

spacing for a lesser overall risk, which I think it at this stage of the game does involve.

CHAIRPERSON CURTIS: I think that's true. You really have to look at both. Another difference between the two is that the ablation therapy, the intent going in is curative, but you can't attain cure in everybody. With a catheter MAZE procedure, there's going to be a problem where if you don't have contiguous lines, if you don't have a perfect outcome, you're going to have some recurrence, and so you can't hold it to a 100 percent cure rate or a 90 percent cure rate. I think we have to be somewhat more liberal than that and understand that. But certainly if you've got 25 percent of the patients better, nobody would bother. You know, it's just--and it's not even so much the risk. Focally, fib ablation is done with a pretty low risk. It's the catheter MAZE procedure that is more of an issue with that now. It's just that nobody wants to spend all day in the lab, you know, and putting a patient through a procedure that may take hours, and have most of them fail the procedure. I mean, just better ways for everybody to spend their time in other therapies we'd like to use.

So, you know, the intent in the first place is curative. It's not a management issue if the intent is cure. And so it should be held to a higher standard than the other, but yet, we can't go all the way. I think the 50

to 70 percent as a goal is a minimum where you want to be if you're going to go through the effort of that therapy, and certainly for the pacing, I think you do have a lower standard--a lower requirement for how much you have to lower the burden, because it isn't as difficult to do, although it is an invasive device you're putting in people, and recruiting for these trials has always had to take that into account, that you've got to get patients with at least some problems with these. So I think that's very well put, that you do have to consider both, but I think we have stated some rough guidelines in what we've said here that would guide you in that.

Other questions that the FDA has regarding these issues that we haven't answered or dealt with?

MR. DILLARD: From the standpoint of, I think, pacing and defibrillation, we would say we're in good shape, so you're going to go back through, I think, for ablation now?

CHAIRPERSON CURTIS: Oh, yeah. Oh, yeah, we'll do that specifically.

MR. DILLARD: Thank you.

CHAIRPERSON CURTIS: Are there any other comments from the public before we get off this?

MR. FONSECA: I just have a question. My name is Todd Fonseca. I'm an employee with Medtronic, and maybe a

point of clarification, especially since a lot of the discussion here at the end was with respect to risk benefit ratio.

My assumption is--but I could be wrong, and that's why I ask for the point of clarification--that most of the discussion was regarding the purely aponic population. What is the panel's perspective on devices which are being already implanted for approved indications, but may have additional pacing therapies that may be beneficial for patients who have a core morbidity such as atrial fibrillation along with say a brady indication or a currently proved tachy indication? What's the level of acceptability or a clinical trial design that you would be looking for to approve those features in an already approved indicated patient?

CHAIRPERSON CURTIS: I think that if you had a situation where what you wanted to do was to be able to state a claim that that device is indicated for the reduction of atrial fibrillation, then you're going to have to meet the 25 to 35 percent goal. If you just want to turn it on and say, "Well, this is a bradycardia pacemaker", and not make any separate claim about it, then that may not be necessary, but if you actually want to say that, you know, and market it that way, then you have to meet those same sorts of standards.

DR. BRINKER: But you have--maybe I'm--but don't you have a device that contains an atrial fibrillation-- actually, an atrial defibrillator capacity on an ICD already, and that's approved--and that's approved for the treatment of atrial--is it not approved? Is it close? Well, it will be, and it will be presumably approved for atrial fibrillation in those patients who need ventricular defibrillation, correct? And it might be interested to over the labeling for--I remember I sat on the panel for that, but it seems to me that your labeling will allow it to be used for atrial fibrillation in those patients who are candidates for the ventricular defibrillator already, and it's hard for me to believe that you want to extend that device--well, it's hard for me to believe, but I hope you're not suggesting that you extend that device--

CHAIRPERSON CURTIS: We really shouldn't be discussing an unapproved device.

DR. BRINKER: Okay. But his question drove to the question of other devices. So you mean other devices that are already approved?

CHAIRPERSON CURTIS: Well, why don't you--do you want to answer that, Jim?

MR. DILLARD: Well, I just wanted to make a point--Jim Dillard--that we don't want to get specifically discussing a device. I think that question was more on a

generic issue, I think based on a scenario, and I think if you want to try to tackle that, that would be fine, but I think we need to leave specific devices out of the mix here.

DR. BRINKER: Okay.

MR. DILLARD: If the manufacturer wouldn't mind perhaps restating it in a way that you could tackle it, that would be fine.

MR. FONSECA: For any approved, let's say, pacemaker today, that's currently on the market, and a manufacturer wanted to add additional features onto that pacemaker which might be various pacing therapies for-- potentially for atrial fibrillation reduction or atrial arrhythmia reduction, depending on the claim one would want to make, what would be your expectations if it's an add-on to an already existing and approved platform?

I think our perspective would be that it depends again on the claims that you're trying to make. If it's one, purely, you know, we're going to reduce in these patients who also have the common atrial fibrillation, that we would need to show that. However, if someone were just to say, "You know, we have these features. We know they work appropriately. That is to say they do what they claim to do on the labeling. We're not exactly sure that they can actually do a reduction of burden, but we know that they're not unsafe, and we have data to support that they're not

unsafe in that population." Would that be inappropriate, an amount of data to get those features added on to an already approved platform?

CHAIRPERSON CURTIS: Well, how are you going to prove it's not unsafe?

MR. FONSECA: Through clinical trials.

DR. BRINKER: I think you're asking two different--I'm perceiving two different questions. That is, if you have a clinically approved platform and you want to add, presumably, some software modification that will allow the pacemaker to perform a number of functions, which primarily may be geared at atrial fibrillation prevention, it would seem to me--the one question you asked, "How can I add them?" And the second--presuming that you don't make any claims about them--and the second part of the question is, "Well, what evidence will I need to make claims about them?"

And I think the answer to the second question is you need the same evidence that is being presented here for a de novo kind of issue. For the first question, you need to talk to that guy over there.

[Laughter.]

MR. FONSECA: Thank you.

CHAIRPERSON CURTIS: Okay. I think Rahul, you want to--

MR. MEHRA: I'm Rahul Mehra. I'm also an employee

of Medtronic, and I just wanted to clarify one point, because it's related to the way the technology is being developed. And the whole issue of clinical utility came up before, and I wanted to be just sure that the panel members are aware that the devices that are being developed generically, there are two features. In the high wattage devices, the patient can manually activate the shock. So when you ask the question, what is a potential clinical utility, control is in the hand of the patient. If they have a symptomatic AF, they take the activator, they shock themselves, they get rid of their AF and therefore their symptoms. Would that be considered a clinical utility? Because that is the way we perceived the patients are perceiving it, as clinical utilities. That is the first part of my comment here.

DR. BRINKER: Well, I think the answer to that would be yes. Well, it would be yes if in fact it did the same thing, for instance, it worked the same way with the same kind of prolonged success that getting transthoracic shock for the same indication would be. If it turned out that we put these things in patients that were getting recurrent episodes, and that maybe that was a wrong form of therapy for that particular patient, it may not be clinical--in other words, it may not be clinically useful for the patient to keep shocking himself ad infinitum, even though

that each particular shock actually works for a small amount of time. And you have to look at that in the big spectrum of things.

My guess is that in a select population that might need infrequent, but still more than once every six months or a year, defibrillation, that that might be a perfect and very useful form of therapy for that patient, but I think that it has to be shown that it can be done with the same kind of utility that a transthoracic defibrillation can be done.

Utility is usually defined differently than a sort of a cause and effect. So to make the worst example, if it turned out that you could shock these people and then something--something in the method by which the shock was given, whatever, caused the recurrence of atrial fibrillation five minutes later, and then you shocked them again, and than again and again, then you would be successfully defibrillating the patient, but it would be of no clinical use or utility.

MR. MEHRA: I have one other point because it relates to the initial discussion on the pacemakers and the clinical utility of reduction of burden, and I just wanted to propose something here, because, again, as the technology is being developed, future pacemakers may have something called a symptom marker, so the patient has a handheld

transmitter, and they can take that and mark the AF episode as symptomatic. So the issue that came up before is how do we know we are providing clinical utility when we reduce burden. One could propose that we measure the reduction in symptomatic burden, that is, you measure the total amount of AF episodes which were marked by the patient as symptomatic in the on phase and the off phase, whatever the study design is, show a reduction in the AF duration that is marked by the patient as being symptomatic, and that is in fact the definition or the metric of clinical utility.

Again, I just wanted to pose that because it relates to the technology and what things would be possible in the future, because trying to go the route of quality of life, again, is a very important endpoint, but a very non-specific endpoint, and here we can actually measure the duration of symptomatic AF and its reduction with therapy on this.

CHAIRPERSON CURTIS: I think if a patient had a statistically significant reduction in symptomatic atrial fibrillation, that what would be a goal here. I think that would be a good way to go.

Any other comments, Brian?

DR. O'SHANSKY: Brian O'Shansky from Loyola. If I just may--

CHAIRPERSON CURTIS: Do you have any financial

interest in any of this?

DR. O'SHANSKY: No, I don't. But I just had an issue about this whole idea of symptomatic versus asymptomatic, because the issue of hard endpoints in the clinical utility of a device really depends on what we consider are symptoms, and patients might have a feeling of palpitations, and I don't know if that's considered a real symptom. And yet, on the other hand, someone might have 24 to 48 hours of atrial fibrillation, and ultimately develop heart failure and fatigue, but that might not be even noticed at the time, so if you convert someone back to sinus rhythm within an hour or two, you might offset a symptom that would develop over time, and yet the symptom severity is important, because there's certainly a whole range of symptoms and many of them are very subjective in soft endpoints, and that really complicates the whole issue, both for the point of view of a burden of atrial fibrillation and for the efficacy of the device. And certainly the easiest thing to do would be to look at the hard endpoint of just conversion of the rhythm back to normal sinus rhythm, because that you know, you're sure is going to work.

Actually, quantitating symptoms is difficult because the symptom might be changed from one to the other. Patients can become almost connoisseurs of symptoms. The symptom might be much more mild than an episode of atrial

fibrillation that occurs over a period of time. Paroxysmal episodes, 10 episodes in an hour, might be highly symptomatic, but the burden of atrial fibrillation might be a lot less than the individual who has 12 hours or 24 hours of symptoms that reduce over time because they have continuous atrial fibrillation.

So I'm very confused about what the best endpoint would be, and it seems to me which symptom is important needs to be defined, or consider all episodes equally, and try to grapple with that in another venue.

DR. BRINKER: Well, I mean, my feeling is that you not only--what we want to do is to look at the total burden of atrial fibrillation, both asymptomatic--we want to look at B-plus of the answer of that question, asymptomatic, symptomatic, and if there is any other evidence of patient benefit, to try to capture that, and one sort of soft piece of information, but still quantifiable, is quality of life.

Now, you said that there may be some other benefits in reducing atrial fibrillation, even long symptom list episodes like remodeling this, that and that. The critical issue is there may, and if it can proven that there is, then it's great. Then this thing is the greatest thing since sliced bread, but one has to prove that, and intuitively, I don't think it's acceptable to say that there may be some benefit unless you can determine that there is

other modes of benefit that are worth the minimal risk but quantifiable risk of putting one of these devices in.

And again, we have two different families of devices we're talking about, and they probably have to meet different thresholds, but one's preventative and one is therapeutic.

DR. O'SHANSKY: I appreciate that, but from a clinical point of view, again, very difficult, I was wondering what the definition of "symptoms" is. Does it mean the patient is aware that they're in atrial fibrillation? Did they have a palpitation, which is a common thing? Fatigue? How do you quantitate fatigue? How do you quantitate a little bit of shortness of breath? And the other issue I just want to make is also that, certainly risk is important, but many of these patients that would be candidates for defibrillator might ultimately get an antiarrhythmic drug, and there is a certain risk of death on that too. So it needs to be compared against, not necessarily a placebo, but against what would normally be clinical practice, which could be risky.

DR. BRINKER: You know, the symptoms that--you know, the fatigue and the shortness of breath should be identifiable in the quality of life instrument if it's a good instrument, and much better than anything else.

The other issue is that you will have--and in the

defibrillator, and this may make a--again, you reply in your last question, defibrillation, as opposed to the pacing prevention. And this is an interesting issue, because the proposed trial for the defibrillator I think was one of--a single-arm study, so that you wouldn't know in a control group whether there are long episodes of asymptomatic fibrillation necessarily, unless everybody got the device and some people were--just like in the pacemaker issue--some people just kept in a monitoring mode for a certain period. So I think the quality of life issue becomes an important tool in a--especially in a single-arm study.

DR. HARTZ: Brian, is there a well-accepted definition of gradation of symptoms of atrial fibrillation? I mean, there is for heart failure and angina. Is there one that the electrophysiologists use?

DR. O'SHANSKY: Not really, not that I'm aware of. I mean, there are probably five or ten commonly known symptoms. And I think it would be interesting to see a study that shows that patients with atrial fibrillation can predict their atrial fibrillation, whether they have symptoms or not. I would imagine that many patients are symptomatic when they're in sinus rhythm and vice versa, so I don't know the type correlation between symptoms and atrial fibrillation, and certainly there's no gradation of scale that's being used for that.

DR. HARTZ: So we need the O'Shansky scale, so next time we write a study design--

DR. O'SHANSKY: Almost done.

[Laughter.]

CHAIRPERSON CURTIS: Yeah. Thank you. One more comment. Okay?

MR. THANE: Hi. Eric Thane from St. Jude Medical. In terms of pacing algorithms for prevention of atrial fibrillation, I was just wondering if you would consider there to be a difference in the populations between patients who have a standard indication for brady pacing and those who don't? And if so, if that would affect some of your expectations in terms of this questions, in terms of either the type of study design or the endpoints that would be required? Since for patients with a standard indication, they would be getting a device, so event that minimal risk that you had mentioned before would be eliminated for at least that patient group.

CHAIRPERSON CURTIS: I must not be understanding, because that sounds very similar to the other question we had. So--

MR. THANE: Well, in terms of the--I think the other question was based on maybe an approval track question. This is just in terms of clinical trial design. If you would consider the patients who have a standard brady

pacing indication to be different than a patient population that does not, and who you would be treating solely for the prevention of atrial fibrillation?

CHAIRPERSON CURTIS: Well, I mean, obviously, there's a difference in your assessment of risk, because you have to take the risk already in putting the device in because the patient has the brady indication. But what is the question about, would we accept less of a benefit? Is that it, because that's--

MR. THANE: Well, would you consider--I guess from your response, I'm taking away that you wouldn't consider there to be a different expectation in how the therapy would work or the level of benefit that would be required in those two patient--you would consider them to be one patient group?

CHAIRPERSON CURTIS: Probably. I mean, you know, if you wanted to argue, you know, a 10 or 20 percent benefit is good because they already need the device, I suppose you could, but it's just that's going to be hard to measure anyway. Most of the time if you're trying to get a clinically meaningful benefit, and you want to have a labeling for that, then you still have to have that same--I would think you still need that same sort of range of benefit, not the 50 to 75 percent, but in that 25, 35 percent range. Anybody feel any differently?

DR. CHANG: I agree with that. If you make a new claim on an existing pacemaker for standard indications, you want to make a new claim or labeling, saying that that pacemaker actually prevents atrial fibrillation, then you need to be held on the same standard, 25, 30 percent reduction, whatever.

MR. THANE: But you wouldn't see the need to do two different clinical trials on those two populations? Essentially they could be looked at as a group?

CHAIRPERSON CURTIS: I see what you're saying. I don't see why not.

DR. STUHMULLER: I guess as a point of clarification, are you trying to get at with the issue, for example, could you pull data across, say for example, people who have lone a-fib at age 40 and people who have sick sinus syndrome or which a-fib is one part of that, and you're going to put system in of that 70. Is that what you're trying to get at?

MR. THANE: I was really more getting at just a base population itself than just--if you were doing a clinical trial for prevention of atrial fibrillation, whether or not there's a need to look at those two patient populations separately, or if patients who have atrial fibrillation is basically what you'll be looking at, and it really doesn't matter if they have a concurrent standard

brady pacing indication or not?

MR. DILLARD: Jim Dillard. Just thought I'd make a comment. That really wasn't in the table for you today, and I think there are a lot of other co-variables that may be able to be factored in in some of these, and I think that not being very prepared for this and not having background material, I think makes that very difficult for you all, and so I think from FDA's perspective, if you choose not to move forward with that, I would be plenty comfortable with it.

CHAIRPERSON CURTIS: Okay. Thanks.

All right. I think that ends the first part of the discussion here. Let's take a 15-minute break. That would take us to 2:55. And then we'll talk about catheter ablation systems.

[Recess.]

CHAIRPERSON CURTIS: All right. The next topic for discussion is catheter ablation systems. If we could get the first question up, please?

Please discuss the advantages and disadvantages of the following study designs: randomized control study, patients randomized to AF ablation therapy versus control therapy such as drug therapy or other controls, and then effectiveness and safety endpoints are compared between the two groups.

Second one would be a single-arm prospective

baseline study. After enrollment patients are observed for AF during baseline period, then undergo AF ablation therapy. The frequency of episodes is compared pre and post-ablation.

Then there's a single-arm retrospective baseline study. A patient's frequency of AF episodes is determined retrospectively from patient records. Following ablation, episodes are documented and compared to this baseline estimate. Or else there might be other types of study designs we could talk about.

Anybody want to start off the discussion? Tony?

DR. SIMMONS: Didn't we sort of go over this at the last meeting? And you know, I think a lot of the same points we made earlier, a randomized controlled study may be difficult to enroll patients into. I mean, patients aren't going to be randomized to standard therapy when there's a potential for a cure, and you've offered them that opportunity.

And I don't like the retrospective baseline for a lot of reasons we've already talked about, with patients having asymptomatic arrhythmias, they've had patients--I mean, I have to read these loop recorders all the time, and I send patients home with them all the time, and they think they're having arrhythmias and it turns out they're just having PACs. I think the prospective baseline, get some idea of the density of the number of atrial fibrillation

episodes, and then treat them with the ablation. That's what I can say as to--

DR. BAILEY: I would agree. I don't like the retrospective, because you've got the regression of a mean problem, if the patient comes in at a time when they've had a recent atrial fibrillation.

So I like prospective. You know, at least you're starting from scratch, and you can compare--if you're going to do that anyway though, you could randomize patients to immediate versus deferred ablation, and then you'd have a baseline period--an observational period in one group and a randomized comparison with a group that gets immediate ablation.

DR. SIMMONS: What's the advantage on this?

DR. BAILEY: Well, then you get a randomized comparison in addition to a patient as their own control. So it's sort of a hybrid.

CHAIRPERSON CURTIS: Then you can't compare that second group of patients that has that immediate therapy. You don't know--

DR. BAILEY: All you compare the initial period between randomized groups, and then you can look at the pre, post comparison in the group that gets deferred ablation.

CHAIRPERSON CURTIS: Is there any reason statistically to go one way or the other with those--

DR. BAILEY: Well, you always like randomized studies. You know, he said you can't randomize people. Well, you can randomize people.

DR. CHANG: It would depend on what patient population you study. If you compare ablation therapy versus medical therapy, then you certainly can randomize them. If you're studying a group of patients who have failed medical therapy, then you cannot, because by definition they already failed medications.

DR. BAILEY: So why can't you randomize them?

DR. CHANG: Randomize them to what? Because you're going to have--they already failed medications.

DR. BAILEY: Well, if you're trying to show that it reduces--it prevents atrial fibrillation, are you saying it's just--if you say it's obvious, then I guess you don't have to randomize people, but if it's not obvious that it's working, then why would somebody be--if it's not obvious which treatment is best for the patient, then that's presumably the reason you can randomize them.

DR. CHANG: Yeah. That's what I say, it depends on what patient population you study. If you study patients who already failed drugs, all the drugs, there's no reason to randomize them, because they either get ablation or they don't.

DR. SIMMONS: Well, you're not comparing drugs to

ablation. You're comparing ablation to whatever standard--

DR. BAILEY: You can still--there's still a legitimate clinical question. Is it good to ablate people that have failed medical therapies?

DR. SIMMONS: I'm still not sure what the advantage is to delaying it even more. I mean--

DR. BAILEY: Well, you're going to delay it even more for--if you're going to take a prospective baseline observation phase.

DR. SIMMONS: So you're going to delay it for three months, and you're going to get some idea of the density of the number of atrial fib episodes. And then you're going to perform the procedure. Then you're going to compare that patient to his own episodes. I'm not sure how--I don't know.

DR. BAILEY: Well, your argument against randomization was you don't want to wait for--

DR. SIMMONS: Another three months or six months to see what the effect--

DR. BAILEY: But you're going to wait three months if you're going to take the baseline period.

CHAIRPERSON CURTIS: Well, I think it was either everybody waits a baseline period to collect data on their baseline frequency, and then you go ahead and ablate everybody and compare before and after, or what Ken was

talking about, was doing half the patients immediately and having the other half wait, so then only half the patients have to have that baseline period to collect data on.

DR. VETROVEC: That would be a composite of a crossover plus a randomized trial.

DR. BAILEY: So you have to benefit of the baseline period to compare pre and post ablation to see what effect it has on each patient, but you also have a randomized comparison, at least for--obviously only for three months, to see what the comparison is between groups in terms of whether it's good to ablate the person right away or not.

CHAIRPERSON CURTIS: I mean, it has the attractive feature of letting half the patients get treated right away, and I think they both would be valid ways to go.

Question number two: inclusion criteria. Recent articles in the medical literature suggest that in some AF patients, ectopic foci originating in the pulmonary veins are responsible for the patient's arrhythmia. Are there inclusion criteria that may be reliably used to identify patients in whom AF is believed to originate in the pulmonary veins? Examples: such as patients with monomorphic and/or inferiorly directly premature atrial contractions, patients with ectopic foci mapped during electrophysiologic study to the pulmonary veins, patients

with a history of paroxysmal AF or other--

DR. VETROVEC: This is clearly going to depend on what the pre-test probability is that it makes a huge difference. I mean, if you're really confident that the patients that are going to benefit are the patients with the pulmonary vein, then it makes sense to make that an inclusion criteria, and perhaps exclude other groups that are going to be some much less likely to respond. Conversely, you limit yourself if you're not sure what-- where it's going to have its efficacy. I'd be more for broader and define the patient populations than excluding people, but maybe that's because I don't know.

CHAIRPERSON CURTIS: Well, the problem I see with "B" here is that you're only going to know that if you get as far as getting all your sheathes and catheters and everything else in there to see where these things are coming from, and you can't enroll a patient in a clinical trial at that point. And you know, I think we've got some pretty good evidence ahead of time, who we'd look for to do these things on.

You may want to have some definition of what somebody without structural heart disease is, because the more you have problems with valvular heart disease and the rest, that that's probably not your best candidate. And a lot of electrophysiologist look for frequent PACs, little

short runs of atrial fibrillation, more as an aid to doing a procedure, because if you get a patient into the lab, and they're the kind of person who every month has an episode of sustained atrial fibrillation, but there's absolutely nothing in between, they're impossible to ablate, because you can't localize the thing.

So there are some of those things that we look for, but in terms of knowing ahead of time that it's going to be in the pulmonary vein, that's just not feasible. That's not going to be where you can go.

You'd want to have somebody with PACs, and the way we usually screen patients is with Halters, to look for what I said, frequent PACs and little short runs of atrial fibrillation. If you start defining the P-wave morphology you want, that may become somewhat difficult to screen patients for that, and what you're really getting at is the very small percentage of patients whose foci are outside the pulmonary veins, because most of them are in the pulmonary veins. So I think if you got the normal heart with the right kind of Halter, that's the kind of patient you want to include in the trial, and I think that's the best you can ahead of time. A history of paroxysmal a-fib tells you nothing without those other factors.

DR. SIMMONS: I agree. I'm not sure what the point of the question is for sure.

CHAIRPERSON CURTIS: Well, I guess I could find out if I answered it, or if there's something else--

MR. DILLARD: Jim Dillard. I think that was very clear. I mean, I think what we wanted to do is try to get you to discuss what some of those important factors might be clinically that might help define the inclusion of certain patients, and I think that was helpful.

CHAIRPERSON CURTIS: Okay. Then we can move on to number 3. If a patient is not in AF at the time of the pulmonary vein ablation procedure, and if the patient is also non-inducible for a-fib, can you recommend what electrophysiological criteria investigators might use in identifying which pulmonary veins to ablate?

And the only way you're going to be able to do that is if you get frequent PACs and they map to one of the pulmonary veins. And if you don't have that at all, then you don't know where to go. I mean, you'd have to do an apparat [ph] procedure.

DR. SIMMONS: And there is no apparat procedure.

CHAIRPERSON CURTIS: Right, that I'm aware of.

DR. SIMMONS: Might be able to do some things to bring out PACs, but unless you get the target.

CHAIRPERSON CURTIS: Yeah. I mean, the problem with the provocative maneuvers is that there's about ten of them, and that's because none of them's reliable. So you'd

have to have frequent PACs mapping to one of the pulmonary veins.

DR. BAILEY: Would this be a another area that you'd randomize? That is, with or without pulmonary vein ablation? No?

CHAIRPERSON CURTIS: How would you envision that? Because, again, you'd have to be in there with the catheters in there to know whether or not, you know, and you have to have the PACs.

DR. BAILEY: This is an additional ablation to the atrial ablation, or is this instead of?

CHAIRPERSON CURTIS: There are two kinds of ablation procedures that we are being asked to look at here. One is a catheter MAZE procedure where you don't worry whether it's coming from, and you basically burn lines in the right or left atria or both, and by compartmentalizing the atria, you're not going to have any more atrial fibrillation.

Focal atrial fibrillation is a different approach to this, whereby the actual origin of the arrhythmia is in one of the pulmonary veins, and if you--for that one spot, that's it, that's all you need. So it's how it makes it different.

DR. SIMMONS: So are we envisioning two protocols here, where we're trying to say, we're going to enroll

patients into the pulmonary vein protocol or we're going to enroll them into the linear ablation protocol, or is this-- there's going to be an ablation for atrial fib protocol and when you get in there, you're going to decide--

DR. CHANG: The catheters that you use for ablation is different.

DR. SIMMONS: What's that?

