safety for the most part is safety of the procedure, and you'll know that at the end of six months.

DR. YANCY: A few comments have been generated, I think.

Dr. Yaross, did you have your hand up?

DR. YAROSS: I was just going to close out before the discussion on OUS data by remind the panel that the FDA regulations clearly specify when U.S. data -- I'm sorry, when outside-U.S. data are acceptable, and if it meets those criteria, it needs to be looked at in the same way.

DR. YANCY: Dr. Peters?

DR. PETERS: We're talking about risks, and certainly there are definite risks with the invasive procedure. We have to remember, though, that if we don't step in now and find out what the risks are -- people are coming in. The problem they're having recruiting is that all the patients want this

done.

And it's going to be done in the community uniformly, unless we find out exactly what the risks are. And it was great -- you know, suppressing PVCs was terrific. We had no idea that things like flecainide were bad until we studied it in a very scientific way.

I think we need to do that right now and find out what the risks are. Otherwise, it's just going to take over and there may be a lot of harm done to a lot of people.

DR. YANCY: Dr. Milan?

DR. MILAN: Yes, I agree with what Dr. Morrison said, and that is that nothing is completely efficacious, nor is anything completely safe, and that you must always consider the safety of an intervention in the setting of what their perceived benefit is.

I want to emphasize also that atrial fibrillation is not a life-threatening

arrhythmia and that you're really reducing symptoms. That's what you're treating. And the paradigm, at least in the selection of anti-arrhythmic drugs, has always favored safety over efficacy.

That's why we choose flecainide before we choose amiodarone in the management of atrial -- for atrial fibrillation.

DR. YANCY: Dr. Zuckerman?

DR. ZUCKERMAN: Good. I think we're all in agreement that this is a risk-benefit equation.

Now I'd like the panel, if possible, with Dr. Yancy's concurrence, if we could move back to one, because where the FDA and industry is really stuck is what is a clinically useful end point here that will allow us to optimally see the best risk-benefit profile.

DR. YANCY: So that's appropriate, so in turn, then, you're suggesting to us that FDA is satisfied that the panel has addressed

all the issues on question two. Thank you.

So in introducing our shift to question one, there is a brief commentary that the chair is permitting from Dr. Blackstone to help us frame up our thoughts about measures of effectiveness.

DR. BLACKSTONE: So what I wish to do is to address items one A and one B where you ask absence of A.F. -- in other words, a binary type of response -- and B, A.F. burden.

First, in terms of A.F. burden, there will be at some point -- let me just keep that off for the moment. There will be at some point perhaps implantable devices such as the Medtronic device in which one can actually continuously measure burden, and that would be a very -- that would be an implantable device. It would be less burdensome in terms of transtelephonic or what have you. And that might be ideal.

The other thing that is being mentioned, of course, is the periodic

monitoring with wristbands or limited leads that lead to snapshots in time.

Now, the importance of these snapshots in time is that atrial fibrillation is not a binary event in the same sense that death is. It's not a terminating event. It's an event that comes and goes, lasts for a variable duration, and is a variable quality, so that this has led to all sorts of rather complex ways of trying to manage all this.

And I'd like to suggest at least a simpler way that one can manage this, so let me go to this one slide. This slide concerns ablation of chronic, permanent, long lasting atrial fibrillation by surgery.

Now, it is true that there are several things about surgical ablation that we have to remember, and that is it's not just PVI. It's not just bi-atrial Maze. It's actually -- probably affects the ganglia, the left atrium is amputated, and so on, so -- and mitral valves are repaired, large atria might

be reduced, and so on.

But what you see here is time, and this goes now to the one-year point. And what it displays is the prevalence of atrial fibrillation in your population, so it's like taking this trial that we've just heard today in which there has been this wristband data or leads on the patient for, say, weekly or bi-weekly monitoring, and then looking at that load or the impact of atrial fibrillation in your entire population.

And what you see, of course, is that there is an early phase of atrial fibrillation that occurs, and this is why you people talk about, say, blanking periods. But who cares about blanking periods? You can just draw the curves. And one can then take into account the occurrence of atrial fibrillation as it goes.

Now, these are complex models. This happens to be a nonlinear mixed model multiphase -- stuff, you know, that I write

about. But it -- but while the analysis is particularly complicated, in fact, it simplifies a lot of the issues. You don't have to worry about blanking periods. You actually are using all the data that you are -- that you have.

And you can take a look at the relative merits of various catheters or various atrial fibrillation that is occurring with medical therapy and the like.

And so it may just erase this complexity of trying to decide what kind of binary event -- and I'd sort of like to then try to keep this event of whether or not atrial fibrillation occurs rather separate from the issue of quality of life and symptoms and so on that seems to be in some strange way, by placebo effects or some other effects, to be rather dissociated from this rhythm efficacy.

This also reduces sample sizes because you're using so much more data than

you are with binary end points. And so it might make efficacy studies rather smaller in terms of number of patients one has to enroll, but that then gets to my point that if you're dealing with safety, which often is a binary end point, you have -- it takes rather a large sample size.

So maybe if you disconnect those so that you're only monitoring efficacy in a small fraction of the patients and then safety in more, you might be getting a simpler design.

DR. YANCY: Do panel members have any questions for Dr. Blackstone?

Dr. Page?

DR. PAGE: If you could put that back up, is that percent of patients or percent of time in afib? What were your axes? Time was one, but --

DR. BLACKSTONE: Okay. So along the horizontal axis is time, and what you have at -- this is a group of about 500 patients

with about six or 8,000 measurements of data about what their atrial fibrillation is.

And so those particular measurements are a bunch of binary measurements, but what you're seeing here is the prevalence in all 500 patients of atrial fibrillation at any given slice in time, so at six months what you see is about 20-some-odd prevalence of atrial fibrillation.

It isn't saying who is in and out, because patients are always in and out. It's just saying that the prevalence in the population looks like is leveling off at about 20 percent in one case and about 40 percent in another case. That's the simple --

DR. YANCY: So it almost seems as if you're counting episodes of atrial fibrillation rather than patients, is that correct?

DR. BLACKSTONE: Well, you're counting episodes of atrial fibrillation. You're getting slices in time. You're just

having every patient at any moment that they have telephoned this in -- whether or not they're in atrial fibrillation or not, and then analyzing that data.

Now, I very well appreciate what was said about the accuracy of these telephonic things. You guys are saying that you might be able to get it into near 90 percent. Ours is about 80 percent, but every one also read by an electrophysiologist, and I would say the reading is important.

That's another issue. I'm just trying to think of ways that we can simplify this particular efficacy and use all the data that's available.

DR. YANCY: Well, that is, indeed, very provocative.

Dr. Morrison?

DR. MORRISON: Unless I misunderstand it, that's population data, and that doesn't help us taking care of an individual patient. It doesn't tell us are

any of the individuals better, are a lot of the individuals better, or -- I mean, it almost --

DR. BLACKSTONE: It is actually no worse --

DR. MORRISON: -- it almost doesn't make sense from a epidemiologic standpoint or a clinical standpoint.

DR. BLACKSTONE: Well, from a pure epidemiologic aspect, it's the same as a Kaplan-Meier curve for death. People aren't 25 percent dead or 75 percent dead. That is also a population estimate, but you can now also take into account --

DR. MORRISON: But this is not time-to --

DR. BLACKSTONE: -- patient variables.

DR. MORRISON: This is not time-to-event. This is a bunch of mean averages where every --

DR. BLACKSTONE: Correct.

DR. MORRISON: -- mean average is a mean average of lots of different patients.

DR. BLACKSTONE: Yes, so it might say that you -- at six months you might expect, say, for you, 10 percent probability that you'd be in atrial fibrillation versus someone else that might be 80 percent, and that's actually what's going on for patients.

DR. MORRISON: But I mean, you -- it's really a unique thing. I mean, it's one thing to give a vaccine to a whole population and see if you reduce the prevalence of people that don't have antibodies to something. But saying that you've reduced the proportion of time that the average person spends in afib is -- that's not a clinically -- that's not something clinically -- how to grasp, I mean, and used to decide whether, in patient A or B, we've had a success from this treatment.

DR. YANCY: Let's go to Dr. Neaton.

DR. NEATON: Maybe you could put

it back up. I think actually showing the data longitudinally over time, as opposed to a single point in time at six months or 12 months -- that's kind of per-protocol for when the sampling is done -- makes a lot of sense to me, to understand kind of the profile of kind of being able to suppress the arrhythmias kind of at each point in time.

What's really important here, I think, is the -- and I think Dr. Blackstone alluded to it -- is that -- is reducing bias. And so what you want to make certain is you look for the arrhythmia at the same time points, at the same frequency, in both groups.

And so I'm very concerned when I heard things like outcomes that are symptom-driven telephone calls in an unblinded study. I would have a lot of concern about that, as opposed to being able to make heads or tails out of it, because if you look harder, you're going to find it.

And so we heard a presentation

this afternoon about the error in just the assessment of atrial fibrillation. And as long as that's random by treatment group, you can deal with it just by sample size or by taking repeated measurements and kind of averaging things like out over time that way.

But you can't deal with it if we're looking at different points in time for people in the two groups. And so a longitudinal look at the data, but under the same exact protocol for both treatment groups, is very important.

DR. YANCY: Dr. Zuckerman?

DR. ZUCKERMAN: Yes. Let me suggest that the modeling that Dr. Blackstone is providing us with is extremely important, and certainly from the agency's perspective we look forward to following up with him.

I think that this might help the industry in the following circumstances. Number one, I do think this approach will provide -- could potentially provide at least

supportive data.

Number two, when we talk about the device product life cycle, as Marcia did previously when we were talking about iterative changes, if we've shown proof of principle with our first-generation device, this might be a very nice way to show, with minor modifications, that we're really not changing a device significantly from a clinical perspective.

But with those caveats, I would still indicate that the point of question one from the FDA's perspective was really to ask how do we convince Dr. -- someone like Dr. Morrison, a non-E.P., that on a per-patient basis we've come up with a clinically significant result such that the risk-benefit profile is favorable.

Now, I know that all of the clinically end point variables that we talk about have pluses and limitations, but the agency needs to know, given your experience,

which ones would you go with, because patients -- people like Dr. Morrison need to understand this stuff on a per-patient basis.

DR. YANCY: So let's begin to delve into question one. So the comments that proceed should hopefully be focused on that.

Dr. Tracy?

DR. TRACY: Yes. I think that's very important, and I think that's a great model that would help make some sense out of the burden, afib burden, portion of this study.

I do think you need that binary -- looks at binary, primary end points, either they have it or they don't, with the extent of monitoring that you are capable of doing.

I actually prefer -- if you want to get specific, on Slide 36 of the FDA presentation, I prefer the HRS system of monitoring as opposed to the FDA monitoring because I don't know how many people have tried to wear a Holter monitor, but the idea

of wearing it for seven days is just sort of tragic to me.

So I think I think you want to know at what points do you specifically assess and what tools do you specifically use, I think that those points and those tools are the specific right tools to look at.

I do think you need a symptom burden, a -- symptom-driven recordings as well. It's no good for a patient to say I'm just going to look at you at these times and close my eyes to any other symptoms that you -- any other times.

Obviously, you're treating the person, and you need to know when they are having symptoms. So you need symptom-driven recordings as well.

DR. YANCY: So we're talking about effectiveness, and what's on the table now is how do we determine the binary end point absent the presence of afib, perhaps addressing the afib burden, and a symptom end

point which segues to C, a composite functional end point which would include symptoms plus other variables.

So let's frame our comments up in that direction.

Dr. Page?

DR. PAGE: To answer your question in number two there, Bram, I agree with Dr. Tracy.

I think the reason we treat these patients aggressively with a potentially dangerous therapy is we want to change them from coming into our office complaining of symptoms of afib and they're in afib, to coming into our office saying they feel much better, thank you for changing this, and indeed they're in sinus rhythm.

So to -- as an end point, I think symptomatic recurrence has to be there.

We've also heard that the burden of atrial fibrillation is difficult to define, that there -- if you look really carefully,

you'll see little not-clinically-important episodes of asymptomatic afib. But I think we still need to look for it and measure it.

And as with Dr. Calkins' example, if you have a patient saying they feel great and they're in afib, that's not a success.

So I might just throw out as -- one possible way of doing this is symptomatic recurrence with ECG confirmation, because, in fact, patients sometimes say they've had recurrence and they haven't, and we've demonstrated that.

But in addition to that, if we were doing an asymptomatic TTM, for example, every two weeks, if they had one, doing a repeat 24 hours later. If it's lasted 24 hours, then whether they're symptomatic or not, I would consider that a failure.

So just some combination -- and we can work out the numbers -- some combination -- whether we've made them feel better -- they come back in clinic, they feel well and,

indeed, they're in sinus rhythm -- plus some surveillance for meaningful clinically important asymptomatic events.

DR. YANCY: So let's continue along this line of comment.

Dr. Yaross?

DR. YAROSS: Yes, I'd just like to come back to the hypothetical, Dr. Page, that you used earlier this morning, because you did talk about the patient where there may be a substantial success clinically, but that binary method of presence or absence of afib doesn't reflect that benefit.

So from that standpoint, you know, to Dr. Morrison's comment, I think any kind of burden needs to be translated to a within-patient measure, because you need to be able to tell a patient what to expect from a procedure.

But I think it is valuable to expand the discussion from a binary pass-fail to a more nuanced measure to address the type

of patient you're talking about.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: I'm hearing what people are saying, but it's a very complex issue, and I think we really should talk about a symptomatic end point of atrial fibrillation. It's -- and because you want to, you know, prove things, say people live longer or they feel better.

Yes, I heard the extreme example of someone who's asymptomatic -- I guess he -- you have morphine at the end of the catheter, and they're unaware that they're in rapid A.F. most of the time. So you have to check on it. It's sort of a check.

But what happens if someone goes -- you know, it's not that they're always in A.F. but they no longer have symptomatic A.F. but they have -- 35 percent of the time they're in A.F., or they're in A.F. 25 percent, or 20 percent, or 16 percent. You go through these different -- and do we know

clinically if that's meaningful?

We're not going to change their anticoagulation. This is for symptomatic therapy so they don't go into the hospital, they don't get cardioverted, they don't inadvertently get murdered by someone in training or what have you, if you do it enough times.

So the -- I think the end point in the study should clearly be defined as symptomatic A.F. and there should be some way to look at whether you have a problem that you've turned all symptomatic into asymptomatic.

And obviously, if someone came in and they're all in atrial fibrillation, but you did something to cool the nerves, that would not be acceptable. But I don't know what I'm going to do if they're in 50, 65 percent asymptomatic versus 15 percent asymptomatic. What are you going to do with that?

Is one good? Is one bad? Do we have a judgment on that?

DR. YANCY: So tracking this so far, we have opinions on addressing symptomatic afib, but we also have opinions on continuing to look at the afib burden.

We haven't heard from everyone.

Dr. Blackstone?

DR. BLACKSTONE: Let me now go to the separable issue of symptoms. Even though each of those may be binary, what we're really talking about, I think, is again the burden of symptoms.

And so the idea of either using cumulative incident functions, where you have repeated events and you're taking a look at, again, what the prevalence is across time of these symptoms -- that's going to be what the final output will be, so I would -- I'd suggest that it's not just one time that they have symptoms, but what the actual symptom burden is.

And perhaps also then the idea of using quality of life instruments to try and measure those at least at some periodic time so that you have some cross-sectional data, it's not just driven by the symptoms, would make a lot of sense, too.

DR. YANCY: Dr. Morrison?

DR. MORRISON: Are there specific quality of life metrics equivalent to, say, the Seattle angina questionnaire for arrhythmia that could be incorporated that have been perhaps been incorporated into other anti-arrhythmic arenas?

DR. YANCY: We certainly have several skills for heart failure, but from our E.P. colleagues, do you have such --

DR. MILAN: Yes, I know that there are, and I've read them in the papers. I don't know what their names are, but there are --

DR. YANCY: So they do exist.

DR. MILAN: -- quality of life

scales that are specifically --

DR. MORRISON: Well, that's something that could be repeated at the same intervals as the TTM or whatever, and it would add some degree of objectivity and quantitation to this.

DR. YANCY: Are there other comments, then, about question -- yes, Dr. Zuckerman?

DR. ZUCKERMAN: Yes. If I could get us back to one question I have about question one, it looks like, as Dr. Page pointed out, that we need a hierarchy of evidence. Certainly, the primary end point that might be most important is frequency of symptomatic afib.

But I'm wondering if he can or others can try to better define that. If you only have a five-second symptomatic episode, should that count, versus a 30-second, and we can get a little bit more specificity. So that's part A.

Part B is we really are looking at a totality of evidence, so the more monitoring data that one can accumulate, symptomatic, asymptomatic, total burden, the ability to model what you're doing to better understand things will be helpful and supportive.

But I think I heard Dr. Page and Dr. Somberg say symptomatic afib might be the most important variable here.

DR. YANCY: Dr. Page, if you can comment on that.

DR. PAGE: Yes. The question of how much -- how long an afib episode matters is a real question, and I don't think anybody knows the answer to that.

But generally, if it has prompted a visit to the doctor's office and it's -- and indeed, they say I'm having symptoms, and their electrocardiogram shows they're in afib, that's been, I think, a clinically relevant event.

If it's on transtelephonic

monitor, likewise. If they generated symptoms, they get out the device, they've been in it a minute or so and, indeed, it shows atrial fibrillation, generally we consider that to be a meaningful event.

A five-second episode of afib on a Holter, for example -- and this is one of the reasons why I don't necessarily favor Holters. A five-second episode on a Holter I would not consider significant.

So 30 seconds or more, but even better is something that prompts them to get a recording and, indeed, the recording shows atrial fib.

DR. YANCY: Dr. Slotwiner or Dr. Milan, any comment or agreement?

DR. SLOTWINER: Yes. My biggest concern is having the objective information -- I realize the end point is making patients feel better, but I think they'll tell us when they're symptomatic.

I'm concerned about the placebo

effect of the procedure and I think some -- some definition can be created of regular monitoring in the background in addition to symptomatic events. I think patients will -- will report that.

DR. YANCY: So according to this hierarchy of evidence scheme that you've outlined, Dr. Zuckerman, it appears as if the panel favors symptomatic atrial fibrillation at the highest order, but then as a second order initiative what is the absolute absence or presence of afib by a monitoring technology yet to be determined. Is that a fair assessment?

DR. NEATON: You know, I'll just say again I guess I'm concerned about the symptomatic one. It sounds good, except that what you're most concerned about in a trial is making certain that your outcomes are ascertained in an unbiased way in your two treatment groups.

And I'm very concerned about that

in a situation where you'd be in a non-blind trial here, one group that had ablation, one group some medical therapy, and it's being driven by something that the patient has to report.

So I think the primary outcome is better, is more objective, at standard intervals, and as was suggested earlier, that you collect data on symptoms and quality of life also at standard intervals not driven by certain things the patient is perceiving at a point in time.

DR. YANCY: I think these are very important conversations.

Dr. Peters?

DR. PETERS: One other thing that might help is if we get data on the amount of time that people are in atrial fibrillation and don't report symptoms and make some sort of ratio, because -- I mean, I see this all the time with Holters and event recorders, that they have palpitations. They're in sinus

rhythm.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: There's an assumption here that people, because they have an ablative procedure, will under report, and there may be some truth to that early on. There's also -- the other side of the coin is that people undergo procedures and they don't get relief. They get angry.

And they, you know, get very upset about that, too, so I'm not sure, you know, that we have evidence that that is necessarily the case that they'll miss that.

And we have to understand that the reason we're doing the ablations is not that they're going to live longer at this moment -- maybe some effect there may be -- and we're not going to stop anticoagulation therapy, which has a mortality effect, but we're doing it for their symptoms.

And if you take symptoms and you -- even if they have 10 seconds of A.F. and

they're symptomatic, and they pass out, for instance, or something like -- that's very significant to me. But if they don't have symptoms, we -- from then on, we're embarking upon science, research, here, because we don't know what that means.

And I submit to you you'll have one person who may have a burden of total A.F. of 65 percent. Another one may have 15 percent. But they're both out of the hospital. They don't need additional cardioversions. They don't need interventions. And they're happy. And I think that's a success point.

And we've gone from -- what can I say? -- looking at some sort of arbitrary performance to now having a study, so I wouldn't try to squeeze the system so much that we can answer what does asymptomatic A.F. mean.

DR. YANCY: Dr. Neaton, would another approach -- what would be the risks or

the drawbacks to either a co-primary or a composite that had symptomatic afib and burden of afib treated equally?

DR. NEATON: Well, I mean, it very well could be that with some clever thinking one could define asymptomatic afib that you were really confident about kind of it being an unbiased assessment for your two treatment groups.

I would be nervous about that, and I'm not -- I don't know which way the bias would go. I mean, it could -- it could vary in ways that are not predictable right now. But I think the idea that you're posing is not a bad one, where you might have the objective measure.

But I still go back to the idea that it's -- I see the point in assessing symptoms, but do that in a structured way in both treatment groups at the same intervals and make that your co-primary outcome, instead of trying to put them both together and being

driven by an event that occurs at some point in time.

That would be my -- from what I understand right now, an approach that I would consider.

DR. YANCY: Are there other comments about these issues on question one?

Dr. Milan?

DR. MILAN: I just want to add my voice to Dr. Page and Dr. Somberg that I think that the reason we do these ablations is for symptoms, that symptoms should be the primary end point that we're using. I do understand what you're saying about the biases, but I just don't know how to make a composite end point that includes asymptomatic and symptomatic afib, because the symptomatic afib is the reason we're doing it.

Also, for the purposes of labeling eventually when you want to give instructions to the physicians and eventually the patients, what they want to know is what -- what are

their chances of being free of afib over whatever time period.

DR. YANCY: But I do think Dr. Slotwiner had a very good perspective. This is an open label, unblinded circumstance, and there is a placebo effect, and there may be -- and I respect Dr. Somberg's commentary, but we have to account for the fact that bias is a real possibility here.

Are there other statements that we can make to the FDA?

Dr. Tracy?

DR. TRACY: It seems to me that we have basically two different things we're looking at. We're looking sort of at an absolute you had it or you didn't have it, and then you also, on a -- maybe on an equal level, you're looking at symptomatic recurrences. And you're -- and you need clinical judgment in the study in both groups.

What do you do once you find one? Do you automatically go back on an

asymptomatic patient that you've identified afib? I mean, you have to define all that stuff ahead of time, and that can easily be done, but it sounds like you need to look at both things, an absolute yes-no and symptomatic-driven.

DR. YANCY: Any other input with this regard?

Dr. Zuckerman?

DR. ZUCKERMAN: Yes, or to put it another way -- question to Dr. Milan. I can appreciate why he might want to choose as his primary end point amount of or percent of symptomatic A.F., but would you agree that as a key secondary end point the measurement at structured intervals would be key, and if the two data sets don't correlate, you would have trouble approving that device?

DR. MILAN: Yes. I mean, you said it so well that I have nothing more to say but just to agree with you.

DR. YANCY: Meeting adjourned.

(Laughter.)

So where we are to date, then -- we have suggested that the flavor of the panel is in preference of randomized controlled trials. We have continued to talk about, in most regards, against medical therapy.

We've talked about addressing potentially as primary therapy, but we've also talked about it in more restrained terms at secondary therapy.

We basically settle on duration of at least 12 months or longer to address issues of safety and effectiveness.

We've identified this hierarchy of evidence where symptoms should drive the indication for the procedure, for the device, and so symptoms would be highest order, but a key secondary end point would be the afib burden.

We had a brief commentary about composites.

Are there any other issues about

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these incredibly important first two questions that we've addressed? I say this because it's about 4:00 p.m.

Yes?

DR. BLACKSTONE: We haven't addressed the medical group and crossover, and I think -- and crossover -- even though someone has said that is perhaps an end point, crossover is not protected by anything and, you know, is -- is one of these medical judgments that gets interjected in the middle of everything, and there may be very different biases for when you do and when you don't do the crossover.

So I'd like to see at least that -- if that's going to be a measure we use for the medical group, as opposed to just plain truncating their data at the point of crossover, and ignoring what happens thereafter -- some discussion of that.

DR. YANCY: Certainly we heard earlier that it would have size implications,

but let's see if we can address this issue.

Dr. Morrison?

DR. MORRISON: Well, I'd like to offer up what I would hope is a creative possibility that might reduce some of the statistical issues, and that is an intermediary medical crossover.

If you're going to expand the enrollment criteria to solve one problem by taking people who've only failed beta blockers and calcium blockers, how about as the first crossover crossing them over to one of your membrane-active drugs?

And then they really haven't crossed over from the standpoint of the randomized trial thing. It gives you an out, but it doesn't do what crossovers usually do to randomized trials, which is to absolutely, as somebody put it, eviscerate the sample size.

If most of your medical crossovers got propafenone or amiodarone or something,

rather than going onto a procedure, you would have that information for analysis, but it wouldn't destroy the randomization. Is that an option?

DR. YANCY: Dr. Page?

DR. PAGE: Yes, I think -- I think the issue of going on with a drug strategy is not unreasonable, Dr. Morrison, for example, if this is a nuance at afib, starting with, say, flecainide, if that didn't work, going on to amiodarone.

The fact of the matter is, though, once one drug fails, chances are either they won't want amiodarone, if it's a young person, or the next drug will fail, and you'll get crossover again.

I think Dr. Blackstone does raise a very salient point, though, in that crossover will really hurt us in terms of efficacy.

The one completed trial is the CryoCor, and they can't share with us what the

crossover rate was, but I'm afraid it was very high. And those patients might not have ever made it into the trial -- this trial A or modified trial A we're talking about.

So I think one way or another, if we have a randomized trial, we'll end up looking at what was the safety with historical drug treatment, because at least we have longitudinal data from large randomized trials on drug therapy.

My fear is in this trial we're going to have so much crossover it's not going to be a meaningful comparison in terms of safety between the two groups.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: It is an important detail, and I think one cannot be too cavalier on saying why someone crosses over. But if someone crosses over for a serious symptomatic episode of atrial fibrillation, I think that's an important clinical end point.

If we let -- if the study design

lets people cross over because they felt a palpitation or something of that nature, then you have a different -- so it's how you write the protocol.

But then there's going to be the other side of the coin -- is that you have an ablation. They're off anti-arrhythmic therapy. And then they have an episode, a brief episode, when they need an anti-arrhythmic drug. That's also an end point and saying that that person was not that successful.

So I think you can go down -- there's going to be an algorithm of sort of end points here, and you know, an ablative technique or catheter plus technique might give you a certain efficacy, and you need anti-arrhythmic drug in a certain number of cases, and that might be acceptable.

And then you might have patients who go on and -- you know, it could be to the doctors. I can see a protocol permitting

another anti-arrhythmic agent in some patients and then permitting you to cross over to ablation.

And at the end of the day, you will have a certain number of people successful on anti-arrhythmic therapy, a certain number of people successful on ablative therapy. And the question is what is that number, and do you have to be superior? I mean, these are questions we have to ask ourselves.

Do you have to be superior? Or maybe ablation and anti-arrhythmics could be equal, and that would be good. But if one is decidedly different than the other, that may favor one therapy over another, and you have to weigh that against the risk, and that's why all these PMAs are going to come to panel.

DR. YANCY: Certainly one of the things in the hypertension world that is done to minimize crossover effect is that there are two arms and different drugs, but then if you

don't reach a clinical end point, then both arms get applied the same treatment strategy, and so at least the randomization stays clean.

Dr. Tracy?

DR. TRACY: I think it's going to be inherently messy no matter what you do, just because of the nature of atrial fibrillation.

We sort of have slipped back into going with a first-line treatment afib, which I think may or may not be appropriate. I think just -- what your outcome is going to be will largely depend on what group you choose to study.

If you choose to study paroxysmal atrial fibrillation, you're going to have a whole lot easier time in maintaining the two arms.

But as Dr. Somberg points out, there is going to be the patient who has -- and this was raised earlier today, the patient who's had the ablation and previously wasn't

controlled by amiodarone but now is controlled by amiodarone.

It's just going to be messy. We're just going to have to, I think, accept with that and deal with it on a case-by-case basis.

DR. YANCY: We'll take one more comment on this issue from Dr. Neaton and then attempt to go on if the panel will permit it.

DR. NEATON: I think it is -- this is a complicated issue that probably we can't solve today, but -- three things I wouldn't do. I mean, I think -- calling it an end point is a bit problematic unless you can ascertain it in both treatment groups, so what -- Dr. Somberg's point is very important to pre-specify criteria that are kind of relevant for both treatment groups to, quote, cross over, if you will.

I would not truncate follow-up when a crossover occurs, because then you're going to be real sunk in terms of doing an

intend to treat analysis, so continue the follow-up subsequent to the crossover.

DR. YANCY: Well, thank you very much.

Dr. Zuckerman, are you satisfied with our comments and questions one and two?

DR. ZUCKERMAN: Yes. This has been very helpful. I just have one quick question, and if an electrophysiologist could volunteer, it's the second part of one B. Please define A.F. burden and how it can be measured, both pre- and post-treatment.

Again, there's no perfect way, but does someone have a suggestion?

DR. YANCY: Did you say quick?

(Laughter.)

DR. ZUCKERMAN: Yes.

DR. TRACY: I think it is a problem defining it pre-. Your A.F. burden is, I think, taking a piece of time and looking at what's there during that piece of time. You can use that as your definition of

A.F. burden, and that's fine.

The problem is that we have no idea -- none of these studies have been set up to look at the pre-ablation A.F. burden, and that may be something worth putting in there, in these studies, to have at least a period of time, whatever you define, by those seven days of Holter, which I'm hoping nobody goes for, or a week of event monitor, or whatever it is, and using that as your definition of burden.

I think it gets complicated -- the drug studies have always looked at time to recurrence and that type of -- type of monitor. I think that that's a little bit different from burden. I think burden is how much is there during this period of time, simple as that.

DR. YANCY: Dr. Milan?

DR. MILAN: Well, let me just say that I think that all these are different ways of measuring the response to this treatment, and that patients, in my own experience, can

be made happy. Even if they have one or two recurrences over the year after their pulmonary vein isolation, they can be thrilled with the result.

And so I think ideally burden would be something you'd want to measure -- I think it's so problematic to measure, to get a baseline, an adequate baseline, for the patient.

And to ensure that they, for lack of a better word, comply with the monitoring algorithms for the long period of time that's necessary to assess their burden post-procedurally or post-therapy, I think it's very difficult.

I mean, I think what you're really -- if you really want to measure it appropriately, you need an implanted device, either a pacemaker or maybe an implantable Lipocor recorder that has the algorithms that can measure atrial fibrillation.

DR. YANCY: Dr. Peters?

DR. PETERS: I'm trying to remember what I was going to say. I -- well, two things. One, in terms of burden, as long as you do the same thing with both groups, it's just the percentage of time somebody's in atrial fibrillation, as long as you're consistent across groups.

The other thing I was going to bring up earlier -- just in terms of end points, we don't want to totally neglect hard end points for this kind of stuff. In other words, thrombotic events, mortality, hospitalization -- things that are fairly objective may help, because our other end points are relatively soft.

DR. YANCY: Great.

Dr. Page?

DR. PAGE: Yes. We looked at -- kind of looked at afib burden in the Azimilide database and -- and in that database, we actually looked at the frequency that patients were in afib, asymptomatic and actually the

life table analysis. This was all prior to symptomatic recurrence.

And over six months, we found 18 percent of the patients looking at a TTM, 30 seconds, every two weeks had an asymptomatic recurrence before they had a symptomatic recurrence. So there are some data out there for untreated patients.

And just as was mentioned, as long as you're doing the same thing in both groups, but it's not so burdensome as an implanted device or a daily TTM, I think you'd get meaningful data.

DR. YANCY: Dr. Slotwiner?

DR. SLOTWINER: I agree. I think it's just a percentage of time in afib, and as long as you have a standard protocol prior to ablation and after, it should be --

DR. YANCY: Are you comfortable with the intermittent TTM methodology?

DR. SLOTWINER: I think we have to accept the limitations of -- of the monitoring

that we have, and so while it's far from perfect, I think -- I think it's the best we can do.

DR. YANCY: Dr. Zuckerman, is that satisfactory?

DR. ZUCKERMAN: Yes.

DR. YANCY: Let's go on to question three. Given that catheter ablation is an invasive therapy, if the control group is non-invasive medical therapy, what should the comparisons be for safety and effectiveness?

Will someone just summarize how we've addressed it?

(Laughter.)

DR. YANCY: I love being chair.

DR. TRACY: I think that's your job.

(Laughter.)

DR. SOMBERG: I'll give it a try.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: I think the

effectiveness end point was saying that symptoms are important but they're not the only thing to look at, and that in terms of safety, that becomes even more problematic, because we have very -- two disparate interventions here.

And I think what one is going to look at is major events that are -- are going to have to be factored into a clinical decision-making process. So one has to assess those.

One powers a study for some events that might be deemed to be more frequent and -- in a pivotal trial, and having to have a much more large experiential basis for some of the less frequent side effects.

DR. YANCY: I think the panel expressed a pretty strong sentiment earlier that the effectiveness metric should be the same for invasive or non-invasive strategies, and that safety issues are time-dependent, and they're very much disparate. They're

procedurally related. They're related to the medical therapies which may appear over time and perhaps related to the disease process.

But you may want to hone us in more quickly or directly on where we're going.

DR. ZUCKERMAN: Yes, and I think that's the general drift. But there's a point that Dr. Neaton and others have been debating today, and that is because we are comparing an invasive procedure versus medical therapy hypothetically, associated with the invasive procedure in the cath lab may be cert and safety problems, such as pericardial tamponade or development of an esophageal fistula, that you just aren't going to get in the medical arm.

So the real reason why FDA is asking this or Dr. Haines posed the same question is what do you compare those low frequency but extremely important cath lab safety events against.

That's -- you know, we would

recognize that you can compare the number of strokes as a safety variable in both arms, but there are real cath lab complications that need to be minimized in an acceptable level, and we're looking for comparators.

DR. YANCY: But having said that, I mean, there is a bucket of events that go into serious adverse events, and there are serious adverse events taking a patient -- Dr. Somberg's comments -- that do occur with medical therapy, particularly anti-arrhythmic therapy -- proarrhythmias, death, even.

And so there are serious adverse events that occur even though they are dissimilar. But there may be others who want to comment on this.

Dr. Yaross?

DR. YAROSS: I would comment that these are areas once presumably the agency and the panel believe that something has provided a reasonable risk-benefit on its face, that go into labeling, that permit clinicians to look

at professional guidelines that have weighed the -- you know, whether something should be first-line, second-line, et cetera, therapy, and that this is the job of clinicians to interpret -- you know, once you have a well-vetted and well-executed trial, to then weigh those in terms of the preferences of clinicians and their patients in concert.

DR. YANCY: Dr. Weinberger?

DR. WEINBERGER: A slightly different characterization, but maybe along the same lines, what we need is to look at the procedural complications as a separate bucket that you have to pay for in order to get therapy.

Now, we have therapies that we give our patients that are associated with mortality and stroke which are done primarily for patient symptoms, so a great number of patients who undergo bypass surgery are undergoing bypass surgery for symptoms and not for longevity.

And nevertheless, they take mortality and stroke risks and other risks which are well characterized. And you might say well, those are unreasonable.

I think what we need to do is characterize those risks, those procedural risks, and factor that into your clinical thinking, so that when you present to the patient the risk of the procedure, you can tell them you have less than a one percent chance of a major adverse event, if that's what the number will be.

DR. ZUCKERMAN: And certainly with the A.F. procedure versus medical treatment, I think the comparison of mortality and stroke risk are relevant, but we could envision a situation where that's similar, where effectiveness is much greater than medical treatment at one year, but there's, say, a 2.5 percent incidence of esophageal fistula -- hence, not an approvable device.

Now, is the best that we can do

what Dr. Yaross has said, you need to look at the totality of the data, compare some of these events to what professional societies, competent physicians, would say are acceptable rates, or are there predefined standards that people can better define?

DR. YANCY: Dr. Somberg?

DR. SOMBERG: I don't think there are predefined standards, and you're going to have to look at that carefully, and I don't -- I'm going to get kicked off the committee by you, I know that, but I'm going to say I'm not sure that's not an approvable device with that -- it just -- it's all I the labeling. Isn't that, you know, the business?

There's a judgment to be made. And for a lifetime of anti-arrhythmic therapy versus a 2.5 percent risk of esophageal fistula might be acceptable to some people.

On the other hand, if it was, you know, a 10 percent risk of mortality, the -- that might be not acceptable. So anyway, I do

not know myself -- maybe someone else does -- that it is possible to, a priori, specify what would be unacceptable risk when there's no comparator in the other control group. There's just none.

DR. YANCY: Dr. Kato, we haven't heard from you in a few minutes.

DR. KATO: I have to agree with John. I don't think that there's a -- well, actually, I don't think that there's a way to specify what's not approvable, but you may not be able to identify what's approvable either.

That is, the -- there are going to be -- I think as clinicians we always have to make judgment calls about various complications and -- which exist in one therapy versus another, whether it's front-loaded, back-loaded.

And we're always dealing with that kind of probability risk, whether it's multivessel angioplasty versus bypass surgery, whether carotid stenting versus carotid

endarterectomy, or even medical therapy versus, you know, a biventricular device.

So I think we're going to be -- whether we like it or not, we're going to have to just present the data and see how it plays out. And you know, it may be that -- let's say the catheter ablation studies do come out with some horrendous risk versus the drug -- there's some novel drug risk that shows up, you know, a year or two later. And we may have to revisit it. But that's the nature of what we do.

DR. YANCY: Well, the issue here is actually even more complex, because we're talking about operator competency, and then we're talking about the device technology itself.

So, Drs. Page and Tracy, I think there are some competency statements about device interventions, and it may even be covered in COCATS, but maybe you can comment on that. You were about to speak.

DR. TRACY: Yes. Actually, there -- the -- anybody doing these procedures has to meet the competency guidelines for doing these procedures. I mean, on that -- that would go without saying.

What isn't mandated or regulated is what percentage of complications are you allowed to have to still be considered a competent operator.

I think, though, that we're -- at this moment, we're disregarding the fact that we do have a substantial body of literature to know -- even though they are not randomized controlled trials, we have a sense for what the complications and the rates of complications are.

But we do know that when you go specifically hunting for complications, you're going to find a higher percent than is reported in the literature. The literature in this standpoint serves as a background of information that we have available. We can't

totally blind ourselves to that.

But you can't, I think, come up with a specific percentage ahead of time to say if you exceed -- you know, and 2.5 would be a very high atrial esophageal fistula rate -- but you can't exceed X percent of such complication. I don't think you can do that ahead of time.

But certainly, this panel, when they meet to approve or disapprove the device, would take into account all the information that's available in the literature and within the data that's provided by the company at the time of the presentation.

I just don't think you can say ahead of time.

DR. YANCY: So it sounds like we're talking about more than just a single finite measure, but rather as the aggregate safety issues acutely -- medical in device, chronically, and then perhaps using a reference point of what is competent

performance for the procedure itself.

Is that a reasonable summation, Dr. Peters?

DR. PETERS: Also, we have to remember, this is a work in progress. These are techniques that are being developed. If you go back to the early days of CABG, the mortality was extremely high. When we first started doing SVT ablations, we were getting complete heart block.

We don't see that very much anymore, because of the techniques that are involved, so if we can -- if we can approve this now, I would expect that our statistics will get much better.

DR. YANCY: Other comments on this issue?

Dr. Zuckerman, is that satisfactory for number three?

DR. ZUCKERMAN: Yes. I think your summary covered it well.

DR. YANCY: Number four, if a

performance goal derived from the medical literature is used for either safety or effectiveness comparisons, what should the values be and why? And we've had a lot of input from our guest speakers on performance goals and some struggles.

One of our panel members, Dr. Page, believes that that is imminently doable, and certainly, Rick, if you can comment on that more, that would be great, and we'll open this up for discussion.

DR. PAGE: Thanks, Clyde. Yes, I heard Hugh say that he didn't think it was doable. I heard Dr. Haines say that he thought a performance goal could be established. I think even Hugh, if we framed it, could come up with something.

I don't believe at all that this committee's going to be able to do that here today. So I might actually just throw out there that I think it could be done with some thoughtful people in a room spending the day

working on it, but I don't think we're going to come up with anything meaningful right here.

DR. YANCY: Does most of the panel agree with the comments Dr. Page just expressed?

No, Dr. Somberg?

DR. SOMBERG: Well, I like you very much, but I don't --

(Laughter.)

DR. SOMBERG: -- I really don't think that -- I don't even want to address whether it could be or couldn't be done. You know, that's a study. You figure it out.

But I think at this day and from what we've heard, it may not should be tried to be done, because I think things are working out, and we have enough possibilities to not need that.

With that said, I think there will come a time when we have, you know, randomized controlled trials that have given us enough

information where we can develop performance goals both for safety and efficacy.

But I don't think we're there yet, and this is too important an area to obfuscate.

DR. YANCY: And to be fair, this is an important issue, so if Drs. Neaton or Blackstone would comment on developing a performance goal, I think that might help round out the discussion.

DR. NEATON: May I? I don't really have anything to add to Dr. Somberg. I would not rely upon that now at all. I think the trials need to get done, and maybe at a later time.

DR. YANCY: Is that sufficient, Doctor?

DR. ZUCKERMAN: No, I think the discussion is good in that it suggests that we aren't there yet, but I do want to indicate that the methodology suggested by Dr. Yue this morning is extremely important for the

industry to consider.

When we're developing performance goals, there are two options. One is the option that the cardiac surgeons know about. After 30 years, we thought the literature was good enough to develop OPCs.

The other option is for the industry, in an independent, unbiased manner, to start aggregating data such that we can model the data appropriately, fairly, judiciously, such that perhaps within X number of years, much less than 30, we can consider appropriate change in trial design.

Now, these are difficult concepts for the industry because there's a lot of competitiveness there, but it is something that the agency has had recent experience and success with in the area of bare metal stents, with the recent LVAD Enermax registry, so I would really encourage the industry to think about such an approach.

DR. YANCY: Dr. Yaross?

DR. YAROSS: One, I think, very positive consequence of having scheduled this meeting is that, as we heard from the AdvaMed speaker, the industry involved in A.F. clinical trials has come together to form a working group to discuss areas of common interest. So I think your suggestion is one that probably that group could follow up on.

And I think in the interim, to Dr. Page's comment, I don't think there's anything that precludes sponsors from trying to do that work and, you know, present concepts for individual trials before an industry-wide effort might be able to come to fruition.

DR. YANCY: It does seem as if the sentiment on the panel is suggesting that it is theoretically doable with effort and with thought but may not be ready to represent a reasonable comparator for contemporary trials.

Dr. Blackstone?

DR. BLACKSTONE: Just a comment, and that is the Innermax group was set up

originally by the NIH and funded by NIH, and it is also independent of any devices. So I think that your suggestion is actually quite different from that.

DR. ZUCKERMAN: Right, but that's why I also gave the example of the bare metal stent example, where here, under the aegis of AdvaMed and FDA, the industry was able to independently pool data to come up with appropriate statistical modeling that could replace a standard randomized trial.

So there are many ways to do it, even if the NHLBI isn't willing to fund the bill.

DR. YANCY: Any other comments on item four?

Dr. Zuckerman, is this satisfactory?

DR. ZUCKERMAN: Yes.

DR. YANCY: Five, based upon the discussion of trial design for percutaneous catheters, please discuss your recommendations

for trial designs to study surgical ablation in a sole-therapy situation.

And I think we saw data from the surgical registry today that that's occurred in about 1,200 cases. We certainly would appreciate comment here from Dr. Jeevanandam, Dr. Blackstone and Dr. Kato.

DR. BLACKSTONE: Okay. So first of all, in terms of sole therapy, that just isn't going to happen in terms of regular surgical approaches, so that the numbers for lone A.F. have essentially dropped to zero. So I think we don't have to worry about that.

What will come about is both hybrid procedures and robotic, very minimally invasive procedures, and I don't see why those shouldn't be evaluated the same way.

DR. YANCY: I think there was a statement -- and maybe, Dr. Page, you can help us with this. There was a statement that for individuals who have failed repeated catheter ablations, they might be considered for

surgical procedures. Does that need to be studied systematically, or is that a rarity?

DR. PAGE: The issue of what happens with recurrent afib after ablation is something that's debated. That is mentioned in the HRS statement, I believe, as one of the potential indications for standalone afib surgery, although reattempt with catheter ablation is what many operators undergo as well.

DR. YANCY: Dr. Jeevanandam?

DR. JEEVANANDAM: I agree with Gene there about the standalone afib. I think standalone afib has decreased. However, there is an indication for standalone afib, especially if somebody has a clot in the left atrial appendage and you want to do some kind of clot ligation, you know, or removal.

And you know, we sometimes do get consults with people who have clot who -- or an atrial fibrillation who have some anticoagulation contraindication, and then

those are patients who do get standalone atrial fibrillation.

So I think that population of patients is completely different than the population that we're talking about now. I think the population we're talking about now are -- we're actually going back and saying well, it's just primary therapy over anti-arrhythmics. I think certainly surgical therapy is not there yet.

And so surgical therapy would probably be when perhaps catheter-based therapy has failed or multiple drugs have failed.

DR. YANCY: But if there was a clinical trial design to assess that issue, I think I heard Dr. Blackstone say that the issues are the same.

DR. JEEVANANDAM: Correct.

DR. YANCY: Okay.

Is that a benefit -- I'm sorry, we have other comments.

Dr. Somberg and Dr. Tracy?

DR. SOMBERG: I thought one of the aspects of this question has to do with if you have a device that you wanted to add into the surgical ablation program -- am I -- am I in the right area?

But that you had some way to facilitate surgical ablation, a computerized system, a balloon you would place in and that would -- in an open situation, and -- or a device that -- anyway, my statement would be that there are performance -- there's enough information here to compare it to what has been established and you could establish performance criteria in that area instead of having to have a randomized trial with only 100 Maze procedures done each and every year in the United States.

DR. ZUCKERMAN: Not quite. Let me explain the intent of this question. Right now, for the cardiac surgical therapies that are generally being studied in trials, where

there are add-on therapies for when the chest is going to be cracked because you're going to do a mitral valve replacement or something like that -- as Dr. Blackstone indicated, though, another potential large use and indication is as a standalone treatment therapy through a minimally invasive approach.

And what he's indicated is that if you're going to do a minimally invasive cardiac surgery for treatment of afib, the cardiac surgical device should be held to the same randomized trial experience and end points, et cetera.

And is that what people generally are thinking?

DR. YANCY: I think Dr. Jeevanandam has concurred.

Dr. Tracy?

DR. TRACY: Yes, I would -- I would concur with that, if you are contemplating a standalone first-line -- or first- or second-line therapy, it would have

to be held to the same standard.

And I would discourage including people who have failed multiple catheter ablations. That's totally stacking the odds. I mean, the same way we exclude -- we would be expected to exclude prior afib ablations from our entry criteria, prior A.F. ablations should be an exclusion criteria for a standalone surgical device. It's just stacking the odds too much against the device.

DR. YANCY: Dr. Kato?

DR. KATO: Well, that -- I thought that was an interesting comment. Unfortunately, I think we're going to be -- cardiac surgery always seems to be relegated to, you know, multiple medical failures before we see the patient.

So you know, on the other hand, I think what Dr. Blackstone said was correct. I don't think there should be any difference in terms of how the study should be performed.

DR. SOMBERG: I have a question.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: I'm not sure what we're saying this -- the standard or the comparison. If you had cryoablation, pericutaneous or -- you had a surgical technique that was being developed and -- what would the control be? The control would -- or comparator would be catheter ablation? Or would it be the Maze procedure, the standard surgical procedure?

I mean, these are questions one has to think about. I don't think you would randomize it to anti-arrhythmic therapy versus surgical therapy when people are referred for surgical -- you know, as you said, it's probably a tertiary sort of -- you know, they failed multiple medical therapies and maybe catheter ablation.

So I don't see how it could be held to the same standard, because I think it's going to be, you know, an end-stage sort of thing, and maybe this comparator is the

Maze procedure, and maybe we have enough data over 10 years with Maze procedures to be able to do a certain number of them and see how it stacks up versus the Maze.

DR. ZUCKERMAN: Yes, I think we want to plan the clinical trial dependent on the patient population and what's practical, et cetera, no one would disagree. But there are cardiac surgical therapies being potentially developed that are minimally invasive that are really designed to be the analog of some of these percutaneous therapies.

And the question that we have is if they're really designed to do everything a percutaneous therapy is designed to do and to treat a patient very early, should they be held to the same standard.

DR. YANCY: And I think what you're hearing from -- is that they -- they should be held to the same standard, at least some of the panel members believe that, and it

should be a randomized clinical trial format, not a single-arm study with an OPC, and it obviously would be very sensitive to the patient population and the history.

And I think Dr. Tracy's comments are well placed, as are Dr. Somberg's comments that the actual clinical trial design would take a lot of thought, but it would have to be a clinical trial. I think I'm speaking for everyone. Okay.

Question six, please address the following issues with respect to anticoagulation. I remind the panel that there are guideline statements here. FDA agrees with the ACC guidelines which state drugs and ablation are effective for both rate and rhythm control, and in special circumstances surgery may be the preferred option.

Regardless of the approach, the need for anticoagulation is based on stroke risk and not on whether sinus rhythm is

maintained. Please comment.

Dr. Page, please begin.

DR. PAGE: I strongly agree with this, the only caveat being the open Maze procedure, where there's an open appendagectomy and not the external one which may leave a nubbin and I think is less proven.

But we saw data that suggest that the risk of stroke in those patients with open Maze and open appendagectomy -- the risk of stroke is extremely low, and generally those patients were not anticoagulated.

But for everybody else, including minimally invasive surgical techniques, I'd strongly advocate that we treat these patients as if they still had afib and treat according to CHADS guidelines.

DR. YANCY: Dr. Blackstone?

DR. BLACKSTONE: The proposed studies for minimally invasive surgical approaches that I've seen have all included amputation of the left atrial appendage or

some other closure of the appendage. And that is touted as one of the benefits, although much longer term, potentially, of that approach.

DR. YANCY: Dr. Jeevanandam?

DR. JEEVANANDAM: And using those minimally invasive approaches, though -- I mean, by looking at T.E., we make sure that there's no nubbin left behind, so even if by applying a stapler, for instance, there's a nubbin, we actually go back and close it back up with some sutures.

So I think taking out the appendage is probably the biggest advantage, potentially, of doing this surgically.

DR. YANCY: Dr. Page?

DR. PAGE: My only comment would be that needs to be proven in a randomized study.

DR. YANCY: Dr. Somberg? Your light is on.

DR. SOMBERG: Oh, I apologize, and

I agree with Dr. Page.

DR. YANCY: Dr. Slotwiner?

DR. SLOTWINER: Yes, I was happy when I saw this question on the list because it seems one of the clearer ones, yes. I think it's a separate question, and --

(Laughter.)

DR. SLOTWINER: -- I think it -- anticoagulation has to be considered separately.

DR. YANCY: I'm going to assume that the panel is of the persuasion of Dr. Page, and we want to respect the guidelines and move forward.

Item B for question six, what data are needed to support instructions to discontinue anticoagulation after atrial fibrillation ablation. And I remind you of the very clear comments made by Drs. Packer and Estes in this regard this morning.

Dr. Blackstone?

DR. BLACKSTONE: Yes, I think that

that is an issue that needs a randomized, long-term clinical trial. It would be interesting if that were, for example, a trans-industry sponsored, long-term trial, because we're talking about probably a years trial, but would be an important thing to do as perhaps a post-market collective, collaborative study.

DR. YANCY: I'm going to attempt to paraphrase a sidebar conversation I had with Dr. Packer regarding this issue, and he said it is for this circumstance especially when demonstrating complete resolution of atrial fibrillation, including asymptomatic events, becomes critically important, that if you're trying to generate enough information to justify the discontinuation of anticoagulation therapy, then you would have to demonstrate complete resolution of atrial fibrillation, symptomatic and asymptomatic.

Dr. Morrison?

DR. MORRISON: Well, that makes me

jump in, because I think we have to remember that it's never really been proven that the stroke risk is from the atrial fibrillation, so it seems to me in addition to that statement we need an adequately powered trial with long enough follow-up to see there's no difference in late stroke.

DR. YANCY: Certainly no disagreement.

DR. MORRISON: Because it may well be this is all epi phenomenon, that --

DR. YANCY: Certainly no disagreement.

DR. MORRISON: -- stroke risk is a function of the hypertension, the age, the coronary disease --

DR. YANCY: Exactly.

DR. MORRISON: -- the diabetes, and it has nothing to do with afib.

DR. YANCY: Dr. Somberg?

DR. SOMBERG: I don't think it approaches zero. I think it was in the low --

in the low numbers, but if I remember -- there was some data presented this morning and other data that was presented later from a Maze procedure, where it goes down 10, maybe, percent of the time.

So I just think we have to be careful. Your summary said it should go to zero, and I don't know if zero is the number.

DR. YANCY: Yes, I think the data that Dr. McCarthy showed was a nadir of one percent, so it's not zero.

But, Dr. Blackstone, you know that register well. It was about one percent.

Any other comments on these issues, then? I mean, it seems like there's a strong sentiment that it would absolutely require clinical trial.

Dr. Yaross?

DR. YAROSS: Yes, I would only suggest based on the magnitude of the sample size required from Dr. Packer's comments this morning that this may be the type of study

that requires NIH type of funding rather than looking to individual sponsors to carry the burden on this one.

DR. YANCY: Certainly I think Dr. Blackstone suggested trans-industry or a global effort.

Dr. Zuckerman, may be we proceed to question seven?

DR. ZUCKERMAN: Yes.

DR. YANCY: If trial end points focused on symptomatic recurrence, how important is it to capture asymptomatic afib occurrences? What are the implications of asymptomatic atrial fib occurrences in terms of the long-term risk of afib -- for example, tachycardia-mediated cardiomyopathy -- and, for example, the need for anticoagulation?

Since my field of interest is heart failure and left ventricular dysfunction, I can tell you to implicate a tachycardia-mediated cardiomyopathy, it would have to be incessant and fast, so I think that

would be a lesser issue, but the other issue certainly we can develop more.

Comments on this?

Dr. Slotwiner?

DR. SLOTWINER: Well, I think it's critically important and it gets back to the issue of the placebo effect that the procedure may have, and comparing the benefit of the procedure to the risk, so I think it's critically important.

DR. YANCY: Thank you.

Other comments in this regard? How important is it to capture asymptomatic afib occurrences?

Dr. Tracy?

DR. TRACY: I think to a large extent we sort of addressed this earlier, talking about the need for follow-up and that being one of the end points that you're looking at. And it does go back to what is -- what is the risk of this condition to the patient.

So I think we all have sort of expressed that it is important to know about the asymptomatic recurrences because of those implications for the patient.

DR. YANCY: And I think everyone felt that at the least, it needed to be measured, and some felt it needed to be incorporated as an end point. Is that fair?

Let's go on to question eight.

Is that acceptable, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, that it needs to be in the totality of evidence, sure.

DR. YANCY: Yes.

Question eight, FDA currently classifies patients with atrial fibrillation into three groups -- paroxysmal, persistent and permanent -- according to criteria proposed in the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation.

I'll remind the panel of the important modification from the HRS consensus

statement removing the concept of permanent.

Item A, do you believe that different types of afib should be studied separately? B, should there be differences in the definitions of effectiveness for each patient group following ablative therapy, and should they be followed differently? If so, please provide recommendations, for example, with respect to duration and type of monitoring.

Dr. Page?

DR. PAGE: We talked about this a fair amount already, I think, in terms of follow-up, that sort of thing. I, frankly, think it's somewhat difficult to distinguish between the paroxysmals and the persistents. As I said, they're not permanent anymore if you think you can convert them.

I personally would advocate bringing them together and studying them similarly in terms of follow-up, but if you wanted to absolutely cut it down to just one

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perfect little group, it could be the paroxysmals.

But I think we'd learn more by including a broader range, not the heart failure patients, necessarily, but the paroxysmals and the persistents.

DR. YANCY: Yes, it does seem a little bit arbitrary to say that the groups are that discrete.

Dr. Tracy?

DR. TRACY: What may be a little bit more discrete is the structural integrity of the heart. That may be more important to define protocols based on are you going after the structurally intact or nearly intact myocardium versus a patient with advanced disease, heart failure.

DR. ZUCKERMAN: Okay. There's a key point here that Dr. Page has introduced. You're saying that the paroxysmals and persistent could be studied in one randomized trial, that they potentially are poolable

patient populations with similarly expected effectiveness and safety outcomes at 12 months?

DR. PAGE: I'm not sure I exactly said that, but I think they're similar enough where studying them together would be reasonable.

DR. ZUCKERMAN: Okay. But it's important to clarify that. Usually when we use the terminology similar enough, we're implying putting those patient populations in one trial because we think that this is -- these are poolable populations and it can be studied in one trial.

That's the intent of this question, as opposed to doing two trials, one with paroxysmal and one with persistent.

DR. YANCY: Dr. Tracy?

DR. TRACY: I think it would be a nightmare to try to separate those out, because the same person can have paroxysmal as can have persistent. So -- and vice versa.

So I think those two things inherently go together. My distinction would be more based on what type of heart will you include in the study.

DR. YANCY: I would agree, unless one of our electrophysiology colleagues can tell us that there are some discrete clinical demographic markers that really allow you to separate the groups. I think we're setting up an arbitrary circumstance, but I can be corrected by Bob or David.

DR. PETERS: Well, I agree with what Cynthia said. I mean, I think we may have to look at differences not so much in persistent versus paroxysmal, but the person with a normal heart and either type of atrial fibrillation versus the person who's got, you know, ejection fraction of 40 percent and cardios and various other things -- may be a very different thing.

In terms of the use of drugs it's going to have very different implications. So

those may have to be separated out in terms of trials, actually.

DR. YANCY: David?

DR. MILAN: Yes, I have patients who have only paroxysmal episodes, and I have other patients who every time they go into atrial fibrillation they need to be cardioverted. And there may be some patients that have a mix of both.

But it's been my experience, and I think it's also been reported in the literature, that the success rates with pure paroxysmal atrial fibrillation is higher, that pulmonary isolation is more efficacious in that patient population than with persistent, and that mixing of patients in some trials has been used as an explanation for why their efficacy rates have been lower.

So I think that there's sufficient doubt about whether or not those patients overlap enough to pool them that you might want to stay -- I mean, if I were designing a

trial for approval of my catheter, I would try to use patients who had exclusively paroxysmal afib, because I think that's where the efficacy is greatest.

DR. ZUCKERMAN: But on -- we don't know if you're just observing a quantitative interaction, that the risk benefit differences may be different for these different populations because of that covariate or other ones, but --

DR. MILAN: Sure.

DR. ZUCKERMAN: -- Dr. Page's point is that there's nothing intrinsically so different that we're going to see qualitative interactions, and why not pool these patient populations.

DR. YANCY: Dr. Page, Dr. Somberg?

DR. PAGE: Yes, just to follow up, I agree, there are some that are different. There is some overlap. But I'm thinking ahead kind of towards labeling. I think the randomization -- because they're harder to

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take care of clinically with drugs or with an alternate ablation source also.

So if you've got adequate randomization, I think you'd clearly substratify them later and study them separately, but in terms of your end point in your overall trial I think we'd be better off -- when this comes back to us to assess for labeling, I'd rather be able to label it for patients with paroxysmal and persistent rather than paroxysmal alone.

DR. YANCY: Let's do this. We are rapidly losing our critical mass. We've had three people leave and two about to leave.

Dr. Zuckerman, can you accept the feedback we've given you now on question eight?

DR. ZUCKERMAN: Yes.

DR. YANCY: And can you also extrapolate that to question nine?

DR. ZUCKERMAN: Yes.

DR. YANCY: Oh, thank you.

(Laughter.)

DR. YANCY: I forgot the mike was on there.

(Laughter.)

DR. YANCY: Question 10, should atrial fibrillation ablation trials specifically study high-risk patients such as those with heart failure? A, if the panel does not feel that a specific potential high-risk patient population should be included in the clinical trials, can trial results using restricted enrollment criteria be applied to the general population?

B goes on to say if yes, are there specific groups to which such results should not be applied, such as patients with advanced heart failure, severe left ventricular dysfunction, or a giant left atrium?

And then finally, how should such patient groups be handled in terms of device indications, warnings, precautions?

I think we heard quite a bit of

commentary today about the heart failure theme. It kind of permeated a lot of the different discussions. So a couple of summation comments here would be great.

Dr. Somberg?

DR. SOMBERG: Well, I think it's important to try to get a heterogeneous population for labeling, and you want to be able to extrapolate from the study to the -- to the general population.

With that said, I do think there are certain patients with heart failure below a number -- and we can all quibble about this number -- of what their ejection fraction is that you certainly may want to consider necessary in a substudy or in another study before you go ahead and extrapolate it.

And I think people, you know, under -- 25 percent and under are a different subset of patients than those people who are -- have mild left ventricular dysfunction, and that should be taken into account.

DR. YANCY: If I might just editorialize, let me just say that I think the heart failure group is a unique patient population. They have unique sensitivities to anti-arrhythmic drugs as in a greater risk of proarrhythmia, perhaps even precipitating important clinical arrhythmic events.

The requirement for the adequacy of background medical therapy is incredibly important. They are on agents that have been shown to modify the atrial substrate; that is RAS blockers, either angiotensin receptor antagonists or ACE inhibitors.

So I think there are enough nuances in that patient population that it should not be considered a subgroup in a larger trial unless that subgroup is prospectively robustly powered, but rather they should be considered as a separate study objective.

But that's expressing not a position as chair but just from the heart

failure community about this patient group.

Dr. Peters?

DR. PETERS: I'd be concerned with a group like this that the success rate would be much lower, and I'd rather do our original trial and then, as a technique evolves, maybe tackle this other group.

The other point about this group is they're all going to have defibrillators anyway, so --

DR. YANCY: So it becomes yet another issue, that's exactly right.

DR. SOMBERG: What group are you both referring to when you say -- all heart failure patients? So in other words you have to have a normal ejection fraction to be in the persistent, or are you talking about --

DR. YANCY: Reduced ejection fraction.

DR. SOMBERG: Can you --

DR. YANCY: Reduced ejection fraction on evidence-based therapy. That

would be ejection fractions of less than 35 percent, ACE inhibitors, ARBs, beta blockers.

DR. SOMBERG: Okay. I just think that's a little -- 35 percent may be a little too restrictive, because then you're going to have the therapies really studied only in normal populations and normal ejection fraction.

But I do give deference to you that there certainly is a point where heart failure people become very distinctly different.

DR. YANCY: Dr. Kato?

DR. KATO: Yes, I would have to agree. The -- once you go below 35 percent, you're going to be running into a lot of people with defibrillators and maybe even biventricular -- no, I should -- not biventricular devices.

But I think that, you know -- I the industry always has to worry about doing a trial on a patient population that is,

quote, just sick enough to get a benefit out of the therapy but not so sick as their natural history, you know, may change the data -- the complication rate.

But on the other hand, once it becomes clear that it works, it's going to be extrapolated to the general population anyway.

DR. YANCY: But here's just another pragmatic issue. You're talking about patients that may be marginally compensated, who may go through a multi-hour procedure in a prone position, with a dilated left atrium and are subject to a number of potential unexpected consequences just related to the procedural issues.

DR. ZUCKERMAN: Yes. I think the panel has gotten to the point of the question. As Dr. Somberg indicated, ideally we would like these trials to be as inclusive as possible in their enrollment, but Dr. Yancy has helped us define the edges of inclusion.

There is a high-risk patient

population here that we need to be sensitive to, and if the sponsor doesn't want to enroll them in their first trial, there are legitimate scientific reasons for that.

DR. YANCY: Are there other comments about other groups besides heart failure?

DR. JEEVANANDAM: The only other quick comment I make is, you know, you look at giant left atria -- giant left atria are usually associated with some kind of intrinsic mitral valve disease, so if you have valvular disease or any other type of structural disease, I think they need to be excluded.

DR. YANCY: So this is actually an important statement. It would be nice to get some feedback here, because Dr. Jeevanandam has suggested that significant valvular disease might need to be excluded, and atrial fibrillation has a high incidence in individuals that have important mitral valve disease.

Dr. Page?

DR. PAGE: Yes, I think if someone has -- has severe M.R., for one thing, that's indication for surgery, especially when there's atrial fibrillation on board, so I think severe valvular disease would be an exclusion.

DR. YANCY: Is that an agreed-upon consensus?

Dr. Zuckerman, are you satisfied with our responses to question 10?

DR. ZUCKERMAN: Yes.

DR. YANCY: Question 11 -- I'll give anybody a quarter if they can just say yes or no.

(Laughter.)

DR. YANCY: Is it useful and/or important to collect information concerning atrial transport? If so, is there a specific method that should be used? And B, what comparisons should be used? And I think we heard some comment from Dr. McCarthy on this