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FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGIC HEALTH

CIRCULATORY SYSTEMS DEVICES PANEL

OPEN SESSION

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Monday, February 5, 2001

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P R O C E E D I N G S

Call to Order

DR. TRACY: Good morning. I would like to call the Circulatory System Devices Panel. The topic for discussion today is discussion of a premarket application for the PercuSurge GuardWire-Plus temporary Occlusion and Aspiration System, a distal protection device used in the treatment of saphenous vein graft disease.

I would like to ask the panel members to introduce themselves, please.

MR. JARVIS: Gary Jarvis, the industry rep.

MR. DACEY: Robert Dacey, consumer rep.

DR. LASKEY: Warren Laskey, an interventional cardiologist.

DR. KLOCKE: Fran Klocke. I am a cardiologist and director of Vineberg Cardiovascular Research Institute at Northwestern.

DR. TRACY: I am Cynthia Tracy. I am an electrophysiologist at Georgetown University.

MS. MOYNAHAN: Megan Moynahan, executive secretary.

DR. DEMETS: I am Dave DeMets, statistician from the University of Wisconsin.

DR. VETROVEC: George Vetovec, cardiologist, Medical College of Virginia, in Richmond.

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DR. AZIZ: Salim Aziz, cardiac surgeon, University of Colorado, Denver.

DR. DILLARD: Jim Dillard. I am the Director of the Division of Cardiovascular and Respiratory Devices, Food and Drug Administration.

MS. MOYNAHAN: I would like to read the conflict of interest statement for this morning's session. The following announcement addresses conflict of interest issues associated with this meeting, and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. Due to this prohibition, Dr. Mitchell Krucoff will not participate in this morning's panel deliberations. The agency had determined, however, that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interests of the government. The agency took into consideration certain matters regarding Dr. Cynthia Tracy, Warren Laskey, George Vetrovec and David DeMets. Each of these panelists reported interest in firms at issue but in

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matters that are now concluded, unrelated to today's agenda or limited to their employing institution.

The agency has determined, therefore, that they may participate fully in all discussions. The agency determined that Dr. Krucoff, who reported interest in firms at issue but in matters that are unrelated or now concluded, may participate fully in all discussions during the afternoon session.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose product they may wish to comment upon.

DR. DILLARD: Good morning. Jim Dillard again from the FDA. First of all, I would like to welcome you all here this morning, both the panel members that we have brought together as well as all of the representatives in the audience. I would like to thank you for your participation today and I have just one real brief announcement.

In our ongoing efforts to try to staff this panel to its fullest degree, I would like to mention just that both Dr. Laskey and Dr. Salim Aziz have been appointed to serve four-year terms, which has been signed off through the Food and Drug Administration. As well, I would like to announce that Dr. Cynthia Tracy is now our no longer Acting Chairperson but is, in fact, our permanent Chairperson for her duration of her voting status.

So with that, Dr. Tracy, I would like to turn the meeting over to you.

DR. TRACY: Thank you. At this point we are going to move to the open public hearing, and I believe Miss Moynahan has a roster.

MS. MOYNAHAN: Actually, we understand that most of the people who have come here would like to speak in the afternoon open public hearing. If there is anyone this morning who would like to speak to the panel on any topic, they are welcome to do so.

DR. TRACY: We will close the open public hearing at this point but, again, there will be another open public hearing this afternoon. I would like, at this point, to turn things over to the sponsor, and just remind the sponsors to introduce yourselves and state your conflicts of interest.

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[Slide]

DR. WAHR: My name is Dr. Dennis Wahr, and I would like to state that I am an interventional cardiologist at the Michigan Heart and Vascular Institute, in Ann Arbor, Michigan.

As the local site PI for the largest enrolling center in the SAFER trial, I was asked to speak to the panel.

[Slide]

From the inception of the SAFER trial in September in 1998 to the current date, I have not had any equity interest either in stock options or stock ownership in PercuSurge, Inc.

[Slide]

Why is saphenous vein graft intervention important? Well, before we get into the SAFER trial, I think it is essential for people to understand the natural history of saphenous vein bypass grafts. The natural attrition is significant, 15-20 percent of all saphenous vein bypass grafts occlude in the first year. This is followed by a 1-2 percent per year attrition rate between years 1-6 postoperatively, which increases to 4 percent per year between years 6-10. By the time you reach 10 years post surgery, up to 40-50 percent of all saphenous vein bypass grafts are occluded.

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This commonly results in a need for patients to undergo a revascularization procedure. That revascularization procedure, however, is fraught with risk. Specifically in-hospital mortality for re-do bypass is 3-7 percent. The perioperative myocardial infarction rate is 12 percent, and that doesn't include the difficult recuperation and other forms of morbidity associated with the procedure.

[Slide]

As a result of this, interventionalists have looked for a way to prolong the saphenous vein bypass grafts and delay surgery. Different types of interventional procedures have been done, however, these types of procedures, that is angioplasty and stents, have demonstrated that saphenous vein bypass graft lesions are known to have a high incidence of slow or no reflow due to distal embolization and associated microvascular spasm.

While the risk may be increased with bulky, fragmented or thrombus associated lesions, the potential for no reflow is difficult to predict.

[Slide]

If we look at major adverse cardiac events, MACE events, associated with saphenous vein interventions, we know that they are device dependent. Atherectomy devices, which are large and bulky, have the highest incidence of side effects. The lowest amount of side effects is with

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simple balloon angioplasty. Unfortunately, balloon angioplasty techniques are fraught with a very high incidence of restenosis, up to 50 percent in some reported series and even as high as 70 percent.

For this reason, currently interventionists have settled on intracoronary stenting for the treatment of most saphenous vein lesions. However, stenting, while our best option, is still far from satisfactory. The mortality rate with saphenous vein stenting is 3-4 percent at the time of the acute procedure. Q-wave infarctions occur 2-3 percent of the time and non Q-wave infarctions have been reported as high as 15-25 percent. That is with the non Q-wave infarctions being defined as CPK rises greater than 3 times the upper limit of normal. This is important because these CPK rises have been shown to correspond with decreased long-term survival at 1, 3 and 5 years. People have referred to this group of patients as the "walking wounded."

[Slide]

In summary, I think it is fair to say that the historical inability of interventional cardiologists to treat saphenous vein disease with a low complication rate represents an important unmet clinical need -- that is, until the SAFER trial.

[Slide]

This is the PercuSurge GuardWire System. It consists of four components. There is a GuardWire; there is the Microseal adapter. These two items are pictured on the left side of the screen. There is an EZ-Flator on the lower right side and a export catheter, not pictured.

[Slide]

The system itself is relatively straightforward and easy to understand. Initially the GuardWire is passed down the vessel and across the stenosis. There is a small balloon at the end of the GuardWire which, in this schematic, has not yet been inflated.

In this schematic the distal balloon has been inflated, interrupting flow. At this point a stent can be brought in over the GuardWire, and you can see here a stent is being deployed at the site of the stenosis.

I think it is important to understand that debris may be dislodged both at the time of the initial crossing of the lesion, making the need for a low profile important, as well as additional debris that is commonly released at the time of the actual stent deployment.

[Slide]

Here you can see following stent deployment debris, schematically represented as embolizing downstream but it is caught and prevented from migrating into the distal circulatory bed by the distal occlusion balloon.

The export catheter is brought in before letting the balloon down. The debris is removed. Once the export procedure is completed, then the distal occlusion balloon is deflated and you have achieved revascularization without embolization.

[Slide]

Here is a blow-up of the GuardWire with the balloon inflated. The export catheter, the blue shaft to the left, is pictured here. To the right is a typical picture of the types of debris removed during the export procedure. We commonly get large particles as well as small particles and also thrombus.

[Video presentation]

I would like to demonstrate in an actual human a GuardWire case. Pictured here is a saphenous vein bypass graft to the right coronary artery. This graft is severely diseased throughout the entire mid-portion of the graft. There are high grade lesions here, at the arrow. You can appreciate a thrombus within the vessel in this area.

This will be better appreciated in this view where, right to the arrow, you can see a filling defect with a large thrombus within the vessel in addition to the atherosclerotic disease involving the entire middle portion of the graft.

Note that on this slide you can see the distal balloon on the GuardWire inflated. Note the flattening against the wall. This is an excellent sign that we look for when the balloon is inflated under low pressure to 1 atmosphere. Flattening of the side of the balloon suggests that you have apposition to the wall of the vessel. In addition, contrast is injected after the distal balloon is inflated and note that there is no run-off. The dye remains pooled within the graft, which again gives confirmation that you have total protection against downstream run-off.

If you look closely, you will see a little dot here going up and down the vessel. I am trying to follow it with the cursor. I think people can appreciate that. That is actually a radio opaque marker on the tip of the export catheter, which is aspirating debris out of the coronary vessel. I like to do an initial aspiration run to remove the debris immediately at the beginning of the procedure, before proceeding on to any type of stent procedure.

Here, a stent again with the distal occlusion balloon is being delivered to the mid-portion of the vessel. You can see it inflated. At this point an injection of dye into the coronary -- I skipped ahead here a little further than I wanted to go. We let the distal balloon down. At this point, the graft was markedly improved. There is excellent run-off. There is the residual narrowing at this

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point of the vessel. So, at this point the GuardWire was reinflated. An additional stent was deployed more distally. At this point, the GuardWire balloon was deflated and there was a beautiful result in the graft with a wide-open graft and excellent run-off into the distal right coronary artery.

So, that is a successful example of a PercuSurge case. Now I would like to show one brief example of a case done without the GuardWire. This is an injection into a saphenous vein bypass graft to the obtuse marginal branch of the circumflex. This graft is also severely diseased, with multiple narrowings and filling defects involving the entire middle portion of the graft.

Going ahead, here is a stent being deployed through the diseased portion of the graft over the wire. There is no PercuSurge protection balloon in place here. This patient was randomized to the control arm of the study.

Following stent deployment, this is a vivid example of what we call no reflow. Dye is injected into the vessel. You can see that the vessel is actually open. There is no obstruction. The run-off into the distal capillary bed is extremely poor. This is what we all dread in an interventional lab.

Another view of this, again no run-off. Just very, very sluggish filling. The dye pools and, in fact, the dye never really washes out from the myocardium. This

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is due to microvascular obstruction of emboli. At this point, doing this case, the patient first said to me, "I'm having chest pain." He said, "my chest pain is getting worse." The next thing he said was, "I'm not going to recommend you as a doctor to anyone."

