options, either new, first-
7 time ever anti-arrhythmic therapy and the
8 route going that direction, or ablation.
9 And finally, in terms of trial B,
10 I don't think it can be entirely discounted.
11 I think good people putting their heads
12 together could come up with performance goals,
13 although ideally we'd have randomized clinical
14 data. It's just whether we can feasibly get
15 the appropriate data.
16 DR. YANCY: Appreciate that.
17 Let's go to this side and, Ms.
18 Mottle, did you have your hand up?
19 MS. MOTTLE: No.
20 DR. YANCY: Dr. Yaross?
21 DR. YAROSS: Yes. I think that no
22 one is arguing that randomized controlled

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trials are not the ideal and the gold standard, and I really appreciate Dr. Zuckerman's comment that one size does not fit all.

I think that it's clear what we're -- from what we're hearing today that there is a group of manufacturers who, by dint of hard work and effort, are going to complete a round of trials.

What I would ask is that the panel keep in mind that this generation is -- of tools is probably not the ultimate tool. We want to make sure that we have a range of options open to sponsors that will encourage them to bring the next generation of tools forward.

In terms of trial A -- and I think the comments that Dr. Page made are very helpful. In terms of option B, the trial design option B, I think it's an extremely creative and appreciated attempt by FDA to bridge these gaps.

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1 But in talking with industry in
2 general, it does not seem to be one that
3 solves the practical issues that they face.
4 DR. YANCY: Dr. Jeevanandam?
5 DR. JEEVANANDAM: I agree that --
6 I think the first trial, or trial A, is --
7 with the randomized clinical trial is the way
8 to go. I think what we can do, though, is
9 broaden the spectrum of that trial, so you can
10 allow the sponsor to pick a control group that
11 has failed beta blockers or calcium channel
12 blockers, or they could also take another
13 control group that perhaps can include
14 amiodarone.
15 It seems like if you include
16 amiodarone and plotted their data, you will be
17 able to enroll a lot of patients, which is
18 what their primary concern was.
19 I think the type B type of trial
20 probably needs to wait till one of these
21 devices actually gets approved, because then
22 you can actually go ahead with that device and

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that would be a legitimate trial.

And then I guess the other question -- are we doing all of one, or are we just -- are we doing all of two? Because two A also means do different types need different control groups, and I do think that if you are going to pick persistent afib or chronic afib or paroxysmal afib, I think the control group and device group need to be similar.

So I don't think you can have one study that will then randomize that completely. I think you should have different studies.

DR. YANCY: Appreciate that input.

Dr. Blackstone?

DR. BLACKSTONE: I'd like to address two B in the following way. As we look at what the ends will be for the current trials, I think we're going to end up in the panel saying that they're underpowered for safety, because the -- even though safety is driving the ends, the complication rates I

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1 think we're going to find are very low.
2 So we're going to be again in that
3 conundrum, so perhaps -- and part of the
4 conundrum of B is the following, and that is
5 that as someone said, the front loading for
6 the catheter ablation is balanced against a
7 very long-term safety issue for the drugs, so
8 that you have crossing lines, and how are you
9 going to deal with those.
10 So there may be -- need to be a
11 completely separate mechanism set up for
12 evaluating safety. And for example, that
13 might need to come from a very careful
14 national registry or something that would have
15 the thousands of patients needed to try and
16 set up some safety goals, because I just don't
17 think that any of these studies that we've
18 heard about -- there's plenty of patients for
19 efficacy.
20 I think there's going to be too
21 few patients for safety and some other
22 mechanism may need to be devised.

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DR. YANCY: Dr. Neaton, would you care to comment on that? That seems like a very important issue if we're saying that it will be very difficult to power for safety because of the characteristics of the events, the necessity for really large numbers, and perhaps an alternative strategy like a registry -- if you could comment on both of those things.

DR. NEATON: Well, I think that's -- I agree with Dr. Blackstone. I think there -- you could be in a difficult situation, and so the -- in terms of the power for comparing the catheter versus medical therapy, if that's what it is, for safety outcomes is a function of the number of events that you observe.

So you might say -- you might divide them in two ways, those that occur around the time of the catheterization and those that occur some time later where you don't have the problem that we were talking about earlier, about the higher risk, and so

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one solution to that that I alluded to earlier is longer follow-up.

And that still may not give you very satisfactory -- kind of put you in a satisfactory position, but one solution is a longer follow-up of people in the trial. That might come as a second stage or as a registry, as was proposed here.

Maybe while I have the mike I can just say I think the plan A with broadened inclusion criteria makes a lot of sense, and I guess I have the same feeling about plan B that Val mentioned, and I think that might be more appropriate when there's a -- an approved catheter out there to kind of compare against.

DR. YANCY: Dr. Morrison, we haven't had your input.

DR. MORRISON: Well, as I mentioned earlier, I came here with three big-picture goals and I've added a fourth since listening to this.

The first two are randomized

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1 controlled trial against medical therapy. The
2 third that I think is absolutely critical is
3 the end points, whatever they are, have to be
4 objective. And we've heard all kinds of
5 technical issues about burden, and diagnosis
6 of afib and so forth.
7 Now, all of this is relevant and
8 starts with a population of low risk, young
9 people, no structural heart disease and
10 predominantly paroxysmal atrial fibrillation.
11 And to put it bluntly, as a non
12 E.P. person, I'm just anxious to give you all
13 enough rope to hang yourself, because I think
14 what you'll demonstrate -- what is likely that
15 you will demonstrate in low-risk people who
16 have lots of symptoms is that it's very hard
17 to demonstrate, even compared to beta blockers
18 and calcium blockers, that ablation changes
19 life very much.
20 And as I've also let out of the
21 bag, I don't believe that's where the
22 companies want to go anyway. So that leads to

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1 the fourth point, which is it's critical to
2 design separate trials with separate end
3 points for people who have structural heart
4 disease.
5 And when you do that, which is
6 where they want you to go, I think, then
7 you're talking about populations where there
8 is substantially higher likelihood of getting
9 both efficacy and safety end points. That the
10 generic principle of trials.
11 You need to enroll huge numbers of
12 low-risk people to get a few outcomes. You
13 don't need so many people that are really
14 sick.
15 So again, I come down strongly on
16 randomized trial against medical therapy. I
17 think for purposes of helping the device
18 companies getting the devices that you want
19 and really starting the learning process, with
20 all that we've heard from the Heart Rhythm
21 Society and the AHA and the ACC, why not
22 include people who have failed beta blockers,

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1 calcium blockers, amiodarone?
2 But you've got to have something
3 objective, whether you want time to event, or
4 whether you want A.F. burden, or whether you
5 want whatever. It can't be just oh, I feel a
6 whole lot better since you did that really
7 neat thing with your catheter to me as the end
8 point.
9 And I think then, when you want to
10 extrapolate to the people that are really
11 sick, does this make a difference in heart
12 failure, diastolic dysfunction, stroke, well,
13 you're going to have all the complications and
14 all the effectiveness outcomes you want.
15 And it would be a real street
16 fight, it seems to me, between beta blockers
17 and amiodarone versus a complex, invasive
18 procedure in those kind of patients.
19 DR. YANCY: Well, I -- we
20 appreciate that input, and I'm assuming that
21 your comments would also be pertinent to the
22 later question 10 about the high-risk

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patients, and so both of those are points well made.

I want to be certain we get to everyone who has not yet spoken.

So, Dr. Slotwiner, and then Dr. Milan, and Dr. Peters. Okay.

DR. SLOTWINER: Yes. Just for the record, I would like to state that I do think the randomized controlled trial, trial A, is much more likely to yield meaningful results and not mislead the sponsors.

And I would like to agree with Dr. Morrison on the need for hard end points. I think pacemakers and vasovagal syncope and other similar interventions have demonstrated how critical it is to have objective information.

And I think, as Dr. Packer says, we may accept a lower mark as a success, but to get that information I think is at least critical.

DR. YANCY: Terrific.

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Dr. Milan?

DR. MILAN: I want to also voice my support for a randomized controlled trial design of the type A. And I want to speak just for a minute about the apparent enthusiasm for expanding the enrollment to include patients who have never failed an anti-arrhythmic drug.

And I think that ablation is first-line therapy -- widely accepted as first-line therapy for SVTs, where the success rates are well in excess of 90 percent and the complication rates are extremely low. And I'm very comfortable with that.

I think what we've heard mostly around discussions of how difficult it will be to develop effective performance criteria is that the reported efficacy rates in the literature, if anything, are overstated or inflated. And we've heard concerns that the safety reports in the literature, if anything, are under reported.

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1 So what I hear is that however
2 good we think it is, it may not be that good,
3 and however safe we think it is, it may not be
4 that safe. And to then sort of start saying
5 that we want to use this as first-line therapy
6 for patients who have never failed anti-
7 arrhythmic drugs, that raises some concerns of
8 my own.
9 And I want to say that when I put
10 a patient on an anti-arrhythmic drug and get
11 a clinical success, I think we've won the
12 game. I mean, we've avoided the risk of an
13 invasive procedure and they've received the
14 benefit. They don't have any more arrhythmia.
15 So I'm not really saying that I'm
16 opposed to investigating the possibility of
17 using ablation as first-line therapy for
18 patients with paroxysmal atrial fibrillation,
19 but if we do so, we have to pay careful
20 attention to the safety of the procedure.
21 And given what we've heard about
22 crossovers for failures of medical therapy and

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that we expect crossovers to occur in up to 50 percent of patients, I think that what that would mean is you have to enroll an awful lot of patients in order to gather the safety data for anti-arrhythmic drug therapy, those patients who would be successful and wouldn't want to cross over, and follow them for a sufficient period of time to get safety data in the anti-arrhythmic drug arm to be able to compare it to ablation therapy.

DR. YANCY: Dr. Peters?

DR. PETERS: Yes, a couple of things. One, I agree, I think that plan A is probably the best idea. I personally would favor expanding the enrollment to do primary ablation. I agree that there's some -- you know, there definitely is greater risk, but I think this is our only chance to get that information.

And I'm not really bothered by the fact that the official recommendation for HRS, AHA don't do that, because that's with

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clinical treatment. This is in the setting of a randomized clinical trial. This is the only way that you're going to kind of get that information.

In terms of the crossovers, I wonder -- I mean, you could make that an end point. You continue to follow people, perhaps, in terms of the complications, but, I mean, if somebody fails a drug and goes to ablation, that's an end point right there, and that might sort of make it a little bit easier to get -- get what you want.

The other thing is that I think that we certainly want to know what the long-term complications of the procedures are. We really -- even though it would be very nice, and we should do it in terms of the drugs, we really know what the complications of these drugs are. There's a lot of historical data. I think we could sort of use that, if necessary, as a comparison in case -- because you don't know that two years down the road

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that somebody's not going to develop amiotoxicity.

But we really know what the incidence of that is anyway -- maybe not in this exact population, but not that terribly different.

DR. YANCY: Terrific.

We haven't heard from Dr. Weinberger.

DR. WEINBERGER: Yes, I'm firmly in the type A randomized clinical trial category, particularly since this is the first device of its class that's going to be going through the process of getting FDA approval and will then be bootstrapped against for all subsequent devices in the class.

So if you get an R.F. catheter through number one, and then you want to come along with a cryocath, or you want to come along with some new method of ablation, it's going to be compared against the first standard ablative mechanism in the class.

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1 And I think that that particular
2 sponsor bears an additional burden trying to
3 come forward with an FDA-approved instruction
4 for use. And I think that, you know, if you
5 want to compete to be first at the gate,
6 you're going to be -- you're bearing a little
7 bit of a higher cost along the way.
8 So just to give you an analogy in
9 another area, if you come along with a new
10 bare metal stent today, the threshold is a lot
11 different than it was in 1989 or '87. So
12 that's my feeling.
13 DR. YANCY: I think the only panel
14 person left who hasn't expressed an opinion is
15 the chair.
16 So I'll just simply say that the
17 one issue that I'd like for everyone to keep
18 in context has to do with the gravity of the
19 safety issues. Even though the frequency is
20 low, the severity is substantial, including
21 death.
22 And so if we're talking about

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1 randomizing patients as primary treatment for
2 a disease that at that point in time is not
3 life-threatening and subjecting them to a
4 procedure that has even a small finite risk,
5 when that risk has a magnitude that includes
6 death, we have to think about that fairly
7 carefully.
8 Dr. Zuckerman?
9 DR. ZUCKERMAN: Thank you.
10 I want to get back to a key point
11 that Drs. Milan and Peters have mentioned.
12 Now that you've done a very good job
13 summarizing two A, I think both the agency and
14 the industry have a good idea of where the
15 panel sits.
16 I think the movement that we've
17 made since this morning is certainly, as Drs.
18 Peters and Milan have pointed out, doing a
19 clinical trial now for studying percutaneous
20 afib as a primary therapy is a doable type
21 trial, with the caveat that at the end of the
22 day the risk-benefit profile and clinical

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1 utility that the agency would require would
2 need to be different than for the secondary
3 therapy trials.
4 And so in two B and two C, when
5 you try to answer for second-line therapy, I'd
6 like you to also add on with considerations if
7 the sponsor wanted to do a first-line therapy
8 trial. Thank you.
9 DR. YANCY: I'm sorry.
10 Drs. Kato and Somberg, Kato first,
11 please?
12 DR. KATO: Well, I think that --
13 one thing that I think -- I hope the panel
14 shares is that the concept here is that this
15 is a clinical trial designed to get a device
16 through the FDA process.
17 This is not -- we are not here to
18 design the trial of all trials to figure out
19 what should be done for atrial fibrillation.
20 And so I guess my caution to manufacturers --
21 device manufacturers is, you know, if you want
22 to get your device to market quickly and

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efficiently, pick your question carefully. Pick your end points carefully. But don't try to answer every single question along the line that we've all brought up here.

I mean, I think many of the questions are great. I think some of the questions we don't have -- we certainly don't have answers to, such as primary therapy for atrial fibrillation. But that's not what these devices are being tried for.

And that's where I think I would defer back to the sponsors to -- you know, that's your job, is to figure out exactly what you want your device to do, what place in the market -- you know, what place in the market is it designed for, and then set up your clinical trial on that basis.

But it still has to be randomized. It still has to track 12 to 18 months. And it still has to keep track of crossovers and other medical therapies that are involved.

But I would just advise them don't

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-- don't try to answer all the questions that you heard today, because these are -- a lot of the questions I think we're asking are because we just don't know the optimal answers to a lot of this.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: Well, first, I'd just like to -- and I don't mean this in a harsh way, but I want to correct Dr. Yancy. You sort of at the beginning -- and I think it was for purpose of discussion -- we have two bins, trial A or trial B, and I hear myself and others sporting a randomized controlled trial, but it doesn't have to be exactly as A.

And we talked about a lot of modifications, and one of them, I think, is important -- is if you randomize the patients, then you're randomizing it -- you know, about 20 percent are going to be on amio, or more, but that's fine. They're going to be in both arms, and that will encourage a large number of patients in the trial, so I think that's

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1 important.
2 Number two is the other
3 modification that was spoken of was going
4 directly to an anti-arrhythmic drug versus the
5 ablation. And you know, I respect your
6 concern about an interventional procedure, but
7 I'm the pharmacologist on the panel, and I can
8 tell you drugs kill.
9 And anti-arrhythmic agents -- I
10 mean, you know, a lot of my colleagues in
11 pharmacology look at me as like I'm the
12 poisoner of the crew here because I'm an anti-
13 arrhythmic pharmacologist, and gee whiz, I
14 mean, you know, every doctor I've ever tried
15 to prescribe an anti-arrhythmic for, you know,
16 needs about two hours of consultation, because
17 they're very -- anyway.
18 So I think you have my point that
19 there is a balance here, and that leads into
20 the last problem, and that is safety. And I
21 think, you know, we heard one side saying too
22 many patients, you know, we can't get those

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1 patients, too many, because we're powering for
2 safety, and then the other side saying well,
3 we're not going to see -- we don't have enough
4 patients to see those more infrequent events.
5 So I think it's wrong to think for
6 a sponsor -- and we see it all the time here -
7 - is we do one study, you know, a preliminary
8 thing. We do one study, and we expect to see
9 efficacy and safety and all answers in that
10 study.
11 There is a pivotal study, but then
12 there's a need for other studies or registries
13 where you get a large body of patients. And
14 if you try to put it all together into one
15 thing -- and I do that, too. I mean, you
16 know, if you get one study that will answer
17 all my questions I've ever asked -- and it
18 comes to usually failure.
19 So I just caution -- I think the
20 studies are properly powered, and I think the
21 FDA is giving -- you know, for the frequent
22 side effects, but the unusual ones -- and you

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1 know, yesterday and other days we've seen --
2 we've always had questions about safety
3 issues.
4 I think those could be answered in
5 registries that have some sort of comparative
6 group in them.
7 DR. YANCY: So this has been a
8 really healthy discussion, and we've addressed
9 in principle question two A. And I think Dr.
10 Zuckerman really wanted to get our very brief
11 input on questions B and C, but framed up in
12 the context of a secondary target where it is
13 primarily focused on the catheter versus
14 another active control, not necessarily
15 medical therapy, where we have these issues of
16 size and duration.
17 Is that correct, Dr. Zuckerman?
18 DR. ZUCKERMAN: I'm a little bit
19 confused myself. I'm sorry.
20 DR. YANCY: Well, I'm trying to
21 help the panel get to where you wanted us to
22 go with your specific question so we can wrap

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1 up question two and go on.
2 DR. ZUCKERMAN: Okay. For two B
3 and C, I think there are potentially two types
4 of indications that a sponsor might go for.
5 We started this morning with a second-line
6 therapy indication, and we'd like to hear your
7 responses to B and C.
8 But appropriately, people have
9 also asked well, why not enlarge the data
10 universe and do a primary therapy trial, and
11 that's fine. But I think it would mandate
12 different responses to B and C.
13 And we'd like to be as flexible as
14 possible, so I think you should give your
15 responses with the caveat what particular
16 patient group and indication are you talking
17 about when you give your response.
18 DR. YANCY: So you've heard our
19 comments about the primary indication, so you
20 want us to focus on an indication for a group
21 that has failed medical therapy, in essence.
22 Is there anyone that wants to

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contribute to that?

Dr. Tracy?

DR. TRACY: Yes. Actually, to comment on the -- as a secondary therapy, I think you can more readily define the duration of -- whereby effectiveness can be assessed adequately.

I mean, there's a finite period in time, maybe a year, of follow-up with the monitoring that's been described either in the HRS guidelines or the FDA proposal for follow-up.

You can tell what the effectiveness of the treatment is, and you can specify whether you're looking at the primary success as being that quantum phenomenon, either you have it or you don't, and then the other secondary end points of somehow dealing with the concept of the burden of A.F.

So I think that one is easier to assess, either -- for that matter, either as a first-line therapy or a second-line therapy.

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1 The safety for secondary therapy -
2 - again, I think you're going to just have to
3 pick some finite period of time to look at,
4 because as Dr. Somberg points out, your drug
5 problems may not show up -- the pulmonary
6 fibrosis may not show up for two, three, four
7 years.
8 So you can't keep following these
9 people as part of this study. But what you
10 can certainly do is have a registry -- a post-
11 marketed surveillance type of registry set up.
12 I think the follow-up for first-
13 line therapy is going to be entirely different
14 because you'll have an entirely difficult
15 population, entirely different drugs.
16 You'd certainly never put a 27-
17 year-old with highly symptomatic paroxysmal
18 afib on amiodarone. It's just going to be
19 very different. And that would require some
20 very different thought.
21 But I think you can specify times
22 and just anything -- any residual questions be

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answered by ongoing registries.

DR. YANCY: Dr. Neaton?

DR. NEATON: For the -- kind of the indication or the population that we've spent some time discussing for primary therapy, I think you need a longer follow-up to look at the durability of efficacy than for the secondary -- second-line therapy.

And I think that I -- we heard earlier today that there's a large body of data on the safety of the anti-arrhythmics. And just to say it again, the power for your safety comparison arises from a number of events, and that can be obtained by following fewer patients longer, or a large number of patients for a shorter period of time.

And so I think one can do the computations there, but I think you definitely want to kind of power the study around some pre-specified number of events rather than just some fixed time period like six months or 12 months.

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1 You'd want to make certain that
2 there were an adequate number of key safety
3 data in the drug arm that was collected that
4 you can make an adequate comparison with the
5 catheterization.
6 DR. YANCY: Dr. Yaross?
7 DR. YAROSS: Yes, I think the
8 concept that the risk-benefit threshold for
9 first-line is greater than for second-line
10 makes a lot of sense.
11 In terms of the comparison of the
12 duration of follow-up for the ablation device,
13 however, I'm not aware of anything that
14 suggests that the nature and timing of safety
15 events would be different with first-line than
16 with second-line ablation. So I would suggest
17 that the duration of follow-up could be
18 consistent.
19 In terms of the comparison of
20 number of events or things of that nature, I
21 go back to Dr. Haines' comments and the fact
22 that if you are able to show greater

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1 effectiveness for the ablation therapy than
2 for the drug therapy, then I would posit that
3 the comparison of the safety profiles, because
4 the types of events are different, is a matter
5 for clinical judgment and not statistical
6 judgment.
7 DR. YANCY: If there are no other
8 burning -- Dr. Milan?
9 DR. MILAN: I want to second what
10 Marcia Yaross said, which is that I think we
11 should fully characterize the safety of the
12 device regardless of whether it's first-line
13 or second-line.
14 And as I sort of struggle with
15 this question that you posed, I think a year
16 of follow-up for the safety of the ablation
17 devices -- well, 30-day follow-up for acute
18 events, which would capture atrial esophageal
19 fistulas, presumably, and then there, six, and
20 further follow-up for pulmonary vein stenosis.
21 The one thing I haven't heard
22 talked about, and it's been sort of mentioned

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1 off and on during these discussions and during
2 prior FDA panel discussions about this topic,
3 is whether or not extensive ablation in the
4 atrium might be -- create a higher risk
5 situation for a thrombal embolism, and I think
6 that that should probably be followed for a
7 longer period of time -- I mean, at least out
8 to a year and maybe longer.
9 DR. YANCY: So if we can try to
10 frame up -- unless you have a burning
11 statement, Dr. Zuckerman?
12 DR. ZUCKERMAN: Yes. The comments
13 have been helpful, but I'd like the panel to
14 be a bit more specific, if possible. If you
15 could look on FDA Slide 36, for the second-
16 line therapy indications, are the durations of
17 follow-up for effectiveness and safety, one,
18 in the right ball park?
19 And two, if we could have some
20 more comment on Dr. Somberg's point that
21 safety doesn't necessarily have to be shown in
22 just one trial, that registries pre-approval

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1 might be helpful, given that we always see
2 unusual safety events.
3 And I'd like Marcia and others to
4 talk about how is it possible, perhaps, to do
5 these trials more on a worldwide effort, so if
6 you get data from Europe, a registry from
7 Europe, you are more assured of the quality
8 data that you're collecting?
9 DR. YAROSS: Certainly, the FDA
10 regulations and sponsors recognize the need to
11 include all available relevant data in a pre-
12 market approval application.
13 And you know, certainly where
14 sponsors do have significant experience
15 outside the U.S., whether it's under the same
16 trial or other types of experience, you know,
17 that should be information that's brought to
18 the panel at the time of an application.
19 In terms of preapproval
20 registries, you know, I think that's something
21 that, you know, is not what has been
22 industry's expectation, and so, you know,

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anything I would say on that would really be speculation off the top of my head.

DR. YANCY: Certainly, Dr. Zuckerman, there's an experience relevant to your question in December when this panel was considering another device. A certain registry was used to suggest that there was a higher frequency of events in that particular device.

But a subsequent report from that registry at a recent international meeting in August basically refuted that observation. So there are some concerns when we're using registry data that they are not entirely sufficient but certainly are helpful.

Other comments, please?

Dr. Slotwiner?

DR. SLOTWINER: Just to address Dr. Zuckerman's question on the duration of follow-up, I think for the primary -- using ablation as a primary treatment in patients with paroxysmal atrial fibrillation, one year

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of follow-up may not really be sufficient.

I realize that would be a tremendous burden on the sponsors, but we haven't followed these patients for all that long, and the disease process I don't think is very well understood, so -- as secondary therapy or second-line therapy, I think the numbers are reasonable.

There it generally becomes clear sooner, but I think, you know, if we could follow them even longer it would be helpful.

DR. YANCY: Well, note well that for permanent A.F. the follow-up is six months. Do you think that's reasonable?

DR. SLOTWINER: Well, I think that's reasonable. The longer, the better. I think, especially for the paroxysmals, we need longer.

DR. YANCY: We need more comment on this. I think this is the issue Dr. Zuckerman wants us to address.

Dr. Somberg?

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1 DR. SOMBERG: Well, I think the --
2 on just a short note -- is that the follow-up
3 should be a year. I think consistent --
4 that's a little short, for six months.
5 I also want to make a general
6 comment to Dr. Zuckerman's perceptive query
7 about comparability of data.
8 And specifically, in terms of
9 ablation, I think there's a lot of techniques
10 and technology, and I would be concerned of
11 generalizing from a very European experience,
12 if you will, to placing in the hands of
13 operators here.
14 Something that is similar is the
15 stent area, where, you know, we're seeing a
16 lot problems and a lot of discordance between
17 U.S. experience and OUS data and the change in
18 OUS data. So I'm not sure -- I don't think it
19 has to do with reliability of data. I have to
20 -- because I very much respect our European
21 colleagues.
22 I think it has to do with subtle

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differences in procedures, techniques, and that may not be clearly stated in certain protocols and such. So I wouldn't encourage going out and -- to sum that up, to go out and obtain data or, if you can't do a study in the U.S., to introduce a massive -- you know, a massive enrollment from OUS studies. I think that might obfuscate as opposed to clarify.

DR. YANCY: Dr. Page?

DR. PAGE: To answer your questions, Bram, I think in terms of the follow-up, we're making it more complicated than we need to by having six, nine and 12 months. And I agree, 12 months or perhaps 18 months would be appropriate for all comers.

I don't think we're that good at knowing which is which, and actually, permanent afib is no longer permanent once we've converted it. So I really don't know how to work with that.

In terms of the monitoring, which is also one of the questions you're asking for

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us -- and I've studied asymptomatic afib for a number of years.

And I think a transtelephonic monitor every two to four weeks for the duration, assuming that the patients are willing to do it, perhaps with a Holter thrown in at three- to six-month intervals, would get pretty much to the idea of how much asymptomatic afib is going on there without adding the burden of daily studies and this sort of thing, because as was mentioned, if you're looking really hard, you'll see a lot of 30-second episodes of afib.

But I appreciate Dr. Saxena's comment that what's important is clinically relevant asymptomatic afib on top of the end point that all of this is aiming for, and that is reducing the symptomatic recurrence of afib.

DR. YANCY: Having said that, then, if we can -- if you'll permit, we need to move on.

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1 Is there a burning statement, Dr.
2 Morrison, something that really you feel
3 compelled? It's not new --
4 DR. MORRISON: Actually, I wanted
5 to generalize your concern and make it -- and
6 in so doing, try to address Dr. Milan's
7 earlier concern --
8 DR. YANCY: Please continue.
9 DR. MORRISON: -- about irrelevant
10 to safety. And that is I think if -- if you
11 think about it generically, the risk all of us
12 are willing to take is inversely related in
13 general to the perceived benefit.
14 So if the end points we have in a
15 low-risk population aren't much benefit, then
16 one death from atrial esophageal fistula per
17 100, two tampenades -- one may be way too
18 much, and that impacts the risks. If you
19 start including people who failed -- or
20 continue on beta blockers and calcium blockers
21 -- are not much. All the risks -- all the
22 safety concerns are the procedural ones which

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1 you'll see in the first year.
2 Now, when you start moving into
3 people where you're trying to get them off
4 coumadin or make an argument that you're
5 preventing heart failure, well, then you're --
6 it seems to me that's when you start adding
7 different catheters and more lines other than
8 just the B veins and in so doing you increase
9 the risk of embolization and so forth and so
10 on.
11 So that generic concept is part of
12 why I tried to say earlier to me it's bass-
13 ackwards to talk safety first. The risk I'm
14 willing to take in cardiogenic shock is
15 totally different than the risk for STEMI, and
16 that's totally different from the risk in
17 somebody who has stable angina and a positive
18 stress test.
19 And I think it applies here. So
20 if you're going to be inclusive to -- and deal
21 with their enrollment, take it first line,
22 people who've only failed beta blockers,

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