DR. CHANG: The catheters, the ablation catheters, so--

DR. SIMMONS: Oh, I know. That's what I'm saying. When you first sign the patient up, you have to either sign them up for--is what the FDA is saying, or are you asking-- you're going to run one protocol for pulmonary veins, or you're going to run another one for linear ablations?

CHAIRPERSON CURTIS: It looks to me like all the questions that have been posed all relate pretty much to focal atrial fibrillation. Is that because the issues of catheter MAZE procedure have been already addressed at the previous meeting, and you're pretty--okay--satisfied with that? That's what it sounds like.

DR. PORTNOY: Yes, that is correct. Stuart Portnoy, FDA. For the most part the issues for linear ablation have been resolved. I can't remember if you're going to see some cropping up again in here, you know, like number five deals again with linear ablation. But clearly,

if it says PV ablation, then we're talking about the focal procedure.

CHAIRPERSON CURTIS: Okay. Was there a comment from the public? Okay.

MS. MOSER: Hi. I'm Sue Moser from Atrionics. We have a clinical study currently under way that is not focal or linear for the cure of atrial fibrillation. And it involves making circumferential lesions that are pulmonary based.

We've cured many patients, and half of them didn't even have ectopy at the time of their procedure. In some cases the upper veins were targeted or all four veins were targeted if the patients were having ectopy, but I'd like the panel to consider the last question and this question in these patients where the idea is pain isolation whether or not the patient is having ectopy.

CHAIRPERSON CURTIS: Are you saying a circumferential lesion around all four pulmonary veins or--

MS. MOSER: No, each vein in each individual.

CHAIRPERSON CURTIS: Endocardially, around the vein, or inside the vein?

MS. MOSER: From the endocardium.

CHAIRPERSON CURTIS: Okay.

MR. DILLARD: Jim Dillard. Can I just make a comment?

CHAIRPERSON CURTIS: Yes.

MR. DILLARD: Dr. Curtis, I think it's well within your right here to say whether or not you think this is a general enough topic within what we've been asking you, to take this on or to say no, that this is not within the scope of what we're doing.

CHAIRPERSON CURTIS: No, it really isn't. Okay, thanks. Yes?

DR. JACKMAN: My name is Warren Jackman. I'm a clinician at the University of Oklahoma.

CHAIRPERSON CURTIS: Do you have any financial interest in any of the products being discussed?

DR. JACKMAN: I do not. I--

CHAIRPERSON CURTIS: Did somebody pay your way here today?

DR. JACKMAN: My air fare was paid by Dade, by Sinkumental [ph].

CHAIRPERSON CURTIS: Thank you.

DR. JACKMAN: I apologize for that.

I think there has been, the last couple of years, a lot of information that suggests patients with minimal heart disease, that they may have a little bit of left ventricular hypertrophy, or the left atrial may be a little bit large, which is actually the common patient with paroxysmal atrial fibrillation with no structural heart

disease, that the trigger is for that arrhythmia or within the pulmonary vein even if you do not have the ability to demonstrate that. A lot of the information that is coming out suggests that the largest pulmonary veins are most likely to be the trigger. Data from work that Hershey [ph] McDow [ph] has done at our center, suggests that if you looked at the two largest pulmonary veins, the triggers for those--for atrial fibrillation, will be found in 84 percent of patients within the two largest pulmonary veins.

I think as the industry and people who work in ablation are looking towards the future, the concept of the true focal ablation is becoming minimized, that it is very difficult in a large number of patients to find all the foci. We know that in a large number of patients there will be single premature beats coming from more than one vein. In some studies as much as 75 percent of patients will have at least one potentially inciting beat found in more than one pulmonary vein, and I think that for ablation to become practical and effective in this group of patients with minimal structural heart disease, the individual isolation of one, two, three, or even four pulmonary veins, will become gradually the target, the endpoint.

It is a major goal to be able to avoid the need to identify which is the culprit vein. That is technically very difficult, and it is difficult to find all of the

culprit veins on any one EPC, so I think there is a variant that is different from a pure focal ablation that is maybe germane to the discussion, because I think many of the things the FDA will be seeing in the near future, or have already, relates not to focal ablation as in one point of the pulmonary vein muscle, but into complete electrical isolation of the pulmonary veins. And I think that if you require the validation that a vein is involved by seeing an ectopic originating from the vein, that will significantly compromise the effectiveness of the approach. I think as this evolves, you're going to see the value, the accuracy and the ability to localize with of the target veins is going to go way down. And I think the procedures will be moving towards a blind approach, selecting the largest or all four of the pulmonary veins.

CHAIRPERSON CURTIS: Well, before you sit down-- because the way these are done now, is that people spend hours in the lab a lot of times and--

DR. JACKMAN: I know.

CHAIRPERSON CURTIS: So are you suggesting then that one way to design these trials would be--just to argue it--go in there, figure out which is the largest pulmonary vein, isolate it, and stop, and not worry about any PACs at all, or isolate more than one, you know, the two largest, the two superior pulmonary veins and stop?

DR. JACKMAN: That would be the approach that I think would be most efficient and probably safest. The time involved in identifying the culprit veins is enormous and not very accurate. So I think that there probably is no good criteria that you can do non-invasively that tells you that the patient with paroxysmal atrial fibrillation has the episodes initiated by a burst of firing from one of the pulmonary veins.

However, I think what has--the information that's been evolving suggests that this is the case in the bulk of patients, whether you record frequent PACs on the Halter or not. So I think it's reasonable to assume that the pulmonary veins are the culprit in a high enough percentage of patients that you could take that to be the syndrome, that if you've got a patient with paroxysmal atrial fibrillation, that in fact it may be reasonable just to blindly target those veins.

CHAIRPERSON CURTIS: Would you target patients though with normal hearts structurally?

DR. JACKMAN: They would be the people who I think would be most likely benefit in the sense that those are the patients that probably there is triggered firing originating in the pulmonary veins, but I think we have to be real careful how we define that, and we and others have been looking carefully. If you look at these patients under a

microscope, you'll see they have a little bit left ventricular hypertrophy. The left atria is a little bit elongated, even if it isn't wider. So I think we need to use--be a little bit gentle with the definition of "no structural heart disease." A third of these patients have a history of hypertension, and I really think that there is-- I'm repeating myself, but I really think there is no diagnostic criteria that you can use in advance that tells you whether or not a pulmonary vein ablation is appropriate for that patient, and I think that the incidence is high enough, that it is reasonable to assume that all patients with minimal heart disease and paroxysmal atrial fibrillation would benefit from that.

CHAIRPERSON CURTIS: I think the minimal heart disease is a good way to put it, because you're not going to take somebody with moderate mitral regurgitation, with a scheme of cardiomyopathy and say, "Oh, this is the same patient group and I'm going to target a pulmonary vein here." I agree with you totally that mild hypertension, that sort of thing, shouldn't throw somebody out from this, but I think--I'm glad you brought that up, because that is a different way of designing these studies, is simply to say define the patient population, these patients are likely to have the triggers, and just go ahead and isolate the pulmonary veins and not worry about the triggers, it would

definitely shorten the procedure substantially. And the interesting question is what kind of results could we get out of that, and then may well be as good as the 10-hour waiting for the PACs to happen type of procedures.

DR. BAILEY: Can you test after each isolation and see whether it's worked or not?

CHAIRPERSON CURTIS: Well, you can test if it's electrically isolated. You can look and see what's happened to the amplitude of the signals in there, but if you're not looking for PACs and inducibility of atrial fibrillation beforehand, you can't look at that afterwards either. You'll just have to see clinically how the patient does.

There's another comment. Brian?

DR. O'SHANSKY: Brian O'Shansky from Loyola.

Just a comment about study design, and I think it relates to the issues here. Talked about a single-arm versus a randomized trial. A randomized trial against a drug I don't think would work very well, but I do think that a patient who goes through a 12-hour procedure with multiple catheters and with the hope of curing a problem would have a major placebo effect. And I think we need some hard endpoints, and I think symptoms might be a poor endpoint. And it also might be a point of--endpoint to see what happens acutely. I'm not sure what the time interval should be, but there should be some recording methodology built

into this where there's a hard endpoint of amount of atrial fibrillation burden or whatever the endpoint would be, because I think there is certainly the possibility that symptomatic atrial fibrillation could convert to asymptomatic atrial fibrillation simply due to the placebo effect of having a procedure done.

CHAIRPERSON CURTIS: Okay. Any other comments about this, this business about basically finding the veins just because you know you've got the right patient population is probably new or a new way of thinking compared to what you were expecting, but I think it would be very valid in something that some of the companies may want to pursue, and it would be an alternative way to go.

MR. DILLARD: Jim Dillard. I just want to make a comment on that. I think we would be interested in seeing the data that sort of supported some of those positions and whether or not that particular trial design has got some background information that would help us understand that. I think we would certainly be willing to look at that.

CHAIRPERSON CURTIS: Sure. No other comments about number three. Then let's move on to number four. During pulmonary vein ablation procedures, it's usually important for the physician to assess whether a particular lesion was properly created. Are there reliable physiologic criteria that may be used to evaluate the acute success of

the pulmonary vein of ablation procedure? Please discuss the following examples: post ablation non-inducibility, loss of atrial capture, decrease in atrial electrogram amplitude, measurement of electrical isolation of the ablated pulmonary vein or other.

Well, generally speaking, you know, the traditional way this has been done, which isn't all that old, but in terms of doing pulmonary vein ablations, don't necessarily look ahead of time for induction of sustained atrial fibrillation before you do the ablations. That's just more of a nuisance, but as I said, the ideal patient has got the PACs and little runs of atrial fibrillation. You do the ablation and they're not there any more. And then what most people will do is stand there and then try to see if they can provoke anything. So post ablation non-inducibility. And if you use that approach of, you know, what you see before and after, that's one way to go.

The other suggestions there about loss of atrial capture, decrease in atrial electrogram amplitude and electrical isolation, that actually has more to do with circumferential ablation of the pulmonary vein, because if you do a focal atrial fibrillation ablation and you ablate one spot, you're not expecting that you've done either of B, C or D, but if the goal is to electrically isolate that vein--and there seems to be a move towards that approach

than just getting one spot just because there's been recurrence rates in these patients, that any or all of those could be valid to be looked at in terms of defining it a success, and in that case, if you're not looking for PACs and short runs beforehand, you don't need them afterwards either. Then you'd be looking to demonstrate that you've electrically isolated that pulmonary vein.

DR. SIMMONS: I agree. I think that--it would seem to me that there isn't enough data to say that one of those is a better method to prove that you've isolated the pulmonary veins at this time, at least not that I've seen. And some of them you would need some fairly sophisticated three-dimensional mapping systems to actually show that you've actually electrically isolated a pulmonary vein, so that you could do mapping inside and outside the ring. So all of those are potentially very good markers, but I don't know that there's enough data to say that one of them's a better marker right now than another marker.

CHAIRPERSON CURTIS: I agree.

DR. VETROVEC: But you certainly can do several of them pretty easily. I mean, you say that you can do the post ablation inducibility--you do that usually. Loss of atrial capture should be a part of that, so you ought to be able to figure that out. And a decrease an atrial electrogram that will be used in the--you could at least do

that whole series of them. I don't think you should limit yourself to one particular endpoint.

DR. SIMMONS: Probably would do all of them.

DR. VETROVEC: The last--is not necessarily as useful?

CHAIRPERSON CURTIS: Electrical isolation I would imagine might mean pacing more distally in the pulmonary vein and seeing that there's no capture in the atrium on that side.

DR. SIMMONS: But I think you know, without a three-dimensional mapping system, that would be pretty difficult to show.

CHAIRPERSON CURTIS: It probably would be.

DR. VETROVEC: So D might be less practical.

DR. BAILEY: And I gather that it's not necessarily necessary for that to be true for the effect to be positive, or would it require electrical isolation for that approach to work?

DR. SIMMONS: I would suspect that's the best.

CHAIRPERSON CURTIS: It probably would be the best.

DR. BAILEY: That would insure it's sufficient, but is it necessary?

CHAIRPERSON CURTIS: We don't know.

MR. SPECTRUM: Peter Spectrum. I'm an

electrophysiologist in Oklahoma, and my flight here was paid for by Dade.

I think it might be useful just for a second to give you a view for sort of a day in the life of ablating for AF if it helps with some of these issues. It appears as if focal atrial fibrillation is in some ways a diffuse electrical problem that is manifest by focal firing at a given site at any time. The two biggest problems that we have when we ablate focal AF is that we'll get to the lab and patients don't have any focal AF, so there's no target to--

Another problem is that they may have focal firing from one area during the study that we're able to successfully ablate, and then they have a recurrence. We bring them back to the lab, and that recurrence is from another area, another vein or another site. And I think any strategies that are developed to try and attack focal atrial fibrillation have to address those two problems, and that's why there is a push towards more of an anatomic or empiric approach to ablation of focal atrial fibrillation. There's no doubt, however, that it's ideal if you can get to the lab and you see clear focal firing in one of the veins, that you want to isolate that vein or get that focus.

I think the endpoints for acute success depend upon what sort of tack you've taken, and there are two

essential tacks you can take for this. You can look to the exact site of focal firing and try to ablate that, in which case measures of electrical isolation of the vein would be irrelevant, but loss of focal firing would be relevant. And the caveat to that is that it's very finicky stuff. So if you have catheters in somebody for 12 hours, you may see nothing for four hours, then a flurry of focal firing, and that flurry may go away during your mapping, totally unrelated to your ablation, or you may have found it quickly, deliver ablation, and the focal firing went away, and you really don't know whether your ablation has had a significant effect. So measures of acute success are very difficult.

The other method would be to say that I've seen firing coming out of this vein or that vein or both, and then I want to electrically isolate those veins. And then your measure of acute success would be looking at electrical isolation. And we have found anyway, in our experience, that probably of those criteria, the easiest thing to do is to determine if you've got successful electrical isolation, put a multi-polar catheter in the vein, it can be very difficult sometimes to get capture in your pacing of the vein, so that you can't easily prove that you're getting blocked out of the vein into the atrium, but you can do the opposite fairly easily, pace in the atrium and show that

you're not getting any activation into the vein, and we use that as a surrogate marker.

I think that because of the large groups of patients that will have recurrence coming from a different vein later on, it's going to be ideal on the long run, to find a safe way to electrically isolate the veins. That would eliminate the problems of not having focal firing when you're in a lab, recurrence from a different vein and so forth.

DR. SIMMONS: Certainly, you also eliminate potentially the risks of ablating in 2 to 4 centimeters inside a vein and getting pulmonary vein occlusion, so you could actually safely, electrically isolate a vein from the endocardial surface of the atrium, eliminate that, which has significant potential, fortunately.

But how do you electrically isolate a vein without mapping all around the vein? I mean, just because you've got a multi-polar catheter laying inside the vein, unless you actually can document a ring, a block all around the vein, having a single linear catheter inside the vein doesn't--

CHAIRPERSON CURTIS: Well, that's the approach as I know it, is putting a circumferential lesion in there, balloons and things like that to--

MR. SPECTRUM: I think the actual isolation has to

be done by killing any possible area of conduction into the vein, whether point by point or with a balloon-type methodology, but the measurement may not require such accurate mapping. For example, you can just put a catheter in the V and a catheter in the A, grade the hiss, and say that there's no conduction to the V, without mapping all along the angulus. And I think similarly you can test the result simply by having a catheter in the pulmonary vein, there's no activation in the vein. The ablation's tough, but the proof is not so tough.

CHAIRPERSON CURTIS: Okay. All right. Number five. I want to get back to linear ablation. In July 1998, the circulatory system devices panel suggested that a 50 to 75 percent reduction in frequency of AF episodes would be a clinically relevant for linear ablation procedures. Please discuss whether your expectation has changed for this endpoint, given the increased use of RF ablation as a treatment modality.

I think the problem we still have with linear ablation is that as much as the technique is being talked about for focal life, it may evolve into something quicker and easier. Linear ablation is still rather time-consuming, and so far nothing in the literature is really all that exciting.

[So I think to suggest that we'd accept lesser

degrees of improvement, I don't know that I would be ready to do that.

DR. SIMMONS: A more strict--no, I think that--

CHAIRPERSON CURTIS: Yes, I think that that number still ought to be a minimum target that we're looking at for going through this procedure.

Anybody else want to make any comments on that?

DR. VETROVEC: When is the endpoint for it? is the other question, it seems to me.

CHAIRPERSON CURTIS: What do you mean?

DR. VETROVEC: Well, do you count it at one week, three months? How long do you give them before you consider it a success?

CHAIRPERSON CURTIS: I'm sure it's not one week. I don't know what we--it has probably been--Jim, that's probably been worked out already, right, in some of the trials that are--

MR. DILLARD: Well, whether it's been worked out or not I guess is a question for us. And I think--I was just talking to my colleagues back here, and I think at the last meeting it was one of the things that wasn't perhaps as clear as we would have liked. But our recollection is that there were six months that was talked about, and there was even a year that was talked about, I think, at the last panel meeting. Whether or not that is still the type of

time frame that you think would be necessary in these kinds of situations--

CHAIRPERSON CURTIS: I don't think you have to wait out a year to find this out. I mean, you're not doing this in people who have an episode every four months, and certainly six months would be more than enough. That's in the three- to six-month range. Looking at what kind of AF burden you've got compared to before, you can tell whether it has worked or not.

DR. SIMMONS: I think that's what we talked about before. It depends on the AF burden, but we wouldn't less than--I wouldn't want less than six months.

DR. BAILEY: Would these be patients that--could they be patients in chronic AF? Or would it just be intermittent?

CHAIRPERSON CURTIS: I don't know how the trials are being designed. I mean, conceivably, it could be for correction of it, but--

DR. BAILEY: Okay. So if someone's in chronic, what's the frequency of AF?

CHAIRPERSON CURTIS: A hundred percent.

[Laughter.]

DR. BAILEY: So it's all frequency. Again, it's back to burden, right?

CHAIRPERSON CURTIS: Burden.

DR. BAILEY: Yes.

CHAIRPERSON CURTIS: Number 6, recent articles in the medical literature suggest that some patients may experience pulmonary vein thrombosis as a result of the pulmonary vein ablation procedure. Is there a relatively low risk, that is, minimally invasive, method for evaluating pulmonary vein thrombosis during the early post-ablation period? Patients may also develop pulmonary hypertension. Likewise, is there a relatively low risk method for evaluating pulmonary hypertension during the follow-up period?

Of course, this comes from the article that was published saying that there were several patients who developed pulmonary hypertension after a catheter maze procedure that was basically connecting the pulmonary veins, isolating them.

I think that that's a real concern everybody has with the idea of pulmonary vein ablation, particularly circumferential. I know there has been some animal work looking at this already, but that would be the concern in a patient, creating pulmonary hypertension. And so I think one of the things that is going to have to be thought about is likely doing one vein--certainly not all of them, one or at most two at any one session to minimize the risk of pulmonary hypertension.

In terms of evaluating this, anybody have any thoughts on this, either pulmonary vein thrombosis or hypertension?

DR. SIMMONS: Certainly the only one case that we've had, the MRI started very nicely and we had the clot inside the pulmonary vein and certainly the non-invasive way. Now, that doesn't answer the question of pulmonary hypertension if you had smaller vein occlusions. But the MRI does pick it up very nicely.

DR. BAILEY: Did you try TEE?

DR. SIMMONS: I think the echo is very bad. Echo is poor. You can do angios, you can do, you know, left atrial angios, but that's pretty invasive. You might try spiral CT. We did both. But the MRI we--we've only had one case.

CHAIRPERSON CURTIS: This is a tough one, you know, if you're trying to do something non-invasive. You want to measure pressures. You're going to have to get invasive for that. And the echo is poor for this.

DR. DOMANSKI: Well, I'm going to think out loud because I really don't know the answer. I do a fair amount of TEE. I wonder if one could look at the flow pattern in the veins and have--if you're looking for just plain occlusion, you ought to be able to see a different flow pattern, but you're only going to see the more proximal part

of it. I'm not exactly--I'm not sure where they're getting the clots. The MRI would show you the whole thing if it imaged it, but I suspect that it's inconstant in its ability to do it.

DR. SIMMONS: It's not a clot, usually, either. It's only a partial clot. And it's--ours was right in the proximal--right in the atrial--right very close to the atrial-pulmonary vein junction.

DR. DOMANSKI: But there may be more--I think more expertise could be brought to bear on that. I don't think this is an imaging crowd when it comes--TEE, yes, and if it's in the proximal part, sure, you'll see it. I'll sign on to that. But I think if it comes to MRI, I'm certainly not an expert at that, and it would be interesting to know what their ability to reproducibly see more of the extent of the pulmonary veins is. So that question I think we can get an answer to, but probably not today.

DR. SIMMONS: I can tell you, the pictures are wonderful. You can really see pretty far into the pulmonary vein. But it's expensive, unfortunately.

[Pause.]

MR. DILLARD: Well, in this silence--Jim Dillard-- I think some of the points--we didn't think that we would answer this question at all today, and some of the other guidance might be the types of people that you think we

ought to consult with, perhaps to get some additional benefit and some additional information. And I think you've helped us with that. Some imaging experts may be helpful here, and then if there's anybody else, in terms of not truly non-invasive, perhaps, but minimally invasive also, might be some good guidance for us.

CHAIRPERSON CURTIS: Well, I guess the other possibility might be screening for pulmonary hypertension with a Doppler and then doing a cath if you found, you know, some evidence of an elevation.

DR. DOMANSKI: It is. The problem would be, though, that if you just thrombosed one of them, you know, you probably wouldn't see it.

CHAIRPERSON CURTIS: You know, there are two issues. There's the pulmonary vein thrombosis and then there's the hypertension, and, you know--

DR. DOMANSKI: Sure, sure.

CHAIRPERSON CURTIS: All right. Are there any other issues related to catheter ablation that we haven't touched on?

DR. VETROVEC: Can I ask you about the issue of fibrosis--later fibrosis and stenosis rather than thrombosis of the pulmonary vein? Do you want to discuss that?

CHAIRPERSON CURTIS: Sorry?

DR. VETROVEC: The issue of late stenosis of the

pulmonary vein, should we comment on that?

CHAIRPERSON CURTIS: You mean that should be looked for? Is that what you're getting at? Yes, I think that's true. I think that definitely would be built in because it's probably one of the major safety concerns with doing the pulmonary vein ablation.

DR. VETROVEC: Well, that kind of wasn't in this. That's why I'm bringing it up.

CHAIRPERSON CURTIS: Okay. Any other comments anyone wants to make? Sonny?

DR. JACKMAN: Warren Jackman. Anne, I just wanted to address one of the things that you had mentioned before about the concern about doing multiple veins in a single study. It would seem that if you wanted to find out if you could isolate pulmonary veins, you could do that in a single-vein ablation or a two-vein ablation. I think if we're truly looking for cure of atrial fibrillation, it may be necessary, even in a single sitting, for the patient to do multiple veins.

The caveat that I would use would be that whatever technology is being proposed for creating that circumferential lesion, there should be adequate animal data to show that there is no acute or late stenosis.

I think if there is adequate animal study and patients undergo either an MR angiogram or a spiral CT

before ablation, immediately after ablation, at three months, six months, I think it will become clear very quickly whether or not there is a stenosis problem. And I'm not sure that in the study design limiting to one vein or one vein per side or something would be advantageous I think for any of the protocols.

CHAIRPERSON CURTIS: Well, I'm not sure that you wouldn't have to at least have some feasibility or safety-- pilot data may be the best way to say it, where you did--I mean, I don't think you could take your first humans and do all four veins, and then find out, you know, three months later that they stenosed everything and say, oh, gee whiz, that wasn't a good idea.

DR. JACKMAN: I think there's a little bit of disagreement, but at least the group from Bordeaux feels that the stenosis is a fairly acute phenomenon, and I think you could do a pulmonary vein angiogram after each vein showing that there is not any acute stenosis, and then use that as a criteria to allow to go to the next. But these do require multiple transseptal punctures, and there is some morbidity to the procedure associated with getting everything in place. And I think that from the patient standpoint, putting myself in their shoes, I think if we have--if there is a reason--if the FDA is convinced that the animal data presented to them shows an adequately low enough

risk of pulmonary vein stenosis, I would hope that the protocols would not be limited to show just one vein. And I think demonstrating a pulmonary vein angiogram immediately after, before proceeding to the next vein might be a reasonable approach, something on that order.

CHAIRPERSON CURTIS: Okay.

DR. SIMMONS: I don't know, Sonny. I think, you know, we all appreciate your technical expertise and guidance. But I don't know, doing all four veins in one sitting, you know, in a larger--anything short of a very small study would seem to me to be, you know, less than conservative. And I'm not sure that all--I mean, I don't know what kind of evidence you're talking about, but certainly our particular patient didn't show up complaining of shortness of breath. Now, maybe you're saying if we had shot dye or done the MRA at that point in time we would have seen something, but certainly clinically she didn't present until almost a month later complaining of shortness of breath, and that's when we discovered what was going on.

So I don't know how many patients have been done and looked at, but it might not be the worst thing in the world to do a small pilot study in less than all four veins.

MR. SPECTRUM: The only thing is you certainly can't then use recurrence as AF as your endpoint.

DR. SIMMONS: No.

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MR. SPECTRUM: So you isolate one, there's no way  
you're--

DR. SIMMONS: Right.

CHAIRPERSON CURTIS: All right. I think if there  
are no further comments, we can adjourn. Thank you all.

MR. DILLARD: One final comment just from the FDA  
standpoint. We'd like to thank everybody on the panel.  
We'd certainly like to thank the audience, the audience  
participation, and one final comment that I'd just like to  
make for our Executive Secretary, John Stuhlmuller. It is  
quite possibly John's final meeting as our Exec. Sec. of  
this panel, and we will be rotating him off and bringing on  
another individual. And I'd just like to thank John for his  
hard work and dedication over the number of years he's been  
this Exec. Sec. It's been very helpful for FDA, and I know  
he's been a joy for the panel to work with, too. Thank you,  
John.

[Applause.]

[Whereupon, at 3:46 p.m., the meeting was  
adjourned.]

**C E R T I F I C A T E**

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



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**THOMAS C. BITSKO**