[Laughter]

The next thing that happened is that his blood pressure started to fall; progressively went down. He required fluid and intra-aortic balloon pump. He needed to be intubated. We tried to resuscitate him with nitroglycerin, verapamil, other types of vasodilators and we never were able to reestablish brisk flow. He ultimately went to the coronary care unit where he remained moderately unstable for approximately a week. We thought that he was better. He died suddenly approximately two and a half weeks later of ventricular fibrillation suddenly.

[Slide]

In summary, I would like to say a couple of things. First of all, in our experience we found that while we kind of had a rough gestalt about which patients were at risk of having this distal embolization and no reflow, in fact, as we went through our cases, 74 cases enrolled in the trial at our site, while we had a general gestalt about who might have no reflow, we were not able to predict it. You could not always tell. Sometimes there were rude surprises.

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A second thing I would like to point out is that in the 42 cases that actually received the GuardWire at our institution, with distal balloon occlusion time averaging around 5 minutes, we had no cases of balloon intolerance. In fact, while patients might have had angina with balloon inflation, as soon as you let it down the angina went away immediately and there was really no lingering discomfort.

Finally, I would like to say that as the study went on it became progressively more difficult to treat patients in this trial because I, who performed 85 percent of all the cases at our institution, as well as our staff started to develop an ethical dilemma about enrolling patients with severe graft disease where we did not do emboli protection out of fear that they would be randomized to the control arm of the study. In fact, when the trial ended and things switched over to a registry mode, approved by the FDA, we had a little bit of down time before our IRB could get the registry paperwork processed. We had cases with saphenous vein graft disease that we actually transferred to other institutions, where they had a registry up and going before ours, to have vein graft disease treated. We did treat two patients with emergency FDA approval during this phase.

MS. HINMAN: We are going to have Dr. Baim speak to us on the results of the SAFER trial.

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DR. BAIM: Good morning.

[Slide]

As the principal investigator of the SAFER trial, it is my pleasure to review the trial with you and some of the issues. In terms of sample cohorts, that will be addressed further by Dr. Kuntz in the next talk, but let me take you through the saphenous vein angioplasty free of emboli randomized trial, evaluation of the clinical safety and efficacy of the PercuSurge GuardWire and saphenous vein graft intervention.

[Slide]

Let me just say in terms of personal financial conflict, from the onset of the SAFER trial to the current date I have not had any equity interest either in terms of stock options, stock ownership or consulting with PercuSurge.

[Slide]

Dr. Wahr has reviewed the fact that vein grafts are programmed for failure in the 8-10 year range, but let me add a couple more details about vein graft atherosclerosis. It is particularly diffuse and friable, and it is well recognized that intervention may cause distal embolization; that the embolization can compromise the distal microcirculation, and that this is manifest either as flagrant no reflow -- that very dramatic case that Dr. Wahr

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showed -- in 8-10 percent of patients or a CK elevation in 17-20 percent of patients. The mortality of vein graft intervention in the series from Washington Heart Center and the Beth Israel Deaconess, reported by Dr. Ho, shows a 3.4 percent 30-day mortality, which increases to 14 percent in patients who have elevation of CK-MB more than 3 times normal.

So, all of these issues make a device that can capture and remove embolic particles before they reach the myocardium of particular interest.

[Slide]

The initial clinical evaluation of the GuardWire compared to the SAFER trial consists of a single-site registry of 24 patients, published in 1999 by Webb, from Canada, and it was intriguing that compared to the 17 percent MACE rate that one has seen in historical studies the MACE rate was only 3.7 percent. That was very similar to the SAFE registry reported at TCT in 1999 by Everhard Grube, 103 patients European registry, that again showed material was removed in 95 percent of the cases, and the MACE rate, the 4.9 percent, that seemed very favorable compared to 17 percent historical control.

[Slide]

This is just an example of some of the material that is removed in each and every one of these cases.

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[Slide]

But the SAFER trial was designed as a prospective, randomized trial to determine if the GuardWire reduced the incidence of MACE compared to conventional standard of care, which was replacement of stents without distal embolic protection.

[Slide]

The study was coordinated by Rick Kuntz and his staff at CDAC; Angiographic Core Laboratory at the Brigham and Women's Hospital under Jeff Patma's direction; ECG Core Laboratory at CDAC; monitoring by Bailer Monitoring; and the sponsor, of course, was PercuSurge.

[Slide]

The primary endpoint of this trial was major adverse clinical events, MACE, at 30 days, defined as a composite of either death, Q-wave infarction, non Q-wave infarction with a CK-MB more than 3 times the upper limit of normal, emergency bypass surgery or repeat target vessel revascularization.

[Slide]

Inclusion criteria of this trial were lesions between 50-99 percent, diameter stenosis in vein grafts was reference diameters of 3-6 mm. The lesions had to be located more than 5 mm from the ostium, and at least 20 mm from the distal anastomotic site to allow use of the GuardWire

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system, and there had to be TIMI 1 or greater flow at baseline.

Exclusion criteria included ongoing infarction with positive CK-MB since this was one of the primary endpoints of the trial, ejection fraction less than 25 percent or serum creatinine greater than 2.5 unless on chronic hemodialysis, as well as planned use of atherectomy devices.

[Slide]

And, 801 patients were enrolled in the randomized trial. Let me just spend a minute going through how these patients have been broken down in various presentations that have been filed with the panel.

The initial 142 patients -- there was an intentional effort to exclude patients with diffuse disease. There was a concern that perhaps it might be more different to use the GuardWire in this situation, that we wanted to have a low complication rate, but enrollment was very, very slow with this high degree of lesion selection. Most of the patients with vein graft disease were being excluded, and Dr. Kuntz will talk about the mechanistic aspects, but with FDA sanction we changed the inclusion criteria to allow the enrollment of patients with more diffuse disease.

A total of 659 patients were randomized in the trial after the inclusion criteria were so broadened. The

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551 patient cohort was a prespecified interim analysis that was reviewed by the data safety monitoring board and led to the recommendation that enrollment be terminated. Those were the data that were filed initially with the panel. Another 108 patients in a run-on cohort were additional patients enrolled before the study could actually be terminated.

So, 801, 659, 551 -- they are all numbers you will see at different points and I will try to be very specific as we look at the trial results as to what we are examining.

[Slide]

This is the 659 cohort. So, these are all the patients including the run-on patients enrolled after the broadening of the inclusion criteria to include diffuse disease. The age of these patients is 8 or so years older than the average interventional trial common in vein graft trials; a rich population of diabetics, over 30 percent. Note that three-quarters of these patients had Canadian cardiovascular class III or IV angina, including over 35 percent with resting angina but preserved ejection fraction for the inclusion/exclusion criteria.

[Slide]

Reference vessel diameter of these grafts was about 3.5 mm, which is typical. Average lesion length was 15-16 mm, but note that the 25-75 percent inter quartile

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ranges include grafts of 76 mm of lesion length representing this diffuse disease inclusion. The distribution of target vessels is shown here. Note that 37 percent of patients had thrombus in their lesions and about 35-40 percent of lesions were described as eccentric.

But, one of the themes that you will hear in subsequent presentations is that it is very difficult, looking at these standard angiographic parameters, to predict the risk of distal embolization.

[Slide]

Technical success was defined, according to the instructions for use, as successful delivery of the GuardWire to the intended target site, inflation of the occlusion balloon, and then aspiration of the export catheter before balloon deflation to restore antegrade flow.

Procedural success, in contrast, was defined as achievement of a final diameter stenosis less than 50 percent, with no in-hospital MACE.

[Slide]

Technical success with the GuardWire according to that definition was 91.6 percent. Procedure success was 90.7 percent compared to no GuardWire protection procedure success of 84 percent. The number of stents was roughly equal, 1.4 versus 1.3, in the GuardWire and the conventional arms.

[Slide]

This slide shows MACE at hospital discharge from the index hospitalization in the 659 patient cohort. In terms of MACE as a composite endpoint, there was a 40-plus percent reduction in MACE, from 15.7 percent in the group without GuardWire protection to 8.1 percent in the group with GuardWire protection, and this was significant at the 0.001 level. That consisted largely of reductions in myocardial infarction, particularly the non Q-wave infarctions with CK-MB greater than 3 times normal, although there were trends in reduction in death, emergency surgery and target lesion revascularization.

[Slide]

The primary endpoint though was specified to be MACE out at 30 days from the procedure, again, in the 659 cohort. There is still a 48 percent reduction in MACE, from 17.8 to 9.0 percent, significant at the 0.001 level, consisting largely of reductions in myocardial infarction but, again, with strong trends in death, 2.8 to 0.9, a p value of 0.08; emergency surgery; and target lesion revascularization, 2.5 to 0.6, again, just missing statistical significance at the 0.06 level but the composite endpoint, the prespecified primary endpoint of this trial was extremely positive at the 0.001 level.

[Slide]

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This is just showing graphically the 48 percent treatment effect in hospital, 49 percent treatment effect at the 30-day primary endpoint.

[Slide]

Secondary endpoints included preservation of TIMI flow and a series of complications. TIMI flow -- 3 normal TIMI flow was present in 97.6 percent of GuardWire patients and 94.9 percent of conventional patients, with a p value of 0.07 which missed independent significance, but the incidence of this clinical no-reflow phenomenon that Dr. Wahr showed you so dramatically was reduced by more than half, from 8.3 to 3.3 percent, and that was significant at the 0.005 level. There was no significant increase in complications related potentially to the GuardWire in terms of perforations or dissection or subacute closure. The dissections that did occur in the GuardWire group were all of the mildest severities, A and B on a scale that goes to F in severity.

[Slide]

One interesting question is whether IIb/IIIa receptor use obviated the need for distal embolic protection. As you know, the data on benefit of IIb/IIIa receptor blockers in saphenous vein grafts are controversial. One meta-analysis of the EPIC and EPILOG studies showed no net benefit, but still operators felt that

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I Ib/IIIa receptor blockers should be allowed in this trial, and what we did to track the independent effect of distal embolic protection with PercuSurge was that we stratified the randomization to whether the operators chose up front to use a I Ib/IIIa receptor blocker or chose up front not to use a I Ib/IIIa receptor blocker.

In 60 percent of patients roughly in both arms of the trial the operators chose to use a I Ib/IIIa receptor blocker and what this slide shows is that the PercuSurge GuardWire had a major MACE reduction benefit with or without the use of a I Ib/IIIa receptor blocker. In the patients where the operator chose to use I Ib/IIIa receptor blockers the GuardWire reduced the incidence of MACE from 20.8 to 10.1 percent, and this was significant at the 0.003 level. In patients where the operators had chosen not to use a I Ib/IIIa receptor blocker the MACE rate was reduced from 12.4 to 7.1, just missing significance at the 0.051 because of the lower event rate.

I think what the rate difference is between no I Ib/IIIa and I Ib/IIIa receptor blocker use reflects not so much a toxic effect of these drugs but the fact that operators were looking at subacutes that may not be reflected in quantitative angiography of higher risk lesions to use the I Ib/IIIa receptor blockers. But the fact that GuardWire protection offered additional benefit with or

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without the use of IIb/IIIa receptor blockers is because those blockers prevent platelet thrombi but don't dissolve the atherosclerotic plaque that was retrieved in each and every one of these cases, and is the primary inciting factor for the ischemic complications.

[Slide]

So, again, we talked about the 659 cohort in the endpoint slide so far. That was the 551 cohort that was used by the DSMB to stop the trial and the 108 patient run-on, and Dr. Kuntz will talk about the statistical rationale for looking at this group but let's finish by looking at the entire 801 randomized cohort which includes the 142 patients who were enrolled prior to allowing diffuse disease to be included.

[Slide]

This shows the primary endpoint for the 659 patients and for the 801 patients. You will see that in both groups the reduction in the primary endpoint, MACE, was over 40 percent and was highly significant at 0.001 and 0.004 respectively with or without the inclusion of those initial 142 patients.

[Slide]

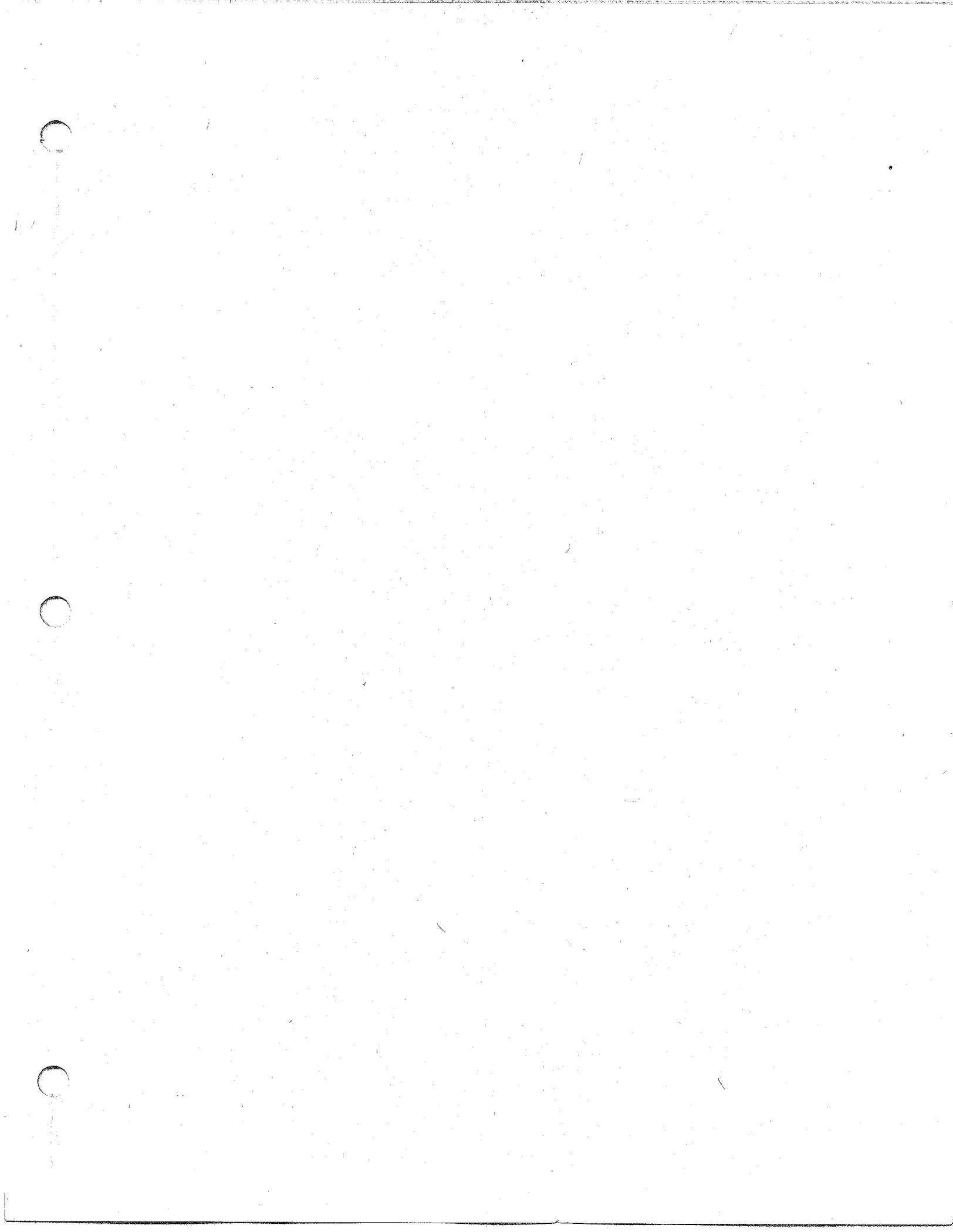
In conclusion, ladies and gentlemen, the PercuSurge GuardWire system in the SAFER trial proved both safe and effective in terms of recovering embolic material,

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in terms of preserving normal flow, and in terms of reducing the incidence of major adverse clinical events by 40-50 percent during the percutaneous interventional treatment of saphenous vein grafts. I think that these data underscore the importance of using the GuardWire system during saphenous vein graft intervention. Thank you.

MS. HINMAN: At this point we are going to have Dr. Richard Kuntz take us through the statistical rationale and study design components of the SAFER trial.

DR. KUNTZ: Good morning.

[Slide]

My name is Rick Kuntz. I am an interventional cardiologist at the Brigham and Women's Hospital, and also a clinical trialist in charge of designing and coordinating this trial.

[Slide]

I have no disclosures. I don't have equity. I haven't been a consultant and I am not being paid for my testimony today.

[Slide]

I would like to review for you three aspects of this trial. First, I would like to talk about the consideration of using a single-arm study design to begin with and our final decision to use a randomized trial design because of special considerations for vein graft disease.

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need for repeat revascularization clinically driven, and the same, similar variables pop up. That is, the size of the lumen, length of the stent, presence or absence of diabetes and all of this.

[Slide]

What is interesting is that while predictive models can be quite accurate, the range of outcomes varies widely. One can see the influence of case mixed covariates on these outcomes in this grid. If we just look at the difference of three variables, that is, the presence or absence of diabetes, the size of the lumen in certain terciles, as well as the lesion length, one can show a wide range of outcomes suggesting restenosis can occur as low as 6 percent, in the lower left-hand corner, to as high as 46 percent, in the upper right-hand corner.

This slide demonstrates the importance of being able to adjust for outcomes when trying to look at the expected outcome of any single registry. That is, if, in fact, we were to do a registry of stents and have these kind of characteristics we would expect a low complication rate. If we had, in fact, stents and variables in diabetics with long lesions and small vessels we would expect almost a 6-fold increase in outcomes. Therefore, it is important to be able to adjust and measure these covariates and we think, in

the case of stents, these outcomes are quite scalable; they have been tested and they are quite robust.

[Slide]

As a matter of fact, we have been work in collaboration with the Food and Drug Administration and members of HIMA, now called ADVOCARE, in order to develop a more robust model which has included more proper analytical techniques for combining trials and some Bayesian techniques for proper weighting of outcomes.

[Slide]

This model, in development, offers the promise of potentially using proper variance estimates to predict both the estimate and with some certainty outcomes from registries in the future, and may be used as a tool to help approve coronary stents.

[Slide]

On the other hand, we don't have that capability with vein grafts at this point. Here is a listing of historical controls of vein grafts in trials that we have derived from the literature. Approximately 8 or 9 trials demonstrate outcomes of myocardial infarction and MACE, the endpoint for this trial, and shows a range from 4 percent to 32 percent, depending on the complexity of the data.

As one can see from this data, there are vein grafts that have low risk and vein grafts that have high

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risk, depending on the trials. For example, in the Vingables 2 study, this is a trial of vein grafts with angiographic thrombus, suggesting that some vein grafts can have extremely high complication rates.

One can see from this graph alone that without a risk model, if one were to present a registry with 10 percent or 17 percent complication rate, it would be difficult to know whether that was a good or a bad device, depending on what the control is.

[Slide]

What is more impressive is even in this study, using the PercuSurge device, the historical history of this data has in itself a wide range, that is, a low complication rate, initially studied by Dr. Webb in Canada, and the two cohorts referred to by Dr. Baim with rates that range from 3 percent to 12.5 percent.

Now, all of these studies measured the same endpoint, that is CPK-MB of 3 times normal or greater. One can imagine why, in fact, Dr. Webb's complication rate was quite small. It might be because he used simple vein grafts to test the procedure and had a quick learning curve and became expert in the procedure very quickly. One can also see that as a trial design there might be increasing comfort with the device being used in more complicated patients, again demonstrating the difficulty of being able to predict

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a single number to understand the rates of complications of vein grafts without a risk model.

[Slide]

(In trying to develop an OPC for vein graft disease, a wide range of vein graft clinical complications following these catheter-based therapies requires case-mix adjustment to be sure of precise expected outcome predictions. The lack a stable scalable covariate risk model upon which to build a predictor model and makes derivation of a precise expected outcome impossible. That is, in the FDA's responses in this study it was curious that among our two cohorts, which I will talk about, there wasn't much difference in the baseline characteristics between the two groups. However, the two groups are quite different. The enrollment was much faster and most of the interventionists can tell that the vein grafts appeared much more risky. The problem is that this riskiness, this ugliness of the vein graft and its degenerative appearance does not have right now a scalable list of covariates that we can retrospectively go back and measure and adjust. Therefore, in this situation randomized trials are critical for the evaluation of saphenous vein grafts and it was our decision to do that with a concurrent control.

[Slide]

With this decision to do a randomized trial, let's talk about sample size determination and the need for group sequential analysis.

[Slide]

In our retrospective review of the data from the Beth Israel Deaconess Medical Center, a cohort that we felt would represent our control rate was 16 percent. That is, we derived a rate of 16 percent and using that as the base case and expecting a treatment rate of over 40 percent, an absolute rate of 9 percent, allowing an alpha error of 5 percent and a power of 80 percent, we designed a study with group sequential analysis with 2 interim looks and a final analysis.

Why we picked a group sequential analysis -- we don't do a lot of group sequential analysis mainly because our studies are of restenosis and long-term determined endpoints. That is, the ratio between the realization of an endpoint and the enrollment is not favorable for us to look at this trial and at those endpoints and stop early. On the other hand, this is a trial which has moderate enrollment and a realizable endpoint of 30 days. Therefore, it has features that might allow us to realize the endpoint and stop enrollment so that we can arrive at the answer much quicker. Ethically speaking, we should try to do group sequential analysis whenever possible because we would like

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to limit the number of patients that are randomized to a bad therapy.

[Slide]

This is the design of the group sequential analysis that we developed. We used the Geller Pocock algorithm published in 1987, and in a discussion with the FDA we negotiated an agreement that this distribution of nominal p values would be used for 2 looks and a final analysis.

The sample size was gaged as 800 patients, and you can see their nominal p values are 0.014, 0.021 and 0.026 according to schedule F of the Geller Pocock paper. If we break the trial into exact thirds that would be 267, 533 and 800. We discussed with the FDA that we might want to right-shift this a little bit in order to allow a little more convincing potential to stop the trial early but maintain the same Geller Pocock nominal p values for the earlier values in a move to be conservative, understanding that we were actually making the nominal p values slightly more restrictive by right-shifting to some degree.

We also calculated the alpha spending characteristics for boundary shape of 0.6, since it wasn't mentioned in this paper, using two models, Wang and Tsiatis and Lam and DeMets model, and you can see the covered probabilities for that underneath, and they corresponded

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very nicely and are actually more liberal than what we used for our study.

[Slide]

These are graphs of the boundary conditions that we used for the calculated nominal Z value for 350, 550 and 800 at the 2 looks.

[Slide]

And, this is the standard mean difference required in order to stop the trial, and one can see with 550 patients one needed about a 5-7 percent delta difference to stop this trial.

[Slide]

The patient enrollment is as follows. This trial has enrolled 801 patients in the randomized trial and 303 patients under a roll-in phase learning curve. The learning cases were allowed 10 cases per center, and a total of 303 patients were enrolled at 68 sites. The average number of enrollment per center was 4.5, with a range of 209 patients.

The study was also approved for up to 800 patients and the total number of enrollment in this study was, in fact, 801. The interim analysis stopping rules were approved for 350 and 550, as I said earlier.

[Slide]

Let's talk about the patient eligibility changes that occurred in this trial and how adjustment in the final

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analysis, with consultation with the Food and Drug Administration statisticians and a rationale for this design, presented by Dr. Baim earlier.

[Slide]

Under the typical group sequential analysis plan, the randomized trial of 801 patients could be evaluated like this time line.

[Slide]

However, early in the trial extremely slow enrollment was noticed. At this time, the PI, the sponsor and certain PIs at clinical sites had suggested that possibly the criteria were too restricted. That is, the criteria themselves did not reflect the garden variety patients that we treat on a regular basis and, in fact, may not, number one, be representative of patients when this product could possibly be approved and, number two, may not represent patients who would have an adequate risk. If the adequate risk wasn't high enough, then this trial could not show any benefit. So, without looking at the data and just getting feedback about enrollment, the sponsor petitioned the FDA to widen the criteria and that was granted.

When we looked back to see how many patients were enrolled under the initial criteria, it was determined -- and this was done on a site by site basis, again without looking at any of the data of the trial -- it was determined

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Second, I would like to talk about how we arrived at our sample size determination and our decision to sue group sequential analyses.

Finally, the special case of this trial, the patient eligibility changes that occurred and our final analysis considerations and rationale.

[Slide]

First let's talk about the consideration of why we didn't use a registry. Many people in this audience are familiar with our ability in the coronary stent arena to predict outcomes from patients who are enrolled in registries. That is, with the huge accumulation of data from over 11 or 12 randomized trials in the United States alone under Food and Drug Administration, we have developed a pretty robust model of looking at the outcomes of primary clinical endpoints, in this case restenosis.

This is a description of two models that we have developed from over 8000 patients in our database demonstrating three variables, either the size or length of the lesion, presence or absence of diabetes or, in a separate model, where we substitute stent length for lesion length, become rather robust predictors of outcomes.

[Slide]

Moreover, outside that angiographic surrogate predictor, we can also predict the clinical incidence of the

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that 142 patients fit into the beginning of this trial under this restricted criteria.

[Slide]

If we compare what the difference in exclusion expansion was, we can see here, in this graph, that the original criteria required the presence of 2 discrete lesions which, as many of the interventionists here know, is an unusual situation for vein grafts. Staging of coronary cases only after 30 days, that is, if patients had multiple vessel disease that needed treatment they would be excluded from the trial. CKs that were normal for 72 hours, ruling out acutely ill individuals with unstable angina. And, TEC was excluded in the control arm, suggesting that these patients would not have any thrombus appearance -- again, low risk patients. The result of this was a restricted cohort and slow enrollment.

Now, why did we pick these original ones? Well, this is to be conservative in order to test this new product, but it wasn't clear to us or anyone else that this would restrict the trial as much as it did. After consulting with the FDA the enrollment criteria was widened so that multiple lesions and diffuse disease would be allowed; that staging of the cases could be allowed in the lab; that the cardiac enzyme levels could be normalized for 24 hours, therefore allowing the presence of patients with

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unstable angina; and that TEC could be included in the control arm, again, increasing the probability of enrolling patients with thrombus. Thus, the result here was that more complex lesions, the higher risk, would be allowed and that translated into much, much faster enrollment. Almost immediately the enrollment picked up to close to 50 or 60 patients per month from approximately 10 patients per month.

[Slide]

So, as one sees here, we have that initial time line of 801 patients as a reference; the 142 patients enrolled under the initial criteria; and while this decision with the FDA to widen the criteria was going on, the data safety monitoring committee went ahead and evaluated the first 350 patients in the trial, from patient 0 to patient 350.

[Slide]

At the first interim analysis of the data safety monitoring committee, the data safety monitoring committee stated "continue the trial." That meant that there were no safety issues. It also meant that the nominal p value difference was not reached. The sponsor then asked the question, well, since we have identified this restricted criteria patient subset, and the FDA has agreed to expand the eligibility criteria, did the restricted eligibility period reduce the control rate below 16 percent? That is,

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maybe these initial cases were at such low risk it may have diluted some of the potential to show a difference compared to the new group which was riskier patients. The sponsor, by the way, always remained blinded to the data. The data safety monitoring committee were the only people who saw the data, and they were actually blinded to treatment assignment.

The sponsor then consulted us at CDAC, the data safety monitoring committee themselves and the Food and Drug Administration. A statistical review was obtained through Steward Pocock, who is affiliated with CDAC, John Orav, who is a Harvard statistician, and the data safety monitoring statistician on the board and FDA statisticians. FDA consultations were performed by conference phone, and they agreed with the logic but they had no guarantees as to the final analysis plan but understood a proposal as follows:

We considered virtually restarting a new analytical trial subset at point of new enrollment criterion, that is, patient 143. That is, we wanted to propose the possibility of restarting the analysis with patient 143 so that the new first interim analysis would start then. But, in order to pay for the penalty of potentially starting the trial, we and the statisticians agreed that we would use the same 3 interim looks, that is the 2 interim and final looks at 350, 550 and 800; charge

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the same alpha spending penalty at each value but skip the 350 look as a penalty for restarting the trial. So, the first interim analysis was performed at 550 under the nominal p value for a trial in which 550 was the second look. Therefore, the alpha expenditure was charged for restarting. Most people felt comfortable with that idea.

Practically speaking, we also knew that at that point, that is after 350 patient interim analysis, a new 550 patient interim review and the potential run-on that would occur after that analysis would occur would be reached when all 800 patients would be enrolled. So, we felt very comfortable that the trial would continue of 800 patients as it did; that we would possibly be able to look at this analyzable cohort at 550 to determine the actual treatment effect that should be used in this study; and this was totally transparent to everybody in the trial. Nobody introduction the clinical sites knew about this potential virtual analysis plan and, in fact, the trial continued as has been described, from 0 to 800 patients. So, this proposal was purely to look and analyze the subset to get the best estimate, the treatment effect, underneath what we thought were the best criteria representative of patients who are treated with embolic detection devices for vein graft disease.

[Slide]

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So, if we look overall -- it is slightly confusing from your information but I would like to try to clear this up -- we had, in fact, the first interim analysis of 350 patients. The first group of 142 patients represent those under restricted criteria. That has been determined or coined as RCT-I in the documents. Then, there is a group that represents the new cohort, and that new cohort has two sizes. The first size is the analyzable dataset that the data safety monitoring board reviewed, which is 551 patients. That is called RCT-II. The second is that subset plus the run-on which occurs in every interim analysis trial. That is, the DSMB usually looks at a cohort but while they are reviewing it there is a run-on and the final analysis is always done on the total group, not just on the DSMB group. We don't have a name for that, but it is the sample size of 659 patients and that is the proposed analysis subset for this study, and that was presented by Dr. Baim earlier. Again, the entire trial was analyzed. The entire trial is positive. There were two separate groups based on eligibility, an initial group of 142 patients and restricted criteria, and a second group of 659 patients under widened criteria.

[Slide]

This shows the two groups collapsed overall. So, we have analysis to back up also three of these groups, and you have seen some of that so far.

[Slide]

Let's look at these considerations. The FDA position was clear -- the analysis of the new cohort would be considered but not guaranteed. Statistical considerations, on the other hand, were two-fold. One was to evaluate the total 801 patients using the final nominal p value of 0.03 allowed under Geller Pocock. In this case, the trial is completed as planned and the overall p value was clearly attained -- 43 percent treatment effect was demonstrated with a p value of 0.004, much less than the 0.03 required.

The second consideration was to evaluate the 659 cohort using a nominal p value of 0.02, which was allowed in the second look. In this case, the treatment difference was larger at 49 percent treatment effect and a p value of 0.001, and might better reflect the utility of the device in patients with broad criteria, that is, the typical patients who met the fast enrollment and probably the patients that we treat on a regular basis.

The interim group was actually a group that existed just for the DSMB, in which 50 percent treatment effect was obtained, 0.01 as well, and that was something

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that was just a stepwise approach to get to the final sample size of 659.

As you can see, under the two proposals and any way of evaluating this, this trial was significantly positive, more than the nominal p values under the most conservative evaluation. Again, the proposal is to evaluate this cohort. Again, prospectively we asked to restart this trial. We thought we paid an alpha penalty for this. We think this is a legitimate trial to estimate the actual treatment effect that this device can perform on the enrolled patients.

[Slide]

If we go back and then evaluate -- and this data was never seen by anybody in the trial except the data safety monitoring committee until the end, we find that, in fact, it probably was a good decision for us to restart this trial and widen the criteria. The control group, in fact, in this restricted criteria only had a 10 percent MACE rate. When we did widen the criteria the rate did go to 17.8. So, I think it was a good recognition by the PI and PIs at the sites that the criteria were too restricted and may not represent the risk group that we wanted to look at where this device would have value, and that is demonstrated by looking at the control rates between the two groups that we outlined. So, we think that the 17.8 group which

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represented the rapid enrollement and larger criteria actually represented the typical patients that we treat and those at risk.

[Slide]

Therefore, we can look at the overall treatment effects and they are based, in fact, on this group, as Dr. Baim showed earlier.

[Slide]

So, in conclusion, this 659 patient cohort, which had broader eligibility criteria and rapid enrollment, best represents patients with vein graft disease and provides the best dataset in which to estimate the difference in MACE between the two arms. And, I will stop there. Thanks.

MS. HINMAN: At this point we are going to have the final presentation by the sponsor. Dr. Dennis Wahr is going to speak to us specifically about some of the unique uses of the PercuSurge GuardWire in the control arm, and we will let him take that now.

DR. WAHR: Thank you.

[Slide]

I would like to just reflect a little bit on our single-site experience with the use of the GuardWire. At our institution we did 6 roll-in or learning patients. Of the 68 patients we randomized in the trial, 34 received the GuardWire. As I mentioined earlier, on two occasions after

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the trial was completed we used the GuardWire on an emergency use basis with FDA approval. In addition to that, I personally performed 5 animal studies with this device. If you total all of that up, our institution had 47 total GuardWire experiences and I had used that myself approximately 85 percent of the time.

[Slide]

The PercuSurge GuardWire device is a first of a kind, unique and innovative device. We, as interventional cardiologists, know that any time such a first of a kind device becomes available there is a definite learning curve to its use. Certainly, with the PercuSurge GuardWire there was no exception to that rule.

In the next few slides I would like to just review how device malfunctions and adverse events changed throughout the study.

[Slide]

This first of a kind device had at least three separate unique portions. First, there was the distal occlusion balloon. No previous device interventional cardiology had such a feature. Similarly, as a result of that balloon on the end of the wire, wire performance was effected and, finally, there was use of an export catheter for the purposes of aspiration, again a unique feature.

Because of these unique three things, it certainly was

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appropriate that each site was requested to do a roll-in phase which averaged 4.5. I think the trial results, in my personal experience, reflect the fact that approximately 5 learning cases is appropriate.

[Slide]

Another fact that should be pointed out here is that there actually was a modification made in the middle of the trial of the inflation/deflation apparatus. Pictured here is the so-called GuardWire-1 used in approximately the first two-thirds of the patients of the trial. With this device there were actually two syringes. This larger syringe was used for preparation and deflation of the balloon. The smaller syringe was used for inflating the distal occlusion balloon. The smaller syringe had only two potential sizes. You had two notches. You could either put the balloon in the smaller size or the bigger size. If you needed a size larger than that you had to choose a different syringe and system altogether. So, the physician was forced to choose, based on the angiograms, as to which size device to use.

This was modified with the GuardWire-Plus. These two syringes were combined into a single syringe which had a novel dial which allowed the balloon to be sized to multiple sizes, all the way from 3-5 mm. It not only simplified the use of the device, but it removed the issue of choosing the

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correct size of the balloon up front. This was used in approximately the last 144 patients that were enrolled in the trial.

[Slide]

Device malfunctions during this study were defined as the failure of a device to meet any of its performance specifications or otherwise perform as intended. It was an extremely broad definition that included everything from a device being accidentally dropped on the floor to an actual malfunction within the patient.

[Slide]

We defined these types of malfunctions as type I, II or III. Type I malfunctions are those that occurred out of the body during the preparation or treatment. These include such things as contamination, touching it accidentally; kinking the GuardWire while putting in the adapter; milky balloon, and I will say something about that in a moment; or the physician choosing the wrong size.

Type II were malfunctions that occurred with the device in the body but, because of their nature, did not have the potential to affect sequelae.

Then, type III, of course, were the most worrisome where it was in the body and, if it occurred, it could potentially affect outcome.

[Slide]

If we look at these device malfunctions by types - and we divided them here between the original GuardWire, the first 253 patients, and the GuardWire-Plus. You can see that there was a distribution between type I, type II and type III malfunctions. In the type I we had 23 patients, 9.1 percent. As the trial moved to the GuardWire-Plus inflation/deflation device, the type I malfunction dropped significantly. Similarly, we can say the same thing with type II device malfunctions and also with type III malfunctions, clearly reflecting not only a learning curve but also possibly in part related to improvement of the device.

[Slide]

These device malfunctions, as I mentioned, had very broad definitions. Contamination -- you know, dropped on the floor; wrong size chosen for the vessel. A big category where we counted malfunction was use of other devices without protection. A number of times physicians at the end of a case pulled the balloon out and used it off protocol and without the distal occlusion out. That obviously was a malfunction but not the fault of the device.

This milky balloon thing, which I think occurred in like 13 patients early in the trial when the device was preped and contrast as injected to prep the distal occlusion balloon, inside the balloon it looked milky and not clear.

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That was a concern. They were called malfunctions. Ultimately, it was proven that the reason for that is that the contrast was reacting with the residual residue which was within the hypotube. It was entirely unrelated to the function of the device and that was corrected.

In otehr words, these device malfunctions include a large number of malfunctions with no potential to affect the patient. However, I think it is important to include all of them because we wanted to learn as much as possible about the device performance.

[Slide]

Here is really the final thing to point out. If we look at GuardWire-1 and GuardWire-Plus, if you count all of these malfunctions there was approximately 35 percent device malfunction rate in the GuardWire-1. This blue bar includes type I, II and III in there. However, if you look at the MACE event rate within the GuardWire-1 patients, there was approximately just a little less than 12 percent which actually, even in the group where there was reported device malfunctioning, came very close to the overall MACE rate for the entire trial within the GuardWire group. That is the red liine. The grey line is the MACE rate in the control group of the study. So, even the device malfunction group beat significantly the MACE rate and the no GuardWire group. As it went to the GuardWire-Plus device, the MACE

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event rate dropped again. This was almost 7 percent, reflecting an improvement in the learning curve, which is pretty remarkable because the average center still only did about 7 or 8 cases.

At our institution, where we used the GuardWire 42 times, CDAC adjudicated MACE rate had fallen at our institution to 3 percent. So, I think it is interesting to speculate on where this MACE rate might really go as the learning curves continue to improve. However, even at the beginning of the trial, with very low volume operators, the MACE rate clearly is significantly better than the MACE rate within the control group.

I think that this is just a remarkable thing because this is an innovative, first of a kind device and in my experience of 15 years as an interventional cardiologist having seen new devices, I don't ever recall a single device where right out of the chute we were able to achieve this kind of efficacy data compared to a control group. When we look at things like new stents that come on the market, we, as interventional cardiologists, have already used these devices thousands of times and it is a minor thing, and still sometimes you have trouble showing improvement. So, I have been extremely impressed with the initial performance of this device.

MS. HINMAN: The sponsor has concluded their presentation.

DR. TRACY: We need to take a ten-minute break to add additional chairs, and I would like to remind people to please sign in at the desk out there. So, let's regroup at 9:30.

[Brief recess]

DR. TRACY: I would like to call us back to order. We will now proceed with the FDA presentation.

FDA Presentation

MS. KAISER: Good morning. My name is Suzanne Kaiser, and I am a biomedical engineer in the Interventional Cardiology Devices Branch of the Office of Device Evaluation. I am also the lead reviewer for the PercuSurge GuardWire System 510(k) submission, K003992.

Today, Dr. Paul Chandeysson, the medical officer for this submission, and I will present the FDA summary for the GuardWire System. This device is a distal protection system used in the treatment of saphenous vein graft disease.

Originally the sponsor submitted a PMA application for the GuardWire System. However, FDA has determined that the appropriate regulatory pathway for this distal protection system is through the 510(k) process. Based on

this determination, the 510(k) for the GuardWire System was submitted and the sponsor's PMA was withdrawn.

Today you will be asked to discuss and make recommendations on the sponsor's 510(k) submission. Your points of discussion of the clinical study results and labeling recommendations will be taken into consideration by the FDA in their evaluation of the application. You will not be asked to vote on the approvability of this device.

[Slide]

This presentation will identify the FDA review team members; provide a brief summary of the non-clinical tests conducted on the GuardWire System; provide a summary of the clinical investigation of the GuardWire System; and identify the FDA questions for the panel.

[Slide]

Members of the FDA review team include Dr. Paul Chandeysson, from the Office of Device Evaluation, who served as the clinical reviewer; Mr. Gary Kamer, from the Office of Surveillance and Biometrics, who served as the statistical reviewer; and Ms. Liliane Brown, from the Office of Compliance, who coordinated FDA inspection of the investigational sites.

[Slide]

The GuardWire System is intended for use in coronary saphenous vein bypass grafts to contain and

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aspirate embolic material while performing percutaneous transluminal coronary angioplasty or stenting procedures. The system provides temporary occlusion of the vessel during the interventional procedure and is comprised of four principal components: the GuardWire-Plus Temporary Occlusion Catheter, the Export Aspiration Catheter, the Microseal Adapter and the EZ-Flator. The system also includes several accessory components: an introducer sheath, extension tubing for the EZ-Flator, extension tubing and stopcock for the Export catheter, a 20 ml syringe for the Export catheter and a prep needle. The GuardWire-Plus System is a sterile, single-use, disposable device.

[Slide]

The SAFER trial was conducted with two versions of the device, the GuardWire Temporary Occlusion and Aspiration System and the GuardWire-Plus Temporary Occlusion and Aspiration System. The GuardWire-Plus was used in the latter portion of the trial. The GuardWire-Plus includes changes that were validated as part of bench testing. The modified system incorporates several changes. First, the occlusion balloon can accommodate vessel sizes ranging from 3 mm to 6 mm in diameter. The previous design was offered in several sizes to accommodate various vessel size ranges.

Second, the modified device has a smaller crossing profile. Third, the GuardWire-Plus System incorporates the

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EZ-Flator device which delivers a controlled volume and is used for inflation and deflation for all vessel diameters. The previous version of the device utilized two separate syringes that operated independently via a stopcock. The syringes were specific microinflation syringes with fixed volumes matched to the specific vessel size.

The sponsor seeks clearance for the GuardWire-Plus Temporary Occlusion and Aspiration System.

[Slide]

A series of in vitro tests were performed to evaluate the mechanical integrity and function of the GuardWire System and each of the individual components. The results demonstrate that test acceptance criteria were met.

Biocompatibility testing was conducted on the components of the GuardWire System. Biocompatibility testing, conducted in accordance with ISO Standard 10993, demonstrated that the catheter is non-toxic and non-hemolytic.

Animal studies in a porcine model were conducted on the GuardWire System. The animal results show changes consistent with the use of guidewires and catheter-based procedures without inflation. FDA has not identified any issues regarding the animal testing conducted on the GuardWire System.

The results of the animal, bench and biocompatibility testing demonstrate the integrity and functionality of the device for its intended use. The bench testing information presented to date does not address shelf life of the device and its packaging. This issue is being resolved with the sponsor.

[Slide]

As discussed in the FDA summaries, the incidence of device failures and malfunctions during clinical use of the GuardWire System appears to be high. The panel pack contains information about the relationship of these device failures to MACE events, the device design, and the experience of the investigator. FDA continues to work with the sponsor to address this issue. FDA would like the panel's input on the clinical significance of these events and any suggestions for improvements to the labeling and/or physician's training program that may reduce the incidence of these events.

[Slide]

The saphenous vein graft angioplasty free of emboli randomized study is the pivotal study for the evaluation of the safety and effectiveness of the GuardWire System. Dr. Chandeysson will provide an overview of the trial design and a summary of the results.

DR. CHANDEYSSON: Good morning.

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[Slide]

My name is Paul Chandeysson, and I am a medical officer in the Peripheral Vascular Devices Branch of the Division of Cardiovascular and Respiratory Devices.

[Slide]

The pivotal clinical data for the PercuSurge GuardWire are from a prospective, randomized clinical trial of patients needing treatment of a single saphenous vein graft of a coronary artery. The patients were randomized either to treatment with the GuardWire or without the GuardWire in a one to one ratio.

[Slide]

The primary response variable was the rate of major adverse cardiac events at 30 days after treatment. The MACE events include death, Q-wave or non-Q-wave myocardial infarction, emergent bypass surgery, or repeat target vessel revascularization.

[Slide]

There was a roll-in phase for the training of the operating teams, and then 800 patients were to be randomized. Interim analyses were to be done by the data safety monitoring board after the enrollment of 350 and 550 patients. Stopping rules were based on the 30-day MACE rates..

[Slide]

After 142 patients had been randomized and treated, the inclusion criterion which defines the types of lesions to be treated was changed from "a maximum of two lesions within a single saphenous vein graft" to "one or more lesions within a single saphenous vein graft, located in the proximal segment, at least 5 mm distal to the anastomotic site, the mid-body segment and the distal segment, at least 20 mm proximal to the anastomotic site." The purpose of the change was to allow the treatment of lesions which were more challenging and more typical of clinical practice.

[Slide]

The change in the inclusion criterion resulted in two similar randomized clinical trials with different lesion characteristics and numbers of pts. There were almost four times as many patients in randomized clinical trial 2 as in randomized clinical trial 1. Additional data have been submitted, enlarging the size of RCT-II, but those data have not been reviewed.

[Slide]

A comparison of 18 demographic and clinical characteristics of the patients showed that there was no significant difference between the test and control groups in either RCT and no difference between the two RCTs. This

was to be expected because the selection criteria for the patients were not changed.

[Slide]

A comparison of 15 characteristics of the lesions, such as lesion length, percent diameter stenosis, and type of lesion by the American College of Cardiology/American Heart Association classification, showed that there was no significant difference between the test and control groups in either of the two RCTs. The only significant difference between the lesions in RCT-I and RCT-II was the percent of calcified lesions.

[Slide]

The treatment effect of the GuardWire as measured by the difference in the 30-day MACE rates in the GuardWire and control groups was apparently different in the two RCTs. The substantial treatment effect seen in RCT-II was not seen in RCT-I. The primary difference between the two RCTs was in the MACE rates of the control group.

[Slide]

There are several possible causes for the apparent difference in the MACE rates in the two RCTs. The small size of RCT-I may have allowed a fortuitously low MACE rate in the control group to have apparently shown no treatment effect, while the MACE rates in the larger RCT-II were more

representative of the real treatment effect of the PercuSurge GuardWire.

Or, the difference in the calcification of the lesions in the two RCTs may have had a real effect on the treatment effect of the device.

Or, the difference in the characteristics of the lesions, which were not measured, may have had a real effect on the treatment effect of the device.

Ms. Kaiser will now post some questions, the first of which deals with this issue.

MS. KAISER: FDA would like to obtain panel input on the following questions.

[Slide]

The randomized study was divided into two phases that may be considered two randomized clinical trials. The two phases are designated as RCT-I and RCT-II. RCT-I consisted of 142 patients and RCT-II consisted of 551 patients. The criteria for the lesions in the SVG were different in these two RCT phases. The patient selection criteria for RCT-I required that the patients have a maximum of two lesions within a single saphenous vein graft which required treatment. The patient selection criteria for RCT-II required that the patients have one or more lesions within a single saphenous vein graft, located in the proximal, mid-body and distal segment which required

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treatment. The intent of this change was to allow more complex, multiple or diffuse lesions to be treated in RCT-II.

Question 1: Please discuss whether there are any substantial differences in the lesions treated in RCT-I and RCT-II that could affect the poolability of the data.

[Slide]

A substantial difference in 30-day MACE rates was noted in the control arm of the SAFER trial after inclusion/exclusion criteria were modified. After the entry criteria were changed the control MACE rate increased from 10 percent to 20 percent. Review of the demographic and angiographic data between RCT-I and RCT-II, 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 a diseased saphenous vein graft?

[Slide]

A total of 1104 patients were enrolled in the study. The submission includes data collected for 979 subjects; 286 were roll-in subjects and 693 were randomized subjects; 551 of the randomized subjects were enrolled after a change to the inclusion criteria and are the basis of the primary analysis. Of the 551 subjects, 273 were randomized

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to the GuardWire arm and 278 were randomized to the control arm. The data presented are based on an interim analysis and do not include subjects that were 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 plan in which the first 142 patients enrolled introduction he trial are excluded from the primary analysis.

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 I error values that should be associated with each planned or realized look. These values must assure an overall study Type I error of 0.05. Their values may not only impact the results of hypothesis tests bvtut may also change the widths of the reported confidence intervals. These changes could influence the evaluation process and the labeling.

Also, 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?

[Slide]

Table 7 of the SAFER clinical report and the narrative summaries identify the device failures and malfunctions that occurred 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.

[Slide]

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.

[Slide]

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 effects, and explain how the product should be used to maximize benefits and minimize adverse effects. Please address the following questions regarding the product labeling:

Question 6a: Based on the data from RCT-I and RCT-II as discussed in question 2, do you recommend that the PercuSurge device be labeled for use in all SVG lesions? Please comment on the "indications for use" section as to

whether it identifies the appropriate patient population for treatment with the device.

Question 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.

[Slide]

Question 6c: Please comment on the "warning and precautions" sections as to whether it identifies all potential hazards regarding device use.

Question 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.

[Slide]

Question 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.

Question 6f: Do you have any other recommendations regarding the labeling of the device?

[Slide]

A summary of the physician training program has been provided in Section 7.

Question 7a: 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.

Question 7b: please identify any otehr important elements that should be contained in a physician's training program for this device. Thank you.

DR. TRACY: Before I ask the sponsor to step back, are there any clarifying questions that anybody on the panel wants to ask? Dr. Crittenden?

DR. CRITTENDEN: This is for the sponsor. Do we know if the types of interventions that were done once the distal balloon was inflated made a difference in the primary or secondary endpoints? That is something that wasn't detailed in the presentation correctly.

MS. HINMAN: Let me introduce myself since I neglected to do so in the earlier session. My name is Debora Hinman. I am the vice president of regulatory affairs and quality assurance for PercuSurge Metronic, and I am going to allow Dr. Kuntz to address that question.

DR. KUNTZ: You are specifically referring to whether there was a difference in the distribution of devices between the two arms?

DR. CRITTENDEN: Right, and whether there were more stents and more angioplasties in one arm.

DR. KUNTZ: Sure. There were stents used in virtually all cases so they were evenly distributed. The only difference was that there was an increase in the number of TEC devices used when patients were randomized to the control arm compared to that of the PercuSurge arm. This happened mainly after the widened criteria because their cases looked quite degenerative and many operators were not given the option of using embolic protection and opted to use the TEC device. I think their rate was something like 1 or 2 percent in the active arm and 8 or 9 percent in the other arm. We evaluated the difference in performance and looked at both the overall difference in MACE rates and interaction between the TEC device and the randomization, and found that there was no significant difference or interaction.

DR. CRITTENDEN: So, you think it is not meaningful to track that then based on what you just said?

DR. KUNTZ: Well, it is important to track it but we couldn't find that the use of the TEC device influenced the outcome of the trial.

DR. TRACY: How about if I ask the sponsors to step back? We will still permit additional questions. I want to get on to Dr. Laskey, who is the primary reviewer. If you can just step back, but don't leave. Dr. Laskey, you

were the primary reviewer for this project and I will ask you to open the committee discussion.

Committee Discussion

DR. LASKEY: Thank you, and thanks particularly to the presenters this morning who, I thought, did a very concise, coherent job of explaining what is clearly, at least from the first read here, a moving target with varying denominators, and varying sample sizes, and perhaps varying studies.

Let me just back up for a moment and give an overview of this particular arena within interventional cardiology. I think it is important to remind everyone here that we are in the business of making patients feel better. We are not necessarily, as interventional cardiologists, all about making patients live longer, although we should be, but none of our interventions have really consistently been shown to improve survival, cath lab based interventions. Therefore, it behooves us to be very careful about looking at the hazard of what we do and ways to minimize that hazard, to make these procedures not only efficacious overall but safe overall.

As all the discussants said this morning, the hazard of intervening on vein grafts is an order of magnitude -- it is another league of risk that we undertake when we take these patients into the laboratory. It is a

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function of the vessel itself; the procedure we are doing, as has been explained; the underlying substrate; the comorbid disease, etc., etc. There is no more high risk patient than, for example, the diabetic, as Rick Kuntz showed, with diffuse vein graft disease.

So, with that background and looking at the rationale for the study, this is certainly a very defensible and laudable effort, which is to take what is agreeably an unacceptable rate of peri-procedural and long-term complications of vein graft intervention and to minimize that risk.

Now, the risk really does need to be broken down into the immediate peri-procedural risk and the 30-day risk and then, obviously, the long-term risk. Each of these risks in themselves will have different predictors, different covariates and different implications. Again, I would remind everyone that what we are all about here in general, unfortunately, is symptom relief and not survival. I wish it were the latter but more often it is the former. So, a procedure that confers an excess hazard which relates to altered survival I think needs to be looked at very, very carefully.

Really the four studies that have been submitted to us and that were discussed this morning, the roll-in, RCT-I, the RCT-II and the continued accrual all, I think, as

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has been convincingly demonstrated, show a statistically significant difference in the composite rate of adverse events at 30 days as defined by MACE.

One of the lessons learned from benefits of treatment, taken from the pharmacologic area that I would like to apply here and ask the sponsor and Drs. Baim and Kuntz to further elaborate on is the use of the composite MACE as an endpoint and, in particular, the use of peri-procedural MI as an index of procedural safety or success, and now that relates to either 30 days and, not discussed here but certainly to be discussed, the one-year rate of events in these patients.

I note that, just as there is a consistent treatment effect across the four studies or the one study, about 80-plus percent of the overall reduction in MACE is due to the overall reduction in the prospectively defined peri-procedural myocardial infarction or CPK release. I think we need to think carefully about that. While that certainly is a prospectively defined endpoint, is it a clinically relevant endpoint, and how does it impact on 30-day survival or 30-day symptom relief and, less importantly for this discussion but ultimately important for those of us who do this stuff, the one-year survival rates?

So, I could use some further clarification about where you all stand with respect to relying so heavily on an

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enzymatic benefit, if you will, which carries plus/minus relationship to clinically important endpoints. To that point, is it not the case that the study appeared to be, as you transitioned from RCT-I to RCT-II -- it looked as though you really were setting this up to show a tremendous benefit of PercuSurge because the larger, bulkier vein graft lesions are more apt to embolize and dislodge and create havoc during the procedure. So, yes, a device which is situated downstream would be more likely to catch this material and, therefore, would be more likely to impact on the consequences of distal embolization which are the peri-procedural MI events.

Be that as it may, you certainly have shown statistically significant differences but as it relates to labeling, really what happened between RCT-I and RCT-II? It is unclear in my mind who these patients are. We think we know who they are but to codify them or, as Rick Kuntz said to make them scalable covariates, there has to be something more than the "oh-oh" feature of these lesions when demonstrated at angiography. Nevertheless, everyone seemed to agree at a certain point in time that there are a lot of hazardous procedures out there and that while we may not be able to identify them precisely or to parameterize them precisely, is it fair to say that because we can't identify them precisely they must be equally distributed between the

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two treatment arms here? I would leave that more as a question mark for discussion. It is always nicer to have numbers in boxes. It is unsettling feeling just to say that, well, there probably are these unquantifiable features which are randomly distributed by nature of the RCT, but I wonder really if that is the case.

There are a couple of things -- some large issues and I don't want to touch on everything here that puzzled me as well as impressed me. Perhaps we can come back to some of these things, but one conspicuous absence between the two groups in either of the sub-studies and the overall study was graft age. Now, I can only assume that that was equally distributed but it is not here and, certainly, the age of the graft, which is something that might be a marker for how hazardous the appearance is, should be mentioned here. I think that certainly, right off the bat, usually confers hazard. It more likely is the case that if a graft is old rather than younger there is more risk associated with the procedure. That goes hand-in-hand with these other features which have been difficult to characterize and it really is surprising that the core angiographic lab failed to come up with, again, quantifiable measures of what is it that characterizes a diffusely diseased vein graft.

Just as a corollary, the presence of calcification, in my mind, is puzzling. These lesions are

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not usually calcified. You don't usually find calcified stuff in vein grafts. It is more usually soft, friable, athremotous pultracious material. So, I wonder whether this calcification thing is really a marker for something else. That is not terribly germaine to the interpretation of the results, but it is more to the point of labeling and who is appropriate for this device and, if not calcification, then what? And, what appears to be calcification could be something else. Certainly, the argument goes that often we think lesions are calcified when they are not by IVUS and vice versa. So, I think we need to be careful about that with respect to indications for use.

The issue of the mechanical failures is also one that I know we will address in greater depth but comes through loud and clear in all of the studies or the overview study, and I think that the bottom line here is that the presence or absence of mechanical failure is statistically and strongly associated with a higher MACE rate than without. So, I think that if you wind up with a mechanical failure and a MACE rate which is similar to the control arm, that is, the patients that don't have the device, we certainly should raise our eyebrows and look quite carefully at what these failures are. Are they equipment failures? Are they doctor failures? Are they an interaction of the two? Certainly a training program, etc., etc. might address

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a component of that but there is something inherent about this very complicated, lots of moving parts, clearly first generation device and I think we need to have that pointed out again in the precautions or warnings of labeling and how to trouble-shoot these things. But it certainly is, to my mind, unprecedented to have a MACE rate similar to the control population in the event of a device failure of whatever magnitude.

With respect to the proficiency and the learning curve, one thing that I saw going through the studies, and Rick Kuntz played this out nicely, is that in contrast to other procedures there does not appear to be a volume-outcome relationship. I know that this hasn't been looked at in great detail, but if you broke down the relative risk of the two arms, that is the treatment arm and the control arm, by the operator experience or the institutional experience there didn't appear to be any increase in benefit as a function of increasing volumes of procedures. So, perhaps that reflects just the way the analysis was carried out. Maybe it is just not enough patients. But, while there is a learning curve clearly there is to every technical endeavor we pursue, it is not demonstrable here. So, maybe there is something more to it than acquiring proficiency with this device and, thereby, decreasing the rate of failure and the associated MACE rate.

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One final point which is meant to be congratulatory, I would like to sidestep, basically because I am not capable with it, the statistical methodologic issues that Rick Kuntz initiated discussions about, and I am sure that will be covered later, but I do think that what carries the day here is the study RCT-II. I think RCT-II provides a very convincing, clear-cut, to my eye, example of when you start; when the clock starts and when the clock stops; enrolling a sufficient number of patients to meet statistical criteria and showing a demonstrable benefit. I would suggest that that piece of data carry the day. Certainly be combining all the patients, as Don Baim showed, that carries the day as well.

But, I would like to end with what it is that is carrying the day, and I think that the MACE rate here, comprised not solely but almost entirely of the peri-procedural MI rate, needs to be looked at very carefully and whether that may be an artifact of the way the study was conducted, specifically by looking for large, bulky lesions which will be apt to embolize; which will be apt to be caught by a distal catchment device, thereby conferring the "benefit." I think we need to look a little bit harder at the benefit. I am encouraged to see that there was a tendency towards a decrease in the death rate at 30 days.

That is what I would like to see. That is a different

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study, but it certainly provides a consistency that I am always in search of when I look at these surrogate endpoints. Thank you.

DR. TRACY: I apologize to the sponsor. When I asked you to step back I didn't look around. There is no place for you to step back. So, please remain seated and we will just have the different panel members ask you questions as they come along.

Dr. Laskey, you made a number of allusions to questions. Any specific questions you would like the sponsor to address?

DR. LASKEY: Well, to start with two -- the device failure versus MACE, and how you can help me through -- well, your device malfunctions, failure and MACE as indicated in our panel pack, version one -- that would be the first question.

The second question, as I alluded to, is the endpoint and the CK component of it, and its relationship to the relevance of this study with respect to hard endpoints.

MS. HINMAN: Thank you. I am going to have Dr. Wahr talk in depth and reference back to his earlier discussion on the actual malfunction rate, and his experience and compare and contrast those modes with the outcome of the trial. Of course, Dr. Baim and Dr. Kuntz are both welcome to comment as well. When we get to your second

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point we will have Drs. Baim and Kuntz respond to you on that point.

While Dr. Wahr is getting his slides up, Dr. Kuntz has a statistical point he would like to make.

DR. KUNTZ: I think the device malfunctions were very liberal with the definition of how the device could be seen to fail in both a minor and major mode. Most of those failures were inability to prep at the table when the device was used. That is why the incidence was high. It got better with the second device.

The data that I think Dr. Wahr is going to show actually demonstrates the MACE rates associated with those patients who had failures. Actually, the point of that slide was that they were the same as lower than the overall MACE rates without failure.

[Slide]

DR. WAHR: Yes, in terms of trying to specifically respond to your question, this bar which demonstrates a 35 percent device malfunction, includes the type I, II and III descriptions that were presented earlier. Types I and II really were the types of malfunctions that had no potential to affect the patient. The type III, which were device malfunctions -- and device malfunctions could be either due to the device or to the operator -- your point is well taken that this is a novel device which requires new techniques,

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for the physician to be aware of new techniques. But, despite that fact, even with the GuardWire I, I think that the MACE event rate, which is the red bar right here, still was less than that of the control of the entire study and, actually, with the GuardWire I at the very beginning of the study, was only slightly above the MACE rate for the entire trial.

Speaking about the learning curve and the device malfunctions, I think it is important to point out that there were 68 centers in this trial. The average center still did only about 10 cases. Furthermore, each center had more than one investigator. In most cases there were three or four investigators. So, by the time you break it down to actually how many procedures an average investigator performed, it is going to be a very low number and I think that reflects the reason why, by operator, as the study went on it was not necessarily possible to show a learning curve. If you look at the very few operators that did a higher number, you find, within that subset, a much lower MACE rate reflecting the learning curve.

If we just talk about the so-called type III device malfunctions, it is also important to note that a type III malfunction such as, for example, the balloon inadvertently being deflated during the case -- while that would be called a device malfunction, it may still only have

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had a minor impact on the case because most of the procedure, with several export procedures, may have been done already with the balloon inflated so that a good portion of the debris may have been removed prior to the one incidental point during the case where the balloon came down leaving the possibility of distal embolization. So, I think, that is why even with a type III malfunction it did not necessary get a MACE event.

MS. HINMAN: Now I will have Dr. Baim respond to your second question, Dr. Laskey.

DR. BAIM: If I might, I would like to editorialize a little bit on Dr. Wahr's comment. The failure modes that are subsumed in type III include inability to occlude with the balloon, premature deflation, inability to aspirate, and everything that we saw in this trial suggests that in those cases the MACE rate creeps up towards, but doesn't quite reach, that of the control arms. So, there is no evidence of catastrophic complications induced by those failures, and even with a 10 percent incidence of those type III failures in the trial, the overall trial still shows benefit of the device. Moreover, the failure rates, through both operator learning and device improvement, decreased monotonically during the trial. So, I think that what we are talking about now in terms of the GuardWire-Plus and the current understanding of the

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instructions for use is a much lower incidence of device malfunction than in the early portions of the trial.

I would like to respond to the comments about generalizability of the study and the use of CK as the driving portion of the composite endpoint, and Dr. Kuntz may have some other comments. First, going into this trial, unlike a new stent trial, there was not a lot of experience with this device. It was still a first generation device. And, I think our instincts in patient selection were to pick cases that looked pretty straightforward for delivery. That led to enrollment of only about one out of every ten vein grafts that came through the cath labs because of these very rigid inclusion criteria, and they tended to be the more discrete grafts with lower event rates.

After the broadening of the inclusion criteria with patient 143 and beyond, the percent of patients enrolled increased and that was represented by an increase in the enrollment rate nationally to about 20 patients per week across the sites and the increase in MACE rate that you mentioned from 10 to 20 percent. But I would point out that 20 percent is very close to the free-living, non-protection MACE rates that have been described from our center and Washington Hospital Center report by Kaylen Ho, 17 percent on which the trial was powered. So, I would look at it as a move from an overly selective, uncomplicated group to a more

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representative group, which is why we are making the case for RCT-II being more reflective of general practice compared to the restrictive RCT-I.

In terms of the use of CK elevation in the composite endpoint, our position on CK elevations is that generally it is only the larger CK elevations, greater than 5-8 times normal, that carry an adverse impact on long-term survival. I know this is a hotly contested position certainly in native vessels, but I think the data in vein grafts, particularly the thousand patients studied by Hong et al., from Washington Hospital Center, show a clear relationship between the CK elevation events, particularly the larger ones, and a doubling or tripling in one-year mortality. So, CK is an important event here. When we break the CK elevations down into the relative heights, the benefit is not confined to the 3 times normal elevations seen in each of the categories, on up to 5-8 times normal.

You mentioned the trend towards a reduction in mortality. I also put a lot of stock in the 50 percent reduction in clinical no reflow events, from 8.3 to less than 4 percent, because that is an independent event that carries increased in-hospital mortality with it. So, the benefit is driven, yes, by CK elevations but that includes larger CK elevations that have been linked to mortality as matched by a trend, a strong trend in reduction in mortality

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and also reduction in perceptable clinical complication of no reflow.

DR. KUNTZ: I would like to make two comments as well on the endpoints and also the issue regarding the two cohorts. First the endpoints. The issue of cardiac enzymatic elevation relationship with mortality is very complex. It is clear from a large body of data from IIb/IIIa inhibitor trials and from other retrospective analyses that as you increase the cut-off for cardiac enzyme elevation in the peri-procedural area there is a relationship with late mortality.

It has been my position that this is prognosticating. That is, that the relationship and association are probably not a cause and effect relationship. That is, it is not a true surrogate. Practially speaking, it means that if you lower those CPKs you probably won't reduce the risk of death for native coronary disease because the relationship between CPK elevatioins and death is confounded by the presence of atherosclerosis.

Now, there is no question that the measure of cardiac enzyme elevation does reflect myocardial necrosis, but in the regular patient with native coronary disease, they generally have a sufficient reserve in their LV to not have the cause of death be the LV dysfunction. On the other

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hand, in the vein graft patient, most of these patients have significantly reduced LV function but as they are teetering on the corner even small amounts of LV dysfunction may actually cause major changes in LV dysfunction even with small cardiac enzyme elevations. So, I think the potential for cause and effect relationship with even moderate myocardial infarctions in vein graft patients being linked specifically unconfounded with death is stronger in vein grafts than for native coronary-artery disease. And, despite the fact that there is no other good measure to use to measure complications, other than a very large scale mortality in the trial, which I think would also be linked but would probably require a sample size of 10,000.

The second issue is the concern towards the 142 versus the 659 group. What I would like to say is that while this has been referred to as a post hoc analysis, actually this was done very prespecified. We were faced with a trial that potentially was not going to be a valid trial, and we had to act quickly to understand how to deal with this issue of slow enrollment and the potential that our control groups are not reflecting what our null hypothesis was initially.

The way that we did that, I think we are quite proud of. That is, we acted very quickly, with advice from the Food and Drug Administration, to deal in an on-line way

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with how to make this trial more valid, and that included rapid consultation, changes in the criteria, and alteration of the trial in progress being totally transparent to the sites up front. So, while it may look a little bit retrospective in data dredging, I think that it really wasn't. I really think that we had determined that potentially we didn't take a step in the right direction and quickly we corrected to a direction which would be more valid. All of the decisions about how to redo the interim analysis, all the decisions about how to correct for alpha error were done prospectively without evaluation of the data with risk that I think the company took, as well as the investigators, that potentially that first 142 patients may actually have had quite a different treatment effect and could have contributed strongly. But, it was the feeling that because of the slow enrollment, because of reference from the field, these patients did not reflect the typical cases and the decision was made to go to the new cohort.

So, it is somewhat complicated. It does require some detailed explanation to figure out what we did. At the same time, I think it was the only appropriate action to take when we were faced with the realization that we might not have the actual sample population reflect our reference group.

DR. TRACY: Is that it, Dr. Laskey?

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DR. LASKEY: Yes. Just one apology. In no way, and forgive me if that is how it came across, did I mean to say that there was data dredging going on here. It was clear it was all prospective. You did your usual articulate job of explaining how this was all thought out.

But I would like to leave us all with the same question. Interpreting these results and the differences between the two treatment arms, yes, a change was made from RCT-I to RCT-II. Yes, it was prospectively defined. Yes, it helped to increase the enrollment rate. Those are all good things. But, what is it about these patients that made people jump at the opportunity to participate and become highly motivated? Why is it that we cannot find these ineffable characteristics that led to the inclusion of these patients? And, is there a possibility that some of these ineffable and undefinable, scalable covariates could be driving this? Yes, we can point to an angiogram and say this is diffuse; this is disgusting; this is high risk; but we need to do better than that, and I think that you all need to do better than that for labeling. So, just what do you think was the difference in these patients that defies the core lab to come up with meaningful differences?

DR. KUNTZ: That is an excellent question, and I think that we can review the status of restenosis in coronary disease ten years ago. In 1990, it was not clear

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from a variety of restenosis predictor models what would predict stenosis. As a matter of fact, there was a paper written, a meta-analysis suggesting that of 250 papers written there were 65 different predictors. It wasn't until that time that we and others actually decided to measure the size of the lumen and quantitatively determine that that was a critical predictor, that all of a sudden the ability to predict restenosis could be done with a high degree of certainty. I think we are at that threshold now with vein grafts. That is, the use of the classical AHA ACC morphology criteria, mainly designed for coronary disease, is not serving us well in looking at the morphological problems associated with vein grafts. That is, when one looks at a vein graft disease, most interventionalists, a hundred out of a hundred, would agree that that is an ugly vein graft but we don't have a measure of ugliness right now. We can probably put together -- and maybe the skilled QCA groups such the Thorax Center and others can determine a scale of the length of degeneration, the irregularity of the borders, the presence or absence of characteristics of thrombus which might, and I think will, actually be strong predictors model. As a matter of fact, we are undergoing projects now to retrospectively review data to try to predict this but currently we have no potential model.

The evidence that there is a difference though I think is that when we allowed the criteria to be widened we had a dramatic increase in enrollment. This reflected what most investigators felt was the garden variety patients, and we had an abrupt change in the control rate that was noticed up front. So, I think there is something there. We just haven't unlocked the key to determine what the scale is and how to measure it and predict it.

DR. BAIM: I think that the covariate is the extent of disease in the vein graft. But the problem is that lesion length, defined as the length of the segment with greater than 50 percent narrowing, doesn't accurately capture sub-50 percent disease elsewhere in the graft. So, I think it would be very interesting to look retrospectively at more subtle angiographic predictors in this subset of patients in the control arm who had MACE event rates.

But the important point in this trial I think is that the patients enrolled were a substantial subset of patients in whom the operators would, without distal protection availability, have rendered the percutaneous treatment. Because 50 percent of these patients were assigned to the control arm and would have been done without protection, the operators were still excluding patients with very, very diffused, degenerated vein grafts. But the fact that it is representative of current practice is supported

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by the MACE rates in the control arm that are very comparable to the MACE rates seen in vein graft stenting series.

DR. TRACY: Let's go sequentially around the room. Dr. Crittenden, did you have any additional issues you wanted to raise?

DR. CRITTENDEN: One question for Dr. Wahr. Why do you think five procedures versus four, or eight, or ten and, as a corollary to that, did anybody look at operator specific volume outcome measures as opposed to site? I know there were 68 sites and, as you said, there were maybe two or three investigators at each site. Did anyone look at operator specific outcomes to see if that made a difference?

DR. WAHR: I will take the first question first. I think that five is a reasonable number primarily because with five, approximately five which was what was actually done in this trial, when we looked at the MACE event rates with five procedures, the MACE event rate was slightly less than in the control arm. So, I have some confidence that if you get that far into the training curve you have gotten to a point where you are better than you would be --

DR. CRITTENDEN: So, there is a threshold at five?

DR. WAHR: Well, that is what was demonstrated in the SAFER trial. I mean, at that point I think it is fair to say from the roll-in data that we had an equal or less

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MACE event rate at that point. Now, on an anecdotal, practical side, I think that to become comfortable just with the assembly of the unit and its performance, in my own experience it takes three or four cases, you know, to be able to do that. I think that there is a difference, a fundamental difference in terms of how you perform an emboli protection case compared to just angioplasty that we are all used to. Your eye, the direction of your eye has to be redirected. With a straightforward angioplasty stent procedure you tend to focus on the lesion. You tend not to focus on the distal tip of the guidewire. With this procedure your eye must be trained to refocus at the distal end of the wire so that you don't allow the distal wire to migrate, to go up and down. Catheter exchanges need to be done with your foot on the fluoroscopy pedal. These are fundamental things that you have to kind of get used to. It takes a few cases to do that, and I think it is not difficult but you need to be focused in the training procedure.

DR. CRITTENDEN: If I understood Dr. Baim correctly, it sounds like the patients in RCT-I had lesions that were so benign that most people felt comfortable to do this without distal protection. Do you agree with that? Did I understand that correctