have to operate with the data that are present, is that this device appears to prevent myocardial infarction; that, in fact, it certainly is reasonable to suppose that the worse the ventricle you start out with the more important that becomes in terms of preserving life and at least in the patients that you were doing there is an awfully strong trend in the direction of reduced mortality. So, I think the results are actually fairly compelling.

Let me ask you one other question. There is an extremely strong trend also in reducing target lesion revascularization. What do you think the mechanism of that is?

DR. BAIM: That is 30-day target lesion revascularization. So, the mechanism there is more subacute closure than it is restenosis. I don't think that using distal protection should influence 6-month restenosis rates.

DR. DOMANSKI: So, you think it was just a better result.

DR. BAIM: Well, if you look at the slow flow and incidence of no reflow as being 8.8 percent or 8.3 percent in the control arm, those patients are set up for stent thrombosis and would come back to the lab for treatment of that. So, I think it is mostly mediated.

DR. DOMANSKI: Alsl right, those are my questions.

DR. TRACY: Dr. Klocke?

DR. KLOCKE: I was trying to grapple with some of the issues that might be pertinent to labeling, and I have one question that I probably should be clear on and I wasn't. In the roll-in portion, were those the same criteria as RTC-1? What I am interested in is the learning curve issue, and if I understand it, the MACE rates isn the roll-in study were 17, and then the same patients in the control study were 10. And, that sort of suggests to me that perhaps maybe that is also part of a learning curve circumstance. What I am trying to sort out is that in the RTC-1 patients -- I am not quite sure if they are the same as the RTC-2 or not, and the question is since, in fact, in the RTC-1 study there was actually a greater incidence of MACE in the intervened patients, the question that I am trying to struggle with is -- and I am assuming that the RTC-1 patients, from the data you presented, are in fact the lower risk group. We have trouble identifying that but the people with experience are clearly very good in the area. So, I am sort of trying to figure out the learning curve and the RTC-1 patients -- how enthusiastic we should be in terms of using the device in these lower risk patients who, I understand, are a small subset of patients seen clinically. I have a couple of others but I don't know if you could help me with that.

DR. BAIM: Well, I think the issue about the roll-in, the inclusion criteria were the same but this device, particularly in its original embodiment with the two-syringe inflation and a wire that was somewhat stiffer and less maneuverable than the GuardWire-Plus, really was very different from any device that these people had ever used. Plus, we as a herd, if you will, were collectively learning by interesting challenge with case selectioin and technique where to position the distal occlusion balloon and how to ensure it doesn't move during the procedure. So, it is not at all surprising that the complication rate for the same patients in the roll-in versus the RCT-I would have been higher. The cases that were in RCT-I were also in RCT-II. It is just that they weren't there exclusively. They were a smaller group and more representative vein grafts were covered.

Would there practically be a group of vein graft lesions that were so low risk, looking at their morphology, that one would say, no, I don't need to use distal protection? My own opinion, having done a lot of htese lesions, is that I would never trust any year-old vein graft. I have seen severe no reflow -- Dr. Wahr may want to comment on this, but I have seen severe no reflow in lesions that looked morphologically innocent. So, I think that the standard, based on the RCT-II data, would be in diseased

vein grafts that are amenable to use of the device I would use the device for the endpoint benefit. Dr. Wahr?

DR. WAHR: Yes, I would like to make another comment. I think it is important for you to appreciate that many and, in fact, it is fair to say most of the roll-ins were done on the patients that had had the expanded criteria for enrollment. Of the 68 sites that came on line sequentially -- I don't know the exact number but I would predict that at least two-thirds of the roll-ins were in the high risk group.

DR. KLOCKE: Thank you. That is helpful. When you switched to the EZ-Flator -- I guess that was a little bit more than half way through the RCT-II patients and I understand that is a subset analysis but do you have any information on the relative MACE rates in the RCT-II patients that were treated with the original device that had the problems that Dr. Baim mentioned versus the EZ-Flator device which is clearly preferable?

MS. HINMAN: What I can speak to is the RCT-I was the 142 patient analysis which was approximately a 70-70 split. Those patients were treated exclusively with the GuardWire-1.

DR. KLOCKE: I understand. But, if I am correct, there were probably 183 of the RCT-II patients treated with the old device, and I think you said 144 --

MS. HINMAN: Roughly.

DR. KLOCKE: -- with the new device. Again, I understand that that is a subfraction, and I also understand, as you point out, that it is obviously easier -- there are lots of reasons, and I just wondered if that improved design -- it certainly made it easier for the operators and I wondered if that translated or if there is any hint that that translated into a reduction in the MACE events.

DR. WAHR: I may have had the largest experience with GuardWire-1, and one of the changes that happened when we went to the GuardWire 2, in addition to the inflation/deflation device, as mentioned in the FDA presentation, was that the profile was lower. I don't think there is any question that the MACE event will be lowered by a lower profile device.

DR. KLOCKE: I guess in terms of training criteria, I, like everyone else, realize that you people who are doing -- you have impressions that are sometimes high to quantify but that I believe we all place a lot of stock in. So, I guess in whatever training program is approved you will be anxious to find a circumstance to translate all these things we are discussing into it.

I guess the experience you have so far in terms of trying to figure out patient applicability, ejection fractions less than 25 percent so far are an unknown entity.

MS. HINMAN: That is correct.

DR. KLOCKE: Thank you.

DR. TRACY: One very brief question, do you have enough breakdown of the data to say whether there is a difference in outcomes, adverse events, for older grafts versus younger grafts?

MS. HINMAN: Not at this time.

DR. TRACY: Then I will turn it on to Dr. DeMets. I think there is a number of statistical questions.

DR. DEMETS: Thank you. I would like, as others have, to compliment the sponsors and investigators for a challenging study device. Randomized trials are always a challenge, and I think you have done a good job in pulling this off.

I have three sets or areas of comment and I will just refer to two of them because of time. One group refers to the sequential methods that were presented, and the other has to do with the cohort issue which is really, I guess, related to panel question three.

You piques my curiosity in your presentation, compared to what was in the written material. You mentioned you used the Lan and DeMets spending function but which one?

DR. KUNTZ: In the Tsiatis and Wang we used the 0.6 boundary shape which we though best replicated the design from Geller Pocock. In your paper I think we used the negative 0.5 boundary shape from the '83 paper.

DR. DEMETS: It is not an '83 paper.

DR. KUNTZ: Well, I am not quite sure what --

DR. DEMETS: When you quote that paper, that is not sufficient. You need to specify which spending function and that is not in there. Along those same lines, on page eight of your presentation you show the boundaries that you, in fact, did use which are, by the way, fine. I have no problem with them. Do you have a plot of those boundaries with the accumulated data?

The points on the actual boundaries, themselves. No; I have not plotted that. I could, though, if you want to see that, where it crossed over.

DR. DeMETS: I presume that, since you didn't say to the contrary, that the p-values you quote are not adjusted for any sequential analysis.

DR. KUNTZ: Which p-values are you talking about?

DR. DeMETS: Let's just start with your primary outcome.

DR. KUNTZ: The primary outcome where we used the nominal p-values from Geller-Pocock.

DR. DeMETS: Excuse me?

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DR. KUNTZ: These are nominal p-values from the Geller-Pocock so they--

DR. DeMETS: But these don't provide--there is a difference. The Geller-Pocock paper tells you what p-value you have to hit to claim significance.

DR. KUNTZ: Right.

DR. DeMETS: But when you start quoting p-values, have you adjusted those for the fact you had sequential methods?

DR. KUNTZ: Well, the nominal p-values are corrected for two interim looks in a final analysis using his schedule F.

DR. DeMETS: I would challenge that. They are not.

DR. KUNTZ: We had consulted with Stuart on this.

DR. DeMETS: They are nominal. I am asking you what the adjusted p-values are. You made a comment earlier that you paid a penalty for making the change and all that.

DR. KUNTZ: Yes.

DR. DeMETS: I would submit to you that, if you do not adjust the p-values, you have, in fact, paid no penalty for any interim analysis.

DR. KUNTZ: Right. Maybe I didn't explain myself--maybe very poorly, but the idea was that would maintain the nominal p-values for the 550 look which had already used an

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alpha spending for the 350 look and, therefore, the nominal p-value that we had to hit for 550 would, in fact, represent already alpha spent that we attributed to the decision to start the second trial. That was the idea behind that.

DR. DeMETS: What I am sort of driving at is if you were to, say, have taken those groups sequential plus and plotted your stenoid statistic, presumably you would cross that boundary at the N--at least, whatever the N means here, and you could say you can claim significance at the 0.05 level because you have crossed the--

DR. KUNTZ: That's correct.

DR. DeMETS: But that is different than claiming a p-value that is nominal, which you correctly said, it was nominal, but you have not paid any penalty in using that p-value for all the interim analysis that you have conducted. That is the point I am trying to get at.

DR. KUNTZ: Okay. I understand.

DR. DeMETS: I would like to, if I could refer you to page--in your handout, here, page 13. It is the slide, in your presentation, where you have the different group sequential analysis plans by alternative cohorts.

What I really would like to have you say again, more slowly, is who knew what, when, in this analysis. I don't know whether you can put that slide up, maybe, for the

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rest, but, at any rate, on page 13, you have the--the first line says, "First interim analysis at 350 patients."

Is that the first time at which--

DR. KUNTZ: The projector is off, but I know that slide very well, so maybe I can explain that further.

DR. DeMETS: Okay.

DR. KUNTZ: I'm sorry; state that again, please.

DR. DeMETS: I am trying to understand. In the first line, it says, "First interim analysis at 350 patients." So that is the first time the monitoring board actually saw data.

DR. KUNTZ: That's correct.

DR. DeMETS: To what extent did they participate in the decision to claim RCT1 and RCT2?

DR. KUNTZ: I will work out the sequence in more detail because I think this is critical. During the conduct of the trial, before the 350 patients was summarized for the data-and-safety monitoring committee report to review, under the first interim analysis, a decision was made by the sponsor and the FDA to widen the enrollment criteria.

DR. DeMETS: Okay.

DR. KUNTZ: So that decision was purely made on two issues, and the enrollment was slow and feedback from investigators who felt that this did not represent the garden-variety patient.

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DR. DeMETS: Okay.

DR. KUNTZ: While that was taking place, and actually even before the DSMB had reviewed the 350 look, the criteria had changed at sites.

DR. DeMETS: Without DSMB involvement.

DR. KUNTZ: Without DSMB--well, the DSMB actually was consulted with respect to the fact the they were going to change--and the chairman of DSMB agreed that, with consultation with FDA, it was a reasonable thing to do because enrollment was slow. As a matter of fact, I think the DSMB chairman was the first to talk about the problem of slow enrollment. I should have brought that up because they were being copied with that.

Now, at that point, the data-and-safety monitoring committee had returned their letter and said to continue with the trial, that there were no safety concerns at this point and, obviously, that they had not reached the nominal p-value to stop this trial under Geller-Pocock.

The sponsor then asked the question to--called me and asked the question, if we were concerned about this restricted criteria, do you think that one of the reasons that we didn't reject the 350 was because we had patients who were not at risk. The sponsor felt that this trial should have stopped at 350 based on the previous data. They

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were very anxious to see that this would work, based on the preliminary data from some of the registries.

I, at that time, stated that that was, obviously, an interesting question but in order for us to act on it, we would have to do what I felt to be certain maneuvers, and that is, number one, to consult the FDA, number two, to consult the statistician with the data-and-safety monitoring group, and our statisticians internally.

We raised the possibility that, without looking at the data that if, in fact, there was concern that the first cohort of individuals under restricted criteria did not represent the new group, that a decision to start a new trial could be made and we had to figure out some way of paying for a penalty for that decision to go forward.

After all, there was information acted on. The information acted on was that the trial was to continue. So, clearly, if there was information that it wasn't terminated suggesting that there was--so we did, in fact, have to pay some alpha penalty to some degree under that hypothesis.

DR. DeMETS: I would like to explore that, but go on.

DR. KUNTZ: When we consulted with--I don't want to get into naming names, or whatever, but when we consulted some of our senior statisticians including Dr. Pocock and

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others, some felt that there would be no alpha penalty required, that we could actually start the trial from a new point if we learned something about the old trial based on enrollment alone.

I felt that, to make it more legitimate, we probably should charge some alpha spending for that because, after all, there was a little bit of information acted on. The data-and-safety monitor committee statistician also agreed that that probably was a little bit overconservative but would, in fact, be somewhat valid because it was be overconservative.

So, in essence, what we did was restart the trial with only two planned looks but charged the alpha-spending function as if there were three looks. While maybe that is not a conventional way to do it because this is not a conventional trial or a conventional way to respond to the problem we had in this trial, it seemed to be a reasonable and practical way to deal with the decision to look at this new analyzable cohort.

So that was the sequence. The sponsor made the decision that they would look at the 550-patient cohort and its run-on which is 659 as the analyzable cohort and had committed to the FDA that they consider that to be the primary endpoint and would discard the results of the 142 understanding that they were taking a risk, that possibly

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their initial impressions were wrong, that maybe the 142 patients did not have the low risk.

As a matter of fact, they might have been actually the biggest treatment effect. They didn't know. They never knew the results of the study. They just were acting on their impulses as to their response in the field that these patients did not represent.

DR. DeMETS: So the results, they knew, were pooled over both arms of the trial.

DR. KUNTZ: That's correct.

DR. DeMETS: So it could have been no effect or it could have been a whopping effect, one or the other.

DR. KUNTZ: That's correct.

DR. DeMETS: Again, this issue of paying a penalty, indirectly, you did by keeping the boundaries. But, in fact, you don't make too much of them. And then you proceed on to quote nominal values without any adjustment. So that is why I pushed that point a little bit.

DR. KUNTZ: Okay.

DR. DeMETS: You are probably going to still be okay if you do it, I am guessing, but the fact is to just quote nominal values does not acknowledge the fact of everything you just said.

DR. KUNTZ: Okay.

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DR. DeMETS: So I think you want to, perhaps, do that and at least have that as an adjunct p-value when you present your results. You lead me to my second set of questions on the cohort issue. I think Dr. Klocke got to my first question about when was the device changed and it was sort of two-thirds of the way through what you call RCT2, or something like that.

It strikes me when one restarts trials, a more traditional way, I think, of doing it is if you have a change of therapy, which you might argue--that to continue the device was a change where you have a toxicity or some reason.

I think it is somewhat unconventional to restart studies where you change the eligibility criteria. That happens a lot in trials where you change the eligibility criteria. Yet, I can't think of how many trials where you actually restart the trials.

It was not prespecified. I would take issue with that. I think it happened along the way. It was not a prespecified decision or a subgroup. It was something that happened and naturally happened. I don't take issue with that, but I would like to, I guess, reject the notion that there are two or three trials in this. I think there is a trial, one trial, with some very interesting subgroups.

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The first subgroup is the old criteria. The second subgroup is the new criteria. Perhaps the third subgroup is the new device, a later version of the device. But I think that the analysis that you present, I was not happy reading the written material.

I was not happy to see what you call the Runyan group not presented at all. So I was very pleased that in your presentation today, you presented that. One can always debate how many subgroups one should look at but I would submit that this represents one trial with 801 patients and two or three subgroups that are very interesting and clinically meaningful and that the overall analysis should start with everything you do, the 801 patients.

Present subgroups and argue your way down for those for whatever clinical uses you want to, but I think that the analysis, as presented, with just focussing on one of the subgroups, is selective and it would be inappropriate to not present everything as a starter, and present the adjusted p-values for that overall group.

DR. KUNTZ: I would like to make a few comments and thank you for your comments. We viewed this as one randomized trial to begin with. The nomenclature between the FDA and us has called them RCT1 and RCT2. We never agreed that that was a correct way to break this up. This

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is one single randomized trial and the conduct of the trial was run as one trial.

To 90 percent of the people, or 99 percent of the people. involved, this was a single trial and I agree that these are analyzable subsets more than anything else. As a matter of fact, we feel very strongly that this is an 801-patient trial and we are making the case that the subgroup that was analyzed as we have described should be the cohort, or the subgroup, by which we make the estimate of the treatment effect.

That is the argument. In so far as prespecified versus nonprespecified, clearly, we didn't prespecify at the beginning because we didn't anticipate the slow rate. On the other hand, there is something in between prespecified and a post-hoc analysis that we did hear because we did go forward with that.

Finally, the issue regarding why 551 is in there, why the 551-patient endpoint is in there. This is more of a regulatory issue than anything else. The initial data was filed on the data from the data-and-safety monitoring committee for regulatory reasons of 551 patients with full intention to throw in the run-on patients when they were agreeable.

So there was a body of information the FDA had initially which included the data-and-safety monitoring

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committee report to start the process of evaluation by the Food and Drug Administration with expectation that we would supplement them with the run-on patients.

We had always felt that the analyzable cohort, or subgroup, by which we would make this inference would never be based on the 551 but based on the entire 693 overall. So, because of the way things were filed and the timing it took because it was one or two months before we could realize the importance of the run-on patients, there was that time period where we actually had a group of 551 patients overall.

With respect to the adjusted p-values, we will do those. We did make adjustments on the actual sample sizes calculated using the alpha-spending function that we got.

DR. DeMETS: Okay.

DR. KUNTZ: And those were still quite higher than the net overall. So, if you are referring to the fact that the nominal p-values were based on those breakdowns, we actually went back and used the alpha-spending function under Wang and Tsiatis with Pocock 0.06 for the actual sample sizes that were enrolled.

If that is what you are referring to, we have done that. But that p-value was very close to the exact nominal p-values. I think it was 0.021 versus 0.020 at the second

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look. That has been adjusted for, so I am not sure if that what you were referring to.

DR. DeMETS: The last comment. When you talk about the issue of prespecified, it might be a better description to say it was done in a blinded fashion because it wasn't, as you said, prespecified but it was done blinded. I think that is more critical to describe what you actually did.

DR. KUNTZ: Thank you.

DR. DeMETS: I think that covers the main questions I have.

DR. KUNTZ: Thank you.

DR. TRACY: Dr. Vetrovec?

DR. VETROVEC: One mundane and one sort of theoretical question. The mundane one is when you plant to do training, do you see that as site training or do you see that as individual training and does each individual have to experience five cases, or are you going to replicate what was done in this trial where it is a little hard to understand the experience issue.

The question is, in a lab with ten operators, what is going to be the minimal number of experiences for the lab versus the individual operators?

DR. WAHR: That is a good question. I would see it as a blend. Definitely, you can't only educate the

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physician, train the physician, and you can't only educate the technical staff. However, once a physician, one or two physicians, are trained together in the presence of the staff, I do think that their experience can extrapolate to one, a new person being brought into the milieu, which makes the additional training at that point significantly less.

So, that is how I would characterize it.

DR. BAIM: I have a comment, Dr. Vetrovec. This device is a two-operator device, more than most others that we use, where the people at the groin and the person who is manipulating the adaptor and the inflation device have to work in concert.

I think the best way to look at that is one operator to do five cases at a site before the site is certified for independent activity. They may do those five cases with a variety of second operators and then each of those second operators should have to do a total of five cases in conjunction with the initially certified operator to get up to that point.

But many of the lessons that were learned in the trial can be taught with slides and not with patients in terms of the training period and many of the manual issues, in terms of the coordination between those two operators, can be taught on the bench instead of with patient issues.

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So my feeling would be that the lead operator at a site doing five cases would enable that site to move forward safely.

DR. VETROVEC: Just a comment, and this incorporates--I would be interested in your response to it, Warren's statement about long-term survival. It strikes me that that is going to be hard, perhaps, to prove here because these are going to be the sickest of the sick in many cases with a long-term outcome that is relatively poor for these patients anyway.

With multiple grafts, they are going to start getting into problems in other grafts. It would seem to me that the real advantage here is in the fact that you can get a patient through safely in the short term. I don't know that you can expect to see some major survival benefit long-term.

Any comments about that?

DR. BAIM: I think that beyond a year, certainly, one is looking at the natural history of disease and other grafts and other points in those same grafts that were intervened on, but, certainly, looking out a number of months, the influence of the procedure is somewhat greater rather than the natural history.

So, even at thirty days, we are seeing a very strong trend towards reduced mortality. It might be that,

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at three or six months, that that would reach significance but that was not the prespecified endpoint of the trial. It might be interesting to look at as an adjunctive analysis.

DR. VETROVEC: I have no other comments.

DR. TRACY: Dr. Aziz?

DR. AZIZ: Just a few comments and a few questions. At this stage, where most people are sort of using treponin as measure of myocardial injury--maybe the FDA and you could address that--why didn't you just use treponin as a measure of injury rather than going to CPK?

DR. KUNTZ: The use of treponin is not standardized yet across the sites. We have been interested in that in the last three or four years. At this point, we are probably getting right to the era now where we can use it now across the different groups.

It took us many, many years to find out what the standards were for CKMBs. As you know, they can vary significantly. We have a variety of ways to make sure that we correct for outlyers and normals. Some people have normals as low as 4 nanograms. Others, it is high as 15.

So we have done a variety of different ways to make sure that those outlyers are really not included in the trial. We take people that have more standard systems with the same kits. That level of sophistication does not exist

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yet for treponin, but my guess is probably sometime this year, we will make the switch.

DR. AZIZ: Do you have any idea--clearly, you are reducing the embolic load going downstream. Do you have any animal monitor or experimental model where you could say, let's say, if 80 percent of the embolic load is being captured, do you have any theoretical ideas?

DR. KUNTZ: Let me refer to Dr. Wahr. There is an evaluation done by Dr. Tarakoki at Albert Einstein using his carotid model.

DR. WAHR: I am actually going to speak to that this afternoon in a very short presentation, but, to answer your question, yes; there is data that shows the percent capture in a explanted carotid model.

DR. AZIZ: Maybe you should--obviously a straight tube rather than one of these curved-type things.

DR. WAHR: Yes.

DR. AZIZ: The other thing, clearly, I think you have targeted vein grafts that have one distal anastomosis. I am sure that, in the future, a number of--most of us surgeons do a lot of sequential bypass grafts. Do you have any ideas whether it could be used in that? What technicalities would you see as allowing you to use that in sequential vein grafts?

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DR. WAHR: I think it can be used in sequential vein grafts. However, it would depend highly upon the location of where the stenosis was and whether or not it is possible, it is feasible, to protect the side arm or the Y. For example, if the stenosis is proximal to the bifurcation, and there is room to seed the balloon proximal to where the graft bifurcates, then certainly you can do bifurcation grafts.

Similarly, if the stenosis is significantly downstream in one arm, then it may be feasible. If it is near the bifurcation and both arms are relatively large, then I think that is an area that we don't really know about in terms of protecting both arms of the graft. We do not have any information on using two devices in the same patient simultaneously which would be a way to protect both arms.

DR. AZIZ: The question of no reflow, though, clearly, the embolic load plays a role, there are a lot of humoral factors, obviously, that also play an effect in that. Do you have any thoughts as to what you could do to reduce the humoral aspect of the disease that predispose to no reflow in the use of this device?

DR. WAHR: In this system, which is totally occlusive, certainly the potential is there to remove humoral factors as part of the aspiration with the export

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catheter. But, obviously, we have--this was not an endpoint. We don't really have any data. There was no analysis of humoral factors.

DR. AZIZ: A couple of the patients that you selected, there is one on page 112 which seems like--I would just like to go with that case selection with you, if I may. This is a patient who is 74-years old who had had a CABG in 1980. Then he had, obviously, recurrent disease in the vein graft but he also had concomitant mitral-valve disease and aortic stenosis.

It seems that the plan of action here was to go ahead and first deal with the vein graft. That was done but then, a few days later, he went ahead and had his aortic valve and mitral valve tackled and I think things didn't go quite well and he had to be reoperated on.

In your mind, if you have a patient who is going to be reoperated on again anyway who has vein disease, why not do that patient, let him be operated on and have the surgery to tackle the valve and the vein at the same time?

DR. WAHR: I don't know the details related to that case, but, certainly, if two valves needed to be done, you would certainly do the grafts all in the same setting. There is no question about that. I suspect that, in that case, there must have been extenuating circumstances where it was a difficult call and there may have been a situation

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where the initial plan was to try and revascularize the graft and see if it would be enough to stabilize the patient.

But I am speculating. I don't know the details.

DR. AZIZ: If you had a patient who had vein-graft disease, let's say three or four vein grafts, would you advocate that one of the vein grafts be tackled by this technique and then let the patient go for surgery?

DR. WAHR: Probably not unless there was a situation where, potentially, and this is speculation, that it was a distal target that the surgeons felt might be very difficult to revascularize and that they would want it done for that purpose. But that would be very unusual. I would imagine that most of these people would just be regrafted at the time.

DR. TRACY: Any additional questions before we go on to the FDA questions? Dr. Laskey?

DR. LASKEY: One more that made me think about this. The second bullet in the Indications and Use in your insert says, "To subselectively infuse and deliver diagnostic or therapeutic agents with or without vessel occlusion." How often was this done? To whom? For what? Differentially? Equally? Effect on outcome? Should we ignore it? How can you make that claim in your packaging if we don't have the--

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MS. HINMAN: Let me speak to how that came about. Prior to the establishment of the SAFER trial, we had approached the FDA with some registry data referenced by doctor-lab, the one center, 24 patient-27 lesion study, some animal work, some bench testing, and made a substantial equivalence argument for removal of embolic debris. That was quite a while ago.

At the time, after lengthy discussions, the agency felt that a, there was not a predicate device for what we were asking; b, there wasn't enough known about vein-graft intervention with specific focus on removal of embolic debris and any associated clinical benefit. Accordingly, if we wanted to pursue that labeling claim, then we would need to have the construct of a randomized trial and a premarket approval application.

They also expressed some concern that we had presented some predicate devices for additional labeling claims, the one you just cited being one of them. Their concern was that if the clearance was given for a limited indication--i.e., subselective infusion of diagnostic or therapeutic fluids--that that would, indeed, be detrimental because there was be too much off-label use and we would never really get to the heart of what is the true treatment benefit.

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So, in negotiation with the agency beginning of August of--well, actually, in 1997 and concluding in August of 1998, we reduced our labeling claims for what we initially presented to the subselective infusion of diagnostic and therapeutic fluid with or without vessel occlusion under the constraint of a 510(k) and then, in agreement with the agency, pursued a randomized trial with the full intent of assessing the disease category and the indications that you have seen today.

So, in doing so, we elected, as a company, not to place the device in commercial distribution under this limited indication because we didn't want to erode usage in the trial. We really wanted to look at the treatment benefit that we were after. That is the background history. That is where that phrase came from. It is based on literature predicates that are reflected in K97277.

DR. BAIM: But, clinically, the device has not been used in many of these cases for infusion. If it were used--in the cases in which it was used, I should say, it would be most appropriate for giving calcium channel blockers or nitroprusside or adenosine in the distal graft to treat no reflow, which was reduced in incidence in the trial with GuardWire.

But if that did occur, it could be infused through the export catheter as well as it could through any other

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infusion or a balloon-catheter central lumen. But, in terms of the trial, it really was not a common situation.

DR. VETROVEC: Could I make one other comment about the labeling? I notice that the indication for this is for coronary saphenous-vein grafts and yet, as you go further into the details, it talks about prepping the PTA, PTCA, or stent-delivery catheter which suggests use in a peripheral connotation. There is some inconsistency in the proposed--

DR. BAIM: I think the issue, Dr. Vetrovec, is that at the time when this study was going forward, the availability of large-diameter coronary balloons and stents was limited. That is one of the situations in which interventional cardiologists, as you know, tend to use devices designed for the periphery in the coronary, is to deal with these 5- and 6-millimeter grafts.

So, the intent of that is for the treatment of saphenous-vein grafts and not a surreptitious attempt to gain control of the rest of the body.

DR. TRACY: One more question.

DR. AZIZ: One more question. Going through the patients, the ones that had complications, there were, I wouldn't say a large number, but a fair number of patients who had a fair drop in their platelet counts, I mean, down to, like, 39, 25, et cetera.

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Was there a high incidence of hits, or did you look at the hit syndrome in these patients and, if you did have a patient who preoperatively you know had a sensitivity, or an allergy, to heparin, what would you do?

DR. BAIM: Remember, 60 percent of these patients got a IIb-IIIa receptor blocker. Those are also prone to cause thrombocytopenia and above hits. There is no reason to think that the heparin-associated thrombocytopenias would be increased in this group and they are very low incidence in general.

DR. TRACY: We will move on to the questions posed to us by FDA. I would ask people to try to be as succinct as possible since we are running kind of late at this point.

MS. MOYNAHAN: Just a point of procedure here, normally, during this part, this is a chance for the panel members to discuss among themselves the FDA questions. I know I can't ask you to step back, but they won't be necessarily asking you questions unless the chairperson thinks that that is necessary. Thanks.

DR. TRACY: The first question that they posed to us has to do with the two subportions, the RCT1 and the RCT2, with patient-selection criteria in RCT1 requiring that patients have the maximum of two lesions whereas RCT2 required patients to have one or more lesions with a single saphenous-vein graft, lesions located in the proximal, mid

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or distal with some restrictions in terms of how proximal or how distal.

The intent of this change was to allow more complex multiple or diffuse lesions to be treated in RCT2. The question posed to us is, please discuss whether there are any substantial differences in the lesions treated in RCT1 and RCT2 that could affect the poolability of data.

I would just remind us that the only difference that came across, really, in table 2 was the amount of calcium seen in RCT2 was higher than in RCT 1. Any other comments from the panel?

DR. VETROVEC: What has been stated is that the RCT1-type lesions appear in RCT2 so they are not excluded in the second. So I think, from that perspective, they are poolable. The odds are that they are older grafts in RCT2, the majority of them are older grafts, and might help explain the calcification. And the total lesion length is longer, or the diffuseness of disease, at least.
But I don't think that excludes pooling them.

DR. KLOCKE: I think that that--I was attracted to Dr. DeMets suggestion that there is really one study with the two or three subsets within the study.

DR. TRACY: Additional comments on that, Dr. DeMets?

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DR. DeMETS: I think the point that was made is that some of the patients in so-called RCT2, the criteria applied is from RCT1. So I think the subgroup is those kind of patients that that are represented in RCT2, all the way through, is a subgroup of a certain level of risk and another group is the complement of that.

So I would like to reject the idea of RCT1 or RCT2 period.

DR. TRACY: I'm sorry; reject--

DR. DeMETS: The idea that these--it is a very artificial split. I think there are more logical splits like risk groups represented by the early criteria versus the later criteria.

DR. TRACY: So I think, in summary, there appears to be inclusion within the RCT2 of the same type of patient and the question would come whether it is legitimate to make separate subgroups at all or whether it should all be pooled.

MR. DILLARD: Could I just add one question, if you wouldn't mind just particularly keeping that in mind when we get to some of the labeling questions and how we might represent the data, if you wouldn't mind commenting on that, too.

DR. TRACY: Question 2, a substantial difference in 30-day MACE rates was noted in the control arms of the

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SAFER trial after inclusion-exclusion criteria were modified. After the entry criteria were changed, the control MACE rate increased from 10 to 20 percent. Review of demographic and angiographic data between RCT1 and 2, however, did not suggest major differences in the populations being studied.

Question 2, please comment on this difference in control results. Are there any other methods that should be used to assess interventional risk in the diseased saphenous-vein graft.

I certainly would think that the age of the graft would be important to look at.

DR. VETROVEC: I think is probably the predominant issue to look at.

DR. LASKEY: Also Rick mentioned that, for purposes of discussion, in 2 versus 1, you change the cutoff for the CK entry--that is, 72 hours to get into one and 24--now, lesions often accompany patients. Ugly lesions occur in unstable patients so there is more to just lesions here. There is clinical background so, perhaps, it is worth a closer look at looking at what these CK cutoffs--in other words, if the periinfarct patient, 24 hours remote from the event, who is still potentially ischemic, may or may not be--my belief is he is at higher risk than some 72 hours out.

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So things like that need to be look at particularly if they turned out to have more than a blip on the radar screen.

So what was the effect of the changing CK entry criteria on the clinical profile of the patients in terms of their periinfarct state.

DR. TRACY: So two factors, really, the clinical significance of the CK change in RCT1 versus 2 and the age of the saphenous-vein graft I think should be looked at in a little bit more detail.

Question 3, the background, a total of 1104 patients were enrolled in the study. The submission includes data for 979 subjects. 551 of the randomized subjects were enrolled after a change in the inclusion criteria and are the basis for primary analysis. Of the 551, 273 randomized to GuardWire arm and 278 to the control arm.

Data presented are based on the interim analysis and do not include the subjects that enrolled near the end of the trial. Although several interim analyses were planned in the study protocol, these analyses were not executed as originally designed and the FDA has not formally agreed to the sponsor's revised analysis in which the first 142 enrolled patients in the trial were excluded from the primary analysis.

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Question 3, considering both the planned a priori and realized post hoc interim looks at these data, do you have any recommendations regarding the following questions; please discuss the type 1 error values that should be associated with each planned or realized look. These values must assure an overall study type 1 error of 0.05. Their values may not only impact on the results of the hypothesis test but may also change the widths of the reported confidence intervals. These changes could influence the evaluation process in the labeling and please discuss whether the 142 patients enrolled prior to the change in the inclusion criteria should be included in the primary analysis. If not, which patient cohort should be the primary analysis cohort?

I won't even to begin to try to answer this question.

DR. DeMETS: Are you look at me?

DR. TRACY: Everyone is looking at you.

DR. DeMETS: I think I would sort of try to respond to this question in my earlier remarks. Actually, the preamble to this question how many patients, I really think the relevant number of patients is not the 1104 or even the 979. I think it is the 801. The role-in is interesting, but it is not relevant to the comparison.

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So I would focus on the 801 being the primary analysis of the study overall. As I said, there are some interesting subgroups that one could look at, some of which we have already discussed. I believe you would start there. The sequential boundaries which were presented I think, in fact, do control the type-1 error at the 5 percent level. In fact, that is the way the trial behaved, as if they were always operational.

So that is fine. The issue, though, is, at the end of the day, I presume that the statistic would have crossed that boundary at the end, at least, and perhaps gotten closer even earlier on. But once you are at the end, there are two issues; what should be confidence interval be and what should be p-value be?

My guess is that the confidence interval would be different but not much. If you just do a nominal conventional garden-variety confidence interval, it would have a certain length. If you adjust, it would change somewhat but not by a lot and the issue of the p-value, I think you can quote the nominal p-value and that is fine as long as it is referred to as nominal, but it would probably be a good idea to quote the adjusted p-value just to show that it is different by some and, perhaps, not much. So that would be worthwhile.

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The issue of the 142, I think that is an interesting subgroup to look at but, more interesting to me, is the patients in the entire cohort of 801 patients who are reflective of that risk group as defined by the early criteria, because you want to know does this therapy have an impact and that risk for the patients across the entire 801 for that time period.

So I would not get too wrapped up in the 142. The fact that it was done blinded by the investigators and the sponsor with no involvement from the DSMB, I think, give us a good basis to go that direction.

DR. TRACY: Any other comments for that question? If not, we will move on, then, to question 4 which refers us to table 7 which is on page 36 in section 5, site-pooling analysis. That table, and the summaries that follow, identify the device failures and malfunctions that occur during the study.

Question 4, please discuss the clinical importance of the device failure and malfunction events in the evaluation of the safety and effectiveness of the GuardWire system. I think that the panel questions have all tried to get at exactly what were the impacts of these device failures.

I know we have the graph that shows that the major adverse events were lower than in the control group but I

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still haven't heard a crystal-clear description of what the adverse events were in, say, the class 3 device failures. That would be the only thing that I would have additional questions regarding although it is fair to say that it did not impact overall when looking at the entire group.

Any other comments from the panel?

DR. LASKEY: I don't think it is unreasonable to say that modifications need to continue to the be made, that a device which has upwards of 1 out of 3 failure-rate, malfunction rate, dysfunction rate, whatever you call it, may engender a sequence of events for the operator irrespective of it being trivial or not.

For example, if you have a device and something happens that is of a trivial nature but, you know, operators are human beings, too. They get flustered and you have a device and you are doing a new procedure and--there is a whole sequence of events--there is a psychology of this procedure as well as a science.

You look to have a predictable device. I just personally think something with one out of three could be improved on, irrespective of how serious or not the MACE rate is.

DR. TRACY: I would agree with that. I think that it is going to be vital that there is very adequate training of people who are new to this device to try to clue them on

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what the expected types of problems would be and that could be handled. I think largely in that fashion that additional refinements on the device are probably needed as well.

Question 5, based on the data submitted by the applicant, please discuss whether the benefits of the distal-protection device in this patient population outweigh the risks associated with the use of this device.

My sense is that the sense of the panel is that yes, it certainly outweighs the risk.

The next issue is dealing with product labeling, one aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify the product's potential adverse events, and explain how the product should be used to maximize benefit and minimize adverse effects.

Please address the following questions. 6a, based on the data from RCT1 and 2, as discussed in question 2, do you recommend that the device be labeled for use in all saphenous-vein-graft lesions. Please comment on the Indications for Use Section, page 2, as to whether it identifies the appropriate patient population for treatment with the device.

DR. DeMETS: Can I make just one more comment about RCT1? It has been my experience that the first

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patients in a trial are never typical. I don't care what trial you do, drugs, devices. They are just different. Second of all, this is a very small group. I don't know what RCT1 tells me because it is based on a dozen to a dozen-and-a-half events.

So it is just standard that those patients are not typical and, two, it is very small events. So we can't say too much about that experience. I think the more interesting question is what does that subgroup look like across the entire strip. I don't know the answer to that question, by the way, because we don't have an analysis.

DR. TRACY: It would be my sense, though, that, regardless what they look like across 1 and 2, that the overall data would support using it in all types of saphenous-vein grafts whether you are talking about a maximum versus a minimum number of lesions.

So I would think that the answer to this was that it is appropriate for use in all saphenous-vein-graft lesions until we have a better way of identifying those lesions which are somehow more likely to have no reflow. But I don't think we have the parameters to look at at this point that would tell us that.

So I think from what we know at this point, the answer to that would be that it would be appropriate for all saphenous-vein grafts.

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DR. LASKEY: They did go through the--it is not suitable for osteo, it is not--so, does that have to be reflected in the labeling in so many words, as well?

MR. DILLARD: It is not uncommon for us, based on what the inclusion-exclusion criteria of the trial will be, to certainly include that in the clinical section to the Manual or the Instructions for Use. So I think that our preference would be that it is to contain that in some summary section of the clinical study.

DR. TRACY: It is, in fact, "The GuardWire Plus is not recommended for use in osteolesions," is under the warnings. There is no mention, however, that I saw regarding the distance on the distal lesions which was 20 millimeters in the study. That, I would think, needs to be included somewhere.

DR. CRITTENDEN: What about indication No. 2 about the infusion of--what was it now?

DR. TRACY: "Subselectively infused delivered diagnostic or therapeutic agents with or without vessel occlusion."

DR. CRITTENDEN: I am not satisfied. Maybe I missed it completely that we have data to support that. Are we comfortable with this? Am I the only that had some discomfort with this?

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MR. DILLARD: I think the company gave the long version to why that is there. Let me try to give the short version which is it is already legally marketed for that indication for us. So my expectation would be that you do not have to address that at this point.

DR. TRACY: 6b, please comment on the contraindications as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit. I don't think that we heard any specific contraindications come up in this discussion.

6c, please comment on the Warnings and Precautions Section as to whether it identifies all potential hazards regarding device use. The only additional things that--I forget which of the sponsor mentioned, but the concept that "Increased CK, following percutaneous intervention, has been associated with increased mortality."

The person recommended that myocardial infarction be placed somewhere in this. It is, in fact, listed as an adverse event. So I think that is covered there. I don't know whether it is a warning or a precaution or just a general statement to say something about the need for expert training in the use of this device.

Are there any other comments from the panel?

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DR. VETROVEC: I would support that. There is nothing that I could find in here that suggested that the operator who uses this has to be trained in it. I would assume that that would be a regulatory issue.

DR. TRACY: I don't know whether it is critical to say this, but these were all patients whose EF were around 45 percent. It has not been tested in a lower EF patient category. That might also be commented somewhere in the data.

6d, please discuss whether any improvements could be made to the labeling to help minimize the occurrence of device failures and malfunctions as discussed under question 4. I think we have talked about that, the need for physician training and other issues that we have just discussed.

6e, please comment on the remainder of the device labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events. Any additional comments that anyone has?

DR. LASKEY: Carefully.

DR. TRACY: Carefully. The device should be used carefully.

6f is kind of a global question, do you have any other recommendations regarding the labeling of the device.

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I think we have really stated what our additional comments would be on that.

Question 7 has to do with the training program, the summary of the physicians' training program has been provided in section 7. Please discuss any improvements that could be made to the training program to help minimize the occurrence of device failures and malfunctions as discussed under question 4.

I think the way that Dr. Baim sort of indicated a sequential training of a primary operator with a number of secondary operators and then training within the center from that primary onwards seems to be a rational approach to this. It does seem like something that, once a certain degree of expertise is gained, that that knowledge can be passed on. I don't know that I would have any other specific comments to make on that. Anybody on the panel?

DR. LASKEY: Is it our purview to ask the following--I am going to ask it anyway, but is the company willing to stand behind the commitment not to sell these devices to sites that have not gotten their report cards?

MS. HINMAN: That have not gotten what?

DR. LASKEY: Their pass rate on their--

MS. HINMAN: Correct. There will be a tiered roll-out.

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DR. BAIM: I think the question is, until there is an operator at a site that has five cases completed with proctoring that device availability would be limited to procotored cases. Is that the way you are--your intent? You wouldn't sell a carload of devices to a place that had not been proctored.

DR. TRACY: I think that would be important to adhere to that.

7b, please identify any other important elements that should be contained in the physicians' training program for this device. I think we pretty much have covered those issues. Any other comments by the panel members?

Then I will ask Mr. Dacey or Mr. Jarvis if they have any comments they would like to make at this time.

MR. DACEY: Not at this time.

MR. JARVIS: Not at this time.

DR. TRACY: Any additional questions or comments from either the FDA or the sponsor?

MR. DILLARD: None from the FDA, either. Thank you.

MS. MOYNAHAN: Before we break, I just have a couple of procedural things. When we break for lunch, they are going to open up that back salon so there will be a lot more space when you come back. Any people who are requesting time to speak at the afternoon open public

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session, if you could come to me and I will make sure that your handouts get passed around.

DR. TRACY: Since we did run over a little bit, let's try to regroup here at 12:45.

[Whereupon, at 12:00 p.m., the proceedings were recessed to be resumed at 12:45 p.m.]

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A F T E R N O O N P R O C E E D I N G S

[12:50 p.m.]

Open Discussion Session on Clinical Study Design Issues for Distal Protection: Devices Used in SVG Disease

Call to Order

DR. TRACY: The topic for discussion this afternoon is clinical study design for issues for distal protection devices used in diseased saphenous-vein grafts.

We will be starting with the second portion of the open public hearing. There are number of speakers who have requested time this afternoon. We will be going in order as described on the back of the agenda.

MS. MOYNAHAN: Just a couple of procedural points here. For speakers who are stepping up to podium, if you could state your name and your affiliation, and for those of you who are not affiliated with companies, if you could describe briefly any conflict-of-interest issues; for example, if you have stock options or stock ownership, whether your travel was paid for by a company, whether you are receiving any honorarium to speak or if you have been involved in a clinical study of these types of devices that is being paid for by a company.

DR. TRACY: Dr. Kuntz?

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DR. KUNTZ: My name is Rick Kuntz. I am an interventional cardiologist at the Brigham and Women's Hospital.

[Slide.]

I would like to use my ten minutes to talk about the difficulty of doing single-arm studies for embolic-protection device evaluation.

[Slide.]

How do we evaluate new embolic-protection devices? This is a prescient issue at this point. The problem are, one, a superiority placebo-controlled randomized trial is needed to confirm the safety, feasibility, value and utility of embolic-protection devices, in general, and new devices, in particular; that is, we really have to confirm the evidence that we have seen today that embolic-protection devices are a mainstay of therapy for vein-graft because the results of a singular randomized trial are not necessarily confirmatory.

The availability of an approved device makes randomization to placebo control ethically difficult. We have heard about some of that; that is, once the belief of the operators that a device is available that can reduce complications which, in these cases may even be mortal complications, is available, it is very difficult for many

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operators to participate in randomized trials in which they randomize patients to control arms that are placebo.

The believe that the approved device is the standard of care may occur earlier than the feasibility of using the approved device as a standard control; that is, we may, today, have a strong belief that this device is the standard of care. However, the device still isn't marketed or distributed and, therefore, there is a window period in which individuals would feel uncomfortable randomizing patients, even though the standard of care is not available.

[Slide.]

What are the conventional solutions, especially in our field? Immediately, in our field, single-arm registries have been used commonly in the stent arena where we look at the results and we compare them with the results of historical controls.

The other is noninferiority randomized trials against approved device; that is, if we wanted to preserve the randomized-trial format and felt it difficult to compare against placebo, we would compare it against the approved device.

[Slide.]

In this time line, I have demonstrated, I think, what I think might be some problems associated with trying

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to initiate a trial as of today. In the upper corner is the time line from January in the 2001, January, 2002 and January, 2003.

A placebo-controlled randomized trial could be initiated now. If we use PercuSurge as a device that could be approved for general use under this label, that approval might be reached sometime in March or April, being practical. No predictions, but just practically speaking, it could be.

The marketing and distribution for that device, especially beyond those familiar, might take a few months so that, by mid-second or third quarter of July of 2001, we might start the dissemination of the availability of device. The wide acceptance of the device--that is, full marketing and distribution and use where it becomes a standard--might not occur until the first quarter of Year 2002.

The demand already exists for an equivalency randomized trial; that is, that there are those out there saying that it is impossible for us to randomize against placebo even though the device is not approved formally for this indication, even though the device is not available, marketed or distributed, and even before wide acceptance occurs.

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Therefore, the feasibility of doing and equivalency randomized trial may not actually occur until the first quarter of the Year 2002 because you certainly would not want to do a randomized trial against a device in which people are trying to learn how to use the control. The control, therefore, might be a straw man with respect to its complication rate if there was a learning curve or it takes time to train people, as we have talked about earlier.

So this difference between the demand for not doing placebo-controlled randomized trials or equivalency trials in the top red line there to the feasibility of doing one is a window in which we have to deal with alternative ways of evaluating new treatments which are coming to the fore even today.

[Slide.]

Let's look at this problem with conventional solutions. We talked earlier that the conventional solution of a single-arm registry compared with the results of historical controls could be used because that has been used previously for devices. The expected outcomes are case-mix sensitive, to be sure, and there is no current available risk model; that is, while the randomized trial reigns supreme in any evaluation, the use of a registry should really be used for selected cases in which a wealth of data

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is available for us to make a decent risk model and predict the outcomes.

Secondly, what about the equivalency trial? If the preliminary RCT is erroneous--that is, say, for example, the results of the first trial are purely by chance, which is very low in this case because of a p of 0.001, the new candidate devices will be compared against a device of limited value.

This happens with any approved device. If there is a small change in all the criteria or whatever, one would like to have more than just one randomized trial to establish something as a standard from here to the end of time.

The sample size required to show equivalence for a device expected to have low complication rates is also large assuming that we use a reasonable equivalency delta. What I mean there is that, under a randomized trial against placebo, the base-case rate is 20 percent. One can show reasonable treatment effects, as was shown earlier, with that base-case rate and get a sample size below 1,000 patients.

If we are trying to show equivalency with a base-case rate of approximately 9 to 10 percent, unless we have an overly large equivalency definition of delta--that is,

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the range at which you can alter the difference between the two groups and still call it equivalent, the sample size will be in the thousands.

[Slide.]

We showed earlier today that, in fact, it is impossible, I think, to use the historical literature to predict the outcomes from a registry or new embolic-protection devices.

This is a slide that I used earlier this morning showing the wide range of outcomes in the control arm associated with vein-graft MACE rates all calculated presumably the same way.

[Slide.]

So, in order to evaluate and look at OPCs for SVG device evaluation, one would have to conclude that the wide range of vein-graft clinical outcomes following these therapies requires case-mix adjustment for precise expected outcome predictions. Lack of current scalable covariates on which to build a predictors model makes derivation of a precise expected model impossible.

Finally, randomized trials are critical for the evaluation of SVG devices with that conclusion.

[Slide.]

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One could envision developing a saphenous-vein-graft risk model. In the very least, one would have to do a retrospective review a consecutive cohort of seven vein-graft interventions with proper collection of covariates, CRF, and we would clearly have to test new angiographic covariates for potential risk prediction.

One would then have to develop a robust multivariable predictors model, maybe in the first sense using a bootstrap or some approach to try to shore that up and then, secondly, you would have to test this against a second new cohort; that is, we would use the predictors model and do a new cohort retrospectively of consecutive cases and see how the model fit.

If successful, we could combine the data in order to develop a robust predictors model for estimating the beta coefficient estimations, and we could use a variety of different methods, predictors models, in order to shore up those predictors.

But this protocol would be the very least required in order for us to develop a risk model if it was impossible to do randomization. This has not yet been done.

[Slide.]

One of the other issues is to deal with the problem of doing a randomized trial in which we look at

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superiority in a limited time frame for which we can actually do a placebo-controlled trial. So let's review the conventional trial approach to hypothesis testing.

Generally, when we look for superiority, we have a null hypothesis that treatment standard equals treatment experimental. The alternative hypothesis is, in fact, that the experimental therapy has a lower rate, for example, than the standard therapy if we are looking at MACE to try to evaluate, say, for example, one of the alternatives in a two-sided hypothesis to prove that the probability of them being equal is quite low, showing benefit for the experimental device.

Sample size is calculated, therefore, so that the study is sufficiently powered to detect some difference of delta and using a binary endpoint that delta is correlated with the size of the sample given the base-case rate.

[Slide.]

We are all familiar with equivalency trials because they have been done in the coronary-stent arena. In that situation, the null hypothesis is actually that the experimental therapy is the same or worse than some standard, which would be an approved device, plus some delta and the delta represents the zone of comfort that one has

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saying that any devices that occur within this zone are somewhat equivalent clinically.

An alternative hypothesis would be that the experimental therapy is less than the standard rate and its delta. This is the classical Blackwelder formula in which the alpha error required to reject that null hypothesis is usually somewhat around the same level as the delta and gives us sample sizes in coronary-stent trials of about anywhere from 500 to 1,000 patients.

The quantity delta must be sufficiently small so the two therapies are considered equivalent for practical purposes. In the case of looking at rates, not like 20 or 30 percent in restenosis studies, but 10 percent. Comparing it with the PercuSurge device, for example, sample sizes are going to be in the 2,000 to 3,000 range.

[Slide.]

Here is a schematic of the equivalency definition. In fact, we show the null hypothesis here. We can make an inference about the fact that there is going to be some rate--the standard complication rate is shown as pi, sub s. The delta is shown as the bar above. We try to show the null hypothesis places the rate of the experimental in that zone to the right of the pi, subgroup s, plus delta.

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Our alternative hypothesis is that it is less than that line to the right--I don't have a laser pointer--and, ultimately, the difference between that line and what we actually achieve is the alpha error of the study and, with enough power, we can show those differences if we all agree that the standard therapy is the conventional therapy and delta is a reasonable number.

[Slide.]

One proposal might be to consider new clinical-trial designs. We have played around with a few ideas in order to deal with this probably that we have right now in the Year 2001 where we want to preserve the randomized-trial structure but, at the same time, allow patients to be enrolled ethically in a trial.

So a variety of proposals, I am sure, will come to the FDA over the course of the next few months and I would just like to show you some preliminary ideas we have in which we are working with the statisticians at Harvard to work out, which, potentially, could be an answer although, still, very unconventional.

Can a superiority RCT be combined with an equivalency RCT; that is, can we take a superior randomized trial and commence the analysis, or the trial, and then

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switch the control group to an approved device when poor recruitment and ethical issues dictate.

[Slide.]

Here, what we would do, is have a probability statement that, in fact, we would have the rate of the new active arm minus the placebo arm rate would be greater than or equal to some constant, which is flipping the superiority hypothesis, and that the rate of the active arm minus the rate of the approved arm is less than or equal to some constant which includes the delta for equivalency.

So, what we have done is we have made a probability statement given the data, given the null hypothesis, and we would say that probability would be less than 0.05. What this states is that one potentially could do a trial in which the randomization continues, the active arm stays the same and we would be able to change the control arm and make a combined multiplicative probability statement about those and have the final p-value be less than 0.05.

[Slide.]

In this hybrid trial, one could envision starting the trial now; that is, I think many sites feel comfortable randomizing placebo. But, sooner or later, in the next few months to maybe the end of this year, there is going to be

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more and more interest in not using placebo as the control arm.

In fact, if we reach some point where the trial is not finished, the trials will grind to a halt. So, at this point, we might consider something like this to switch over to an active controlled arm.

[Slide.]

This design is just an offering. It allows initiation under placebo-controlled superiority trial design. It would allow switch to an approved device-controlled noninferiority RCT design, but it could be determined on each site by a site-by-site basis; that is, whenever they feel that the superiority trial cannot continue because of the ethical dilemma of randomizing as placebo, that they could then consecutively switch the falling patients to an approved arm.

It maintains a randomized-controlled trial structure and the active randomized trial throughout. Group sequential analysis could easily be applied to this probability statement over time.

[Slide.]

There are many assumptions that would have to go along with this proposed trial. One assumption is that there is an equal interest between the superiority result

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and the noninferiority result; that is, that we are equally interested in showing that we are better than placebo as well as we are in showing we are the same as an approved device because there may be different amounts of proportions of each at the end of the statement.

The noninferiority approved device result should be compared with prior results for validity purposes as in all noninferiority trials; that is, we would like to make sure that, when we look at this new device, the approved device acted the same way as it did in a similar dataset or, in this case, the SAFER trial, to make sure that there wasn't any variance. Otherwise, a device that performs poorly could be compared to a new active device that has no value and show equivalence. This is true of any equivalency trial.

Finally, the interpretation of the device is essentially one of equivalency to a device shown to be superior to placebo. While the interpretation may be somewhat complex, I think that, more and more, we may have to consider some alterations in randomized clinical-trial design to deal with this dilemma we are going to have over the next year or so before a device like this one is fully rolled out and available to act as a active-controlled arm for an approved device.

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[Slide.]

So let me finish with this tentative presentation about a very complex subject by saying that the current evaluation of new embolic-protection devices is problematic There is no question in my mind that randomized controlled trials are required. Placebo controls will be difficult, to be sure, because of the ethical dilemma in patients who will not be randomized to an active treatment and believed to be superior in the minds of interventional cardiologists.

Retrospective data analysis of risk models might be constructed--that is, if we can't do randomized trials at all, we would certainly have to go to some level like this, but they would have to be done under very strict conditions with an initial predictive subset and a testing subset, essentially a second cohort, in order to test the robustness of the model.

Finally, conditions like the hybrid randomized-trial design might be considered to preserve the randomized-trial structure and to continue the evaluation as needed for devices that are being evaluated as of now.

I will stop there for any questions.

DR. TRACY: I would like to remind people that only myself and the members of the panel can ask questions during this open public hearing. I would like to see if any

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of the members of the panel have questions for Dr. Kuntz. Mitch?

DR. KRUCOFF: I would just comment that I think you are right, that we are going to have to look for some modification of designs to handle this situation. I would agree with you that the registries, while useful, are never definitive. If we rely on them, we should understand what risk we have just taken in terms of approving something or using something on the basis of that kind of data.

I would also point out, there is a sort of ironic twist to this. If you settle on some absolute delta and use absolute rates, one of the answers is that the lower the event rate you have, the better. Pushing it to the extreme, if you had no events, you win.

DR. KUNTZ: Right.

DR. KRUCOFF: There is something wrong with that thinking. So you want to switch everything you have just said to a relative scale. If you put it on an absolute scale, you get into a mind-boggling twist where you want to have power but the answer is no events is better than a few events which is better than a lot of events.

So don't put it on an absolute scale. Put it on a relative scale.

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DR. KUNTZ: That is a good point that the delta becomes a bigger proportion as the rates gets smaller.

DR. DeMETS: That's right. The last thing that I would make is that the issue of the inference of it, is your new therapy better than a placebo which you didn't test, is really a tough one. There are several examples of consecutive trials on similar patients where, let's say, that the treatment group in the first trial does as well as the placebo group in the second trial and the inference there would be that placebo wins, the second placebo was a good treatment.

So this idea of this inference back to some historical treatment versus placebo is really fraught with problems. I don't know what to do about it, but we should also recognize that that problem is there.

But you are right; we have got to think, think, think.

DR. TRACY: Dr. Krucoff.

DR. KRUCOFF: Rick, as always, thinking, coming from you guys, is elegant. I guess what I am sitting here trying to convince myself of, though, is that if what we are really talking about, as we know, is now not the life cycle of a single device but it is the life cycle of multiple devices. As one becomes the standard and another one is

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evolving toward a new application, what is the active control issue versus placebo control issue for the evaluation of the new incoming device.

Is a statistical plan, per se, in a very fast-moving area like this one, going to be the right answer? I am actually not sure. I think your proposal is a fascinating one, statistically is a fascinating one.

But when it really comes down to specific clinical trials, is that proposal going to really look and feel as adequate as these various life cycles move at different paces or as event rates in, say, native coronary application are at one end of the spectrum and vein grafts at another, acute coronary syndromes at another.

I begin to feel like are we going to propel ourselves into elegance that actually makes everything more complex to really know where the truth is, or should we sort of stick with where we are now which is trying to not essentially plan the obsolescence of the trial design with a statistical model but try and do good clinical trials capturing the life cycles of the already approved devices with the incomings as best we can, and then falling back, as I think is sort of the norm now, to a steering committee, a data safety committee, the FDA, ongoing negotiations that, if we get to a point in a trial where there is an ethical

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issue or lack of enrollment in the trial because of the perceived ethical issue, whether the one-by-one problem solving approach that is sort of the current methods, which is what you would love to overcome, is overcomable by a statistical formula.

I am intrigued. I feel a little concerned that essentially a statistical approach to planned obsolescence of a superiority randomized clinical trial may be opening up as big--a new set of problems as it is solving current ones.

DR. KLOCKE: Those are good points. I think that we have a session at the ENR meeting, which is a statistical meeting in March, to address this issue of the quicker time to horizons and life cycles of new devices and the fixed time it takes to do a randomized trial.

As a matter of fact, if we use some of the ideas promoted by Richard Peto that, as technology advances, the delta increments between technology is smaller and smaller requiring bigger and bigger trials, we may be in a situation with two competing issues. One is the requirement for larger, longer randomized trials to tell the difference, the smaller differences of technology, which is actually being rolled over faster and faster.

So it is a big issue. I think we do have to consider other statistical designs. Some of the even more

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outlier designs are to use Bayesian approachs to try to develop large-scale prior distributions where we can use a variety of different inputs as to whether the new data can be updated, the likelihood it can be updated with the prior data, and the inference can be made on the posterior distribution--there are lots of problems with that because it rubs frequentists the wrong way.

But I think that there are a lot of ideas that will have to come forward to deal with this clear-cut conundrum of rapid turnover in new technology that makes important advances in patients and the fixed nature of a good randomized controlled trial.

DR. KRUCOFF: Although the other one of Richard's credos that may be very pertinent here is the push to return to the simple clinical trial.

DR. LASKEY: One other variable, Rich, is things are turning over rapidly but we always seem to get better from year to year at what we do. Even rates seemingly defined in a similar fashion drop. We are just better at what we do every Q2 years. So how do you figure that into the mix?

DR. KUNTZ: I think that, probably, the result of being better has been the result of having good structured randomized trials. I think that it is often difficult

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anecdotally to figure out what is working. All of us know a bunch of devices that we may have liked that ended up not panning out in randomized trials.

I think, largely, our field has practiced evidence-based medicine to a large degree. I think what we are looking at, in the next year or two, is going to be a real crunch that we never saw before. I think that this advancement of new technology, which, through miniaturization and other techniques, really is going to try to compete against the pace of what we have seen in the past in the performance of randomized trials.

DR. TRACY: Thank you.

Dr. Baim?

DR. BAIM: I waive my presentation.

DR. TRACY: Dr. Wahr?

DR. WAHR: My name is Dennis Warh. I am an interventional cardiologist at Michigan Heart and Vascular Institute, Ann Arbor, Michigan and St. Joseph Mercy Hospital. I have nothing to disclose, as stated this morning.

I would just like to say a few words about thoughts differentiating balloon-occlusion technology and filter technology.

[Slide.]

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If we just look at the basic concepts, here--if you take balloon occlusion, with balloon occlusion, you inflate the balloon. You have complete, but temporary, interruption of blood flow into the distal capillary bed. This, in theory, prevents migration of all embolic particles regardless of size during the intervention. These particles are then aspirated prior to deflating the occlusion balloon.

In the case of filters, a mesh is deployed. However, some flow is preserved into the distal capillary bed. This prevents the migration of large embolic particles larger than the size of the pores in the filter. The larger particles are captured within the mesh and the filter is then collapsed for removal.

[Slide.]

This results in some very different mechanisms of action. In the case of balloon occlusion, balloon occlusion is not sensitive to the size of the particles. Obviously, in the case of the filter, there is great sensitivity to the size of the particles.

With balloon occlusion, you subsequently, with the extraction catheter, actively can remove thrombus. In the case of a filter, removal of thrombus is passive. Balloon occlusion allows, with the use of the extraction catheter, the ability of retrieve chemical constituents. In the case

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of filters, chemical constituents will go through the filter.

In balloon occlusion, the aspiration removes particles actively. Obviously, in filters, this does not happen. Balloon occlusion; complete flow of blood with whatever the effects of that may be. In the case of filters, you have preserved blood flow. They are very different.

In the case of the actual deployment of the devices, if we take the balloon, you can be 100 percent certain whether or not your device is being effective. As mentioned this morning, there are two ways you can determine this. One is you can look for flattening of the wall of the distal occlusion balloon against a vessel and a low pressure with one atmosphere. This confirms apposition.

In addition, a small amount of dye injected proximally in the vessel will not have distal run-off, also confirming complete apposition. In the case of a filter, there may be markers on some or all of the struts creating a ring. This confirms deployment but does not, necessarily, confirm apposition.

[Slide.]

What is the importance of particle removal? I think we can say that we don't fully understand this.

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Certainly, in terms of animal work, particles as small as 15 to 100 microns have been shown to induce regional contractile dysfunction in canine myocardium.

Similarly, a perfusion contraction mismatch has been demonstrated in a canine model by introducing embolic microspheres as small as 42 microns in size.

[Slide.]

Now, from the SAFE study, which was the initial European trial of the PercuSurge device, the particle size was analyzed carefully. This was presented by Dr. Grube. It is illustrated here on this chart. 80 percent of all the particles were less than 96 microns in diameter. 20 percent were greater than 90 microns.

[Slide.]

Taking published data from the MedNova filter in an ex vivo human carotid model; in this particular trial, 77.4 percent of particles greater than 130 microns were captured by the MedNova device. This subsequently means that 22.6 percent of the particles greater than 130 went downstream. But, in the paper, it was further characterized at approximately 12 percent of the 22 percent were dislodged during the initial crossing of the lesion and approximately 10 percent seemed to go around the filter and were captured downstream despite the fact that the filter was deployed.

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Of course, in this study, since the pore size is present, particle sizes in less than 130 microns were not accounted for at all. If you think about this for a minute, based upon the SAFE trial, where it was found that with angioplasty and saphenous grafts, greater than 80 percent of particles were small than 130 microns.

If that means that these small particles are all going through a filter, and Ohki's data implies that 77.4 effectiveness on the other 20 percent, that means that you potentially may be capturing only 15 percent of all the particles with the filter.

[Slide.]

If we look at particle conformability, what you see here is a large particle, 4 millimeters in length, but nearly 2 millimeters in width. That is a ruler underneath the particle there. This particle was actually aspirated through the 1-millimeter lumen of the extraction catheter, PercuSurge extraction catheter, which implies that some of these atheromatous particles are clearly conformable.

[Slide.]

If we look at performances here, the PercuSurge device on the top, which is approximately 36 thousands of an inch in diameter, was successful in crossing 97.5 percent of all the lesions in the SAFER trial. A very important thing

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we learned was that, in that 2.5 percent of the patients where we were not able to cross a lesion with a device, where you could just get in with the wire but not get the actual balloon component across, we had a MACE event rate in that group of 70 percent, implying that initial crossing of the device is very important and profile is important.

This leads me to conclude that what this means in terms of crossing of the lesion is something that will need to be looked at comparatively closely.

[Slide.]

So, in summary, I would say there are known issues here. We know that the majority of particles are small. They are less than 100 microns. The particles are conformable. We know that a balloon occlusion system does significantly reduce MACE as demonstrated in the 801-patient randomized SAFER trial.

What we don't know is what is the effect of a small particle size on MACE. We don't know that. We don't know the effects of chemical constituents that go through a filter although we don't really know what the effect of them is in balloon occlusion.

Also, although there is the potential that some of them are extracted, thrombus removal is active with a balloon-occlusion system, not with a filter. So, when you

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think about that, I think these are very different products and it would be very, very difficult to extrapolate, I think, from one system to the other in what we might expect.

Thank you.

DR. TRACY: Any questions for Dr. Wahr?

Thank you.

Dr. Gibson?

DR. GIBSON: I am Mike Gibson from the University of California, San Francisco. I have participated with the PercuSurge Company in the analysis of some pilot films in the past.

[Slide.]

I come today to kind of offer a perspective from the pharmaceutical world in terms of these issues surrounding inferiority and superiority and direct comparisons between devices or drugs that have a similar mechanism of action, and then can we extrapolate to see if they have similar clinical efficacy.

I think all of you are very familiar with this class of agent, the IIb-IIIa inhibitors. They act by binding to the antibody that is expressed on activated platelets in preventing them from clumping. All the drugs have a very similar mechanism of action.

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So a similar mechanism of action, but a very different structure between the different drugs; ReoPro is a large antibody. Integrilin is a cyclic peptide and agristat is a linear peptide, so similar mechanisms of action but different structures.

[Slide.]

When you look at pooled analyses from all these trials, you do see a directionality that is consistent among the different agents in some trials showing some benefits in morality, other trials not showing a benefit, but a consistent kind of directionality to the reduction in clinical events.

[Slide.]

In particular, when you look at the composite endpoint of death, MI and urgent revascularization, you, again, see very consistent directionality to the trends here in reducing this composite endpoint.

[Slide.]

So, the kind of basis for this 4,800-patient trial was that there has been a consistent reduction in events across agents but no direct comparative trial between the agents.

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So that prompted the investigators to do the target trial, the 4,800-patient trial, to compare head-to-head two of the molecules, tirofiban and ReoPro.

[Slide.]

The primary a priori hypothesis was that tirofiban would have comparable efficacy to absiximab in reducing the incidence of averse ischemic events during the first thirty days after stent placement.

[Slide.]

The power was 88 percent to declare tirofiban noninferiority to absiximab. This information was based upon prior studies of absiximab in the EPISTENT trial.

[Slide.]

The composite endpoint was death, MI or urgent TVR.

[Slide.]

Really, again, despite all that consistent directionality, despite the fact that the drugs have a similar mechanism of action, what you see here is about a 1.5 percent increase incidence of adverse events in the tirofiban arm. So, noninferiority was not demonstrated. The boundary was crossed for that. In fact, superiority was demonstrated for absiximab in this trial.

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So I think the lesson that we have learned from recent pharmaceutical trials is that interventions which have a similar mechanism of action and which appear to yield similar efficacy, when you look in retrospective nonrandomized comparisons, these may, in fact, not turn out to be equivalent when compared head-to-head. In fact, one strategy may be superior to the other.

Thank you.

DR. TRACY: Any questions from the panel?

Thank you.

Ms. Hinman?

MS. HINMAN: I would like to address this afternoon briefly one of the regulatory hurdles facing all of us. FDA, as you may know, is required by law to consider the least-burdensome provision. What I want to talk to you today about is what correlation that has in the clinical data requirements for emerging distal-protection technologies as we envision other follow-on devices being brought into full measure of evaluation following the conclusion of the SAFER trial.

I would like to speak with you today specifically to discuss what considerations should be examined to protect the public health in the study of distal-protection devices in saphenous-vein grafts.

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Since FDA operates under this specific law which I have referenced, this discussion will involve the least-burdensome provision set forth in Section 205 of the Food and Drug Administration Modernization Act of 1997, euphemistically referred to as FDAMA.

During my comments, I would like to discuss with you why we recommend that other trial protection devices be randomized against the GuardWire or standard clinical practice.

We urge you to focus on the fact that the SAFER trial is the first and only completed randomized trial of its kind in which the results have been made available for public review and comment. This is a significant point.

Furthermore, the clinical cardiology community readily acknowledges that the SAFER trial involved a patient population that is fraught with severe risk, comorbidities and patient death. As you listen and consider the presentations this afternoon, remember, we are discussing a high-risk patient population. Therefore, clinical benefit and public-health safety must take precedence over the least-burdensome means of bringing products to market.

The legislative history and Congressional intent of FDAMA indicates that, while the least-burdensome provisions were intended to streamline the device approval

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process, Congress did not intent to compromise patient safety in order to achieve this objective. Rather, the legislation was designed to balance expediting the availability of new sophisticated products and protecting patients from devices that are either unsafe or ineffective, irrespective of the regulatory pathway associated with a class II 510(k) product or a class II PMA product.

Specifically, with regard to distal protection, this panel has been assembled to focus and comment on the issue of the appropriate trial design for future clinical studies in saphenous-vein-graft intervention. This is especially relevant now that the safety and efficacy of the PercuSurge GuardWire technology has been reviewed previously this morning, and other distal-protection modalities now hope to accomplish the same venue.

As my colleagues at FDA are required to consider the least-burdensome appropriate means to evaluating device effectiveness that would have a reasonable likelihood of resulting in approval, I would like to begin by addressing the scope and limitations of this provision and its implications to appropriate trial design for distal-protection devices utilized during saphenous-vein-graft intervention.

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As you know, this provision applies both to PMA applications and 510(k) notices. It was meant to balance and encompass well-controlled interventions necessary to establish a reasonable assurance of device effectiveness or to demonstrate that devices with differing technological differences are substantially equivalent.

Today, you are specifically considering the first-of-a-kind device in a new treatment category. The first-of-a-kind device is the PercuSurge GuardWire occlusion-balloon technology and the new treatment category is distal protection during a saphenous-vein-graft intervention.

There are multiple technology approaches represented in this treatment category. The PercuSurge GuardWire is an occlusion approach. Many of the other distal approaches considered today are filter-based, as you have already been apprised of by Dr. Wahr.

Today, the FDA is seeking panel guidance on the clinical requirements for technologically different distal--protection devices, and this is another key point. The regulations would advise both the agency and the panel to prioritize the protection of the public health as primary in determining the appropriate standards for data. The least-burdensome trial design that accomplishes this goal is not

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meant to compromise either the public health or the appropriate standards for such data.

Distal protection during saphenous-vein-graft intervention in an entirely new treatment category. With the exception of the results of the SAFER randomized study, there is little, if any, comparative clinical data with which to examine the impact that entirely different device approaches can have on patient outcome.

Performance data from other distal-protection-device studies are yet to be presented in a formal public venue and we presume that they are underway and yet forthcoming but heretofore unseen. The severity of complications associated with saphenous-vein-graft intervention and the unknown nature of clinical research study results from other distal-protection devices should, and do, provide a measure of caution when considering the comparative clinical standards required for this entirely new treatment category.

In 1998, evidence would have suggested that the interventional cardiology community and FDA supported this premise. At that time, we consulted the community and found the clinicians expected evidence from a randomized trial to justify a change in their standard treatment practice. In spite of the fact that we had previously sponsored two

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registries, totally 130 patients with in-hospital MACE rates of less than 5 percent, randomization was still expected.

FDA was also aware of the results of both of these registries and, although interested, was not persuaded and a randomized-trial design was not only expected but required. PercuSurge approached the FDA with a registry design after approval of FDAMA. The company was told that a registry would not be a suitable clinical trial for approval.

Given the varying clinical results inherent in vein-graft trials, as you recently had illustrated by Dr. Kuntz, little was known about distal protection during saphenous-vein-graft intervention and the potential for unanticipated complications arising out of the use of a new technology.

When the SAFER trial was approved in September of 1998, the FDA held the position that the only regulatory course appropriate to PercuSurge was a class III premarket approval pathway. The SAFER trial was initiated in November of 1998 and, as of October 10, 2000, the PMA was submitted.

Subsequently, in November of 2000, following a series of discussions with the FDA, PercuSurge was informed that the FDA was going to reclassify the GuardWire, the first-of-a-kind device, in a new treatment category as a class II device now subject to a 510(k).

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Regardless of whether a first-of-a-kind device in a new treatment category is brought to market through a 510(k) or a PMA, one still must consider what clinical data is necessary and in what context it should be gathered in order to satisfy the principal goal of protecting the public health and safety.

Given the limited data available at this time on the use of distal protection and treatment of vein grafts, we ask the panel a simple question. What standard would you advocate be set for devices in a new category in interventional cardiology in order to insure efficacy standards are maintained and patient care is not harmed through the premature marketing of an insufficiently studied technology?

The following points may be useful in your deliberation on this issue. The SAFER trial established an approximate 50 percent treatment effect. These results have established a new treatment threshold and provide the evidence needed to support a change in medical practice. There are substantial differences between the GuardWire and other technologies for distal protection. There is no reason to assume that these other technologies will yield comparable results to the GuardWire.

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Device differences include: vessel-wall apposition, vessel radial force, method of debris retrieval, quantity and size of particles captured, and increased risk of potential loss of wire position, to name just a few. Given that distal protection during saphenous-vein-graft intervention is an entirely new treatment category, it would be scientifically and clinically unsound to appropriate the SAFER randomized GuardWire results to that of another distal-protection device.

Vein-graft lesions, by their very nature, are classified as type C lesions and, accordingly, these patients are a very high-risk population. Depending on the study, vein-graft cases rank either No. 1 or No. 2 in death per procedure in interventional cardiology. Accordingly, rigor in the design of clinical trials should be employed in order to prevent the premature marketing of devices that may, in actuality, have little or no clinical benefit.

We believe that the results of the randomized trial lay a strong, convincing foundation as an advance in treatment of vein-graft disease. Such an advance is not achievable within a registry context as the prospective intent-to-treat randomization forum obviates treatment and population biases.

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The precedent in the development of other cardiovascular devices, once an initial device has met rigor of a randomized trial against current standard of care, has been to require an equivalence trial. In these trials, the experimental arm has been the new device and the control arm has been the first in a new category.

In interventional cardiology, the last precedence for this was the approval of the Multi-Link stent from Guidant compared against the approved Palmaz-Schatz stent from Johnson & Johnson.

There is no clear public-health need to hasten the approval of an alternative distal protection technology in vein-graft intervention until such time that comparative clinical data is available.

In light of the treatment effect of the SAFER trial, technology differences between the GuardWire and other technology designs, the new nature of vein-graft intervention with distal protection, the regulatory history of approval of interventional cardiology devices and no obvious public-health need for expedited review and premature rushing of products to market, we recommend that other distal-protection devices be randomized against the GuardWire or standard medical practice.

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Again, there is no need to rush any device into vein-graft intervention without clearly demonstrated clinical benefit. Indeed, there is much potential harm to public health to do so.

I thank you for your time and consideration of these most important issues.

DR. TRACY: Dr. Klocke?

DR. KLOCKE: It is an interesting issue that, obviously, I haven't thought through. You have raised some thoughts in my mind that may not be fully organized but I would be interested in knowing--obviously, if another device comes along that is, in fact, better than the PercuSurge, then, certainly, it would be in the public interest to have that determined as quickly as possible.

I guess what I am wondering is what is the position or responsibility of a company in the sense of facilitating the other trials; in other words, in a situation, should a company such as PercuSurge, if a new device is there and the FDA thinks that an appropriate trial is there, should PercuSurge be required to provide, free of charge, and promptly, the materials to expedite the trial?

In other words, does the company also have some responsibility in terms of making sure that, if that is the appropriate comparison, that it is done expeditiously and

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with minimum costs when, obviously, they have a proprietary interest in not doing that.

MS. HINMAN: I am not an expert on reimbursement of investigational devices, but presuming, if that device was classified by HCFA or preclassified as a B2, one might be able to recoup some reimbursement and, certainly, if it was in the public-health interest, I would think that both companies would work with HCFA and FDA early on to determine the reimbursement that is employed in some of the high-risk carotid studies, for example.

In terms of the PercuSurge company response, we would be delighted to go head-to-head with other technologies and we would work very hard to insure that that product was available. I can't speak for the field force, but I think they would appreciate the opportunity to step up to the plate and train as effectively and quickly as possible.

DR. KRUCOFF: Thank you, Ms. Hinman, for your presentation. Obviously, you guys have thought a lot about this. As a starting point, which I also appreciate--I think all of us are starting with, ultimately, the intent to protect the American public and to bring forward the technologies that help us improve patient care optimally.

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Let me ask a sort of a related issue. I gather from your comments that you are convinced, as it sounded like most people were this morning, that the PercuSurge, relative to standard vein-graft intervention, provides a clinical benefit to patients undergoing revascularization.

MS. HINMAN: Yes, sir; I am.

DR. KRUCOFF: So I guess, from that, in the spirit of protecting the public, an active control type of trial would be where you would be inclined, certainly as opposed to a placebo-controlled trial if we really think that your device has brought forward a new level of protection for people undergoing the control.

My question is that if that is a safe assumption, where would your position be to allow the data from SAFER, which you labored for and worked hard and have broken the ice and all the other points you have made, taken, for a new device to eventuate and to obviate the need to do a placebo-controlled trial, by allowing your data to be used as an historic control for an equivalency-style registry in which a first evaluation of newer other devices might actually be brought forth.

MS. HINMAN: First of all, before I could comment on where or how we would make access to our data available, I would have to know what the power of that registry looked

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like because--let me just say this anecdotally. I think most of the clinicians this morning, Dr. Baim, Dr. Kuntz, Dr. Wahr, Dr. Laskey, Dr. Vetrovec, would attest to the fact that vein-graft patients are the walking wounded. They are very fragile.

So I, personally, would have to be convinced that a registry design would have enough power and enough of a patient population and identical inclusion/exclusion criteria before I could willingly allow appropriation of our data to such a consideration.

Having said that, I think there are compelling statistical reasons in the evaluation of new technology that require rigor in the design. I am not convinced that a registry is an appropriate context. We have been down that road. We have done two registries. We had the same inclusion/exclusion criteria in both registries with the exception of the expanding length of vessel being treated and the results were different across the two registries and the randomized trial that we just completed.

I think if you look at historical controls in the vein-graft trials, as Dr. Kuntz described, you are going to see that, almost irrespective of the study and the registry involved, you can dial in your event rate. I think that is

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kind of an inappropriate roll of the dice for the patient population being considered.

Having said that, I would have to confer with the executives of the company and we would work very closely with the FDA because PercuSurge is committed to patient care and public health. We have hung in there. We have been tenacious. The reason for that is because of the patient stories, the ones that are good and the successes.

We have cried when we have lost patients. This is not a laughing matter. These are seriously ill patients and this is a needed technology. So we won't be immune to the public-health need but we will have to take into consideration all factors.

DR. KRUCOFF: I really hope you will because I think all of the industry represented in the room have been either the groundbreakers at certain times or following the groundbreakers at other times, and recognize that the time and the investment in doing clinical trials changes somewhat over the course of that, that, ultimately, our ability to, in a least-burdensome way, really bring forward technologies that help us improve patient care depends on our ability to find some broader level across the industry that would allow us to really do optimal trial designs.

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If, indeed, you all are convinced you have set a new standard for vein-graft revascularization, then I hope, with some sort of fairness in the equation to accommodate the cost and time of that groundbreaking, that you would still, on behalf of patients with vein-graft disease, help us by allowing trial designs that would bring further modifications or other technologies forward to these patients as well.

One venue where that might, in fact, be the case would be by having your groundbreaking data available for registry equivalence trials.

DR. TRACY: Dr. Domanski?

DR. DOMANSKI: I have spent a lot of time at various times through the years pushing for controlled trials in device approval. They are certainly expensive and it may not be the only way of doing it in a particular case, but can we assume that your zealousness for other vendors following in your footsteps with a long, expensive controlled trial, apply also to your follow-on catheters which, no doubt, will have new designs as well.

MS. HINMAN: Absolutely. We are committed to patient care. We are committed to demonstrate clear and meaningful benefit because the reality is you can rush a product through a trial and you can dial in a result. But

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if the clinical community doesn't accept it or doesn't believe it because the evidence is not sufficient, you have not gained anything.

DR. TRACY: Thank you.

Ms. Broderick?

MS. BRODERICK: My name is Julie Broderick. I am the Vice President of Clinical and Regulatory Affairs at Kensey Nash Corporation. I would like to start by thanking the FDA for the opportunity to speak to the panel this afternoon.

Kensey Nash is a small medical-device company located in the Philadelphia area. We are developing a distal-protection device called the Triactive System which uses a distal-protection balloon rather than a filter.

The biggest challenge facing those of us in industry who are developing products for the interventional cardiology market is the incredible pace of change in this area of medicine. Every time we go to a conference or open an industry newsletter, there is news of a new technology on the horizon.

As you know, stents are becoming obsolete within six to nine months of being launched and new technologies are constantly replacing only recently approved ones. This rapid innovation, while beneficial to patients, presents

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great challenges for those of us who are designing clinical trials, and distal-protection devices are no exception.

Going hand-in-hand with the rapid pace of innovation as the world of great uncertainty. None of us can ever be sure which products and development will succeed and which will fail, how long it will take for the competitors to receive marketing approval and how those products will be accepted by the interventional cardiology community. This, too, adds to the challenges of designing clinical trials in this area of medicine.

With regard to distal-protection devices, in particular, all of us now anticipate the approval of the PercuSurge system in the next few months. However, it is still uncertain as to whether and how quickly the majority of interventional cardiologists will adopt this distal-protection system as their standard of care in treating saphenous-vein grafts.

As a company trying to design a clinical trial for our own distal-protection system, this presents a number of obstacles, particularly in regard to the control group, should a randomized controlled trial be required.

If our study design requires that no distal-protection device may be used in the control group, investigators who have quickly adopted distal protection as

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their standard of care may believe that it is unethical to enroll patients in a study where the control group does not allow distal protection. Consequently, our rate of patient enrollment will surely suffer.

On the other hand, if our study design requires use of a distal-protection device in the control group, investigators who are not comfortable with the available device or devices may refuse to enroll in the study, also. Furthermore, and this was just addressed, the sponsor may be required to pay for the competitor's device to facilitate enrollment in the control group.

Obviously, neither scenario is attractive to us as a sponsor that needs to complete its clinical trial within a reasonable time frame and a reasonable budget. I believe it is not in the best interests of the FDA, patients or investigators to have a clinical trial that lingers or that does not reflect the real standard of care nor is it in the interest of anyone to have a study protocol that is obsolete the day the study starts.

As Dr. Kuntz has described to you, there are solutions to this dilemma and there are methods of designing studies that reflect the dynamic nature of interventional cardiology and specifically distal-protection technology.

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Therefore, I respectively request that the panel and FDA give serious consideration to the design presented by Dr. Kuntz. I ask you to consider the uncertainty facing sponsors who are working in this area and allow us some flexibility and creativity in designing a study protocol that is both scientifically and statistically sound as well as practical.

Thank you.

DR. TRACY: Any questions from the panel? Thank you.

Dr. Stone?

DR. STONE: Good afternoon. Thank you for giving me the opportunity to speak here today. My name is Gregg Stone. I am the Director of Cardiovascular Research and Education at the Cardiovascular Research Foundation. I am involved in a lot of clinical trials, a fairly high-volume interventional cardiologist and I know just enough statistics to be dangerous.

I am also probably the only one here using an Apple, MacIntosh, that is, so it is always exciting to see if it is going to work.

[Slide.]

What I would like to do is, in about ten minutes, ever since I heard of this open forum and the consideration

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about making subsequent distal-protection devices for saphenous-vein-graft applications as 510(k)s with expedited approval processes, I thought long and hard about how would be the best way to do this for the public.

[Slide.]

In terms of disclosure, I have no equity ownership or patent interest in any device or company that manufactures, sells or distributes distal-protection devices.

[Slide.]

What I am going to try to do is summarize a little bit of the discussion that has gone on this morning and up to this point and try to give a very practical viewpoint, a recommendation, anyway, of how I think these trials should run, recognizing that there is always the competing interests of patient care which, to me, is overwhelmingly number one in the public health in general; two, cost effectiveness; three, industry considerations, et cetera.

So when we consider these distal-protection devices in saphenous-vein grafts, and I am going to 99 percent restrict myself to that, the considerations, one, are PMAs versus 510(k)s. I am only going to speak about that for about four words. I am much more interested in, actually, what the clinical data requirements would be to

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support either a PMA or 510(k) application to get a device on the market in the U.S.

What I want to consider for you is either prospective multicenter registries or prospective multicenter randomized trials. I think that single-center registries, or even single-center randomized trials, are pretty much out of the question. I don't think anybody is going to argue that.

If we talk about multicenter randomized trials, everyone has heard superiority trials versus noninferiority trials.

[Slide.]

Now, again, the clinical imperative that I think has to drive us is that it is ethically imperative that new products that are safe and effective be introduced to the United States market as rapidly as possible but not sooner. So what do I mean by that?

Efficacy must be demonstrated because not only is there a risk that if you put a device on the market that is not efficacious, not only is there a risk, obviously, that the cost of healthcare may go up, but alternative therapies with proven benefit may be withheld from patients. So I think it is very important that, before we put a device on the market, given that we have an alternatively effective

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device, whatever the arena we are talking about, that we prove efficacy for the new device.

I think, obviously, the requirement to demonstrate at least a threshold level of safety is obvious.

[Slide.]

So, let's look at some of the hard facts about doing clinical trials in saphenous-vein grafts. What we have seen is that the 30-day MACE rates in a relatively unrestricted saphenous-vein graft historical-control population runs usually between 16 to 20 percent when you use a liberal definition of MACE. This really was not discussed much this morning but a lot of the reasons that those event rates vary so much from one trial to the other is the definition of major adverse cardiac events was variable and, actually using serial cardiac enzymes with sensitive CPKMB criteria, we can get an event rate of 16 to 20 percent. If you get rid of outliers, it usually falls in that range.

Because of these high MACE rates, saphenous-vein grafts have become the favorite target for evaluating the safety and efficacy of distal-protection devices for regulatory approval.

Given the control MACE rate, as you have seen from the initial design of the SAFER trial and other trials that

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have been proposed to FDA and are ongoing, about 800 randomized patients are required in a randomized saphenous-vein graft to show superiority with an alpha of 0.05 at 80 percent power.

[Slide.]

Now, saphenous-vein-graft trials, and this has been alluded to earlier, take significantly longer to enroll than native coronary-artery trials because, one, there are not as many saphenous-vein grafts. There are probably somewhere between 75 to 100,000 saphenous-vein grafts that are intervened on per year in the United States, and there are multiple exclusion criteria in these trials and, also, especially because patients have diffuse disease who have degenerative vein grafts. Usually, we are trying to just intervene in just the saphenous-vein graft, so there are a lot of patients with vein grafts that are excluded from these trials.

Prior randomized vein-graft trials have required about two or more years to enroll, and that is, in general, when there have been no ongoing competing trials.

It is estimated that in 2001 and 2002, and this is, again, the hard fact of reality which I care about because of the public health, at least nine randomized trials in saphenous-vein grafts will be initiated or

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ongoing, four with distal-protection devices, one with a thrombectomy device, a radiation trial, and three stent-graft trials.

These are only the randomized trials in vein grafts that I know about and that I am involved with. So there are probably more out there. If you just look at historically what would go on, I think you get a sense of what it is going to be like in the next year or two to try to get new safe and effective products through a reasonable superiority randomized trial even if PercuSurge didn't exist.

[Slide.]

More hard facts. I truly believe that SAFER has clearly demonstrated that distal protection with the PercuSurge distal-occlusion system should become the standard of care in most saphenous-vein-graft interventions. In fact, we are going to be using our educational pulpit, if you will, to try to hammer this point home. These are some of the sickest patients. Their complication rates are unpredictable and we clearly have a more effective therapy that routine balloon angioplasty or stenting now.

Thus, I don't believe that randomized trials of new devices against unprotected vein grafts are ethical anymore except possibly in low-risk lesions. But, of

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course, that is assuming that you can identify low-risk lesions and, except for a very rare possibility, I am not so sure you are going to be able to in many patients.

Even if you could identify low-risk lesions, given that the baseline MACE rate, by definition, in low-risk lesions is lower than 16 to 20 percent--for example, in RCT1, the first 142 patients in SAFER, it was about 10 percent. If you were going to use that as a control arm, about 1600 to 2000 patients would need to be enrolled in a superiority trial. That is clearly impossible, given multiple ongoing studies.

[Slide.]

Let's consider registry versus noninferiority trials. There are some advantages of considering a registry. I thought long and hard about this. This is a registry where you compare two historical controls. One, fewer patients have to be enrolled. It is a lot simpler. These trials are much easier for the M.D.s, for the research nurse coordinators and for the patients, just to tell a patient, "This is a new device. This is why we think it works. This is what the risks may be. You are going to get it." It is hard to explain randomized trials to patients.

Clearly, a registry is going to enroll faster. You could do either a superiority-type registry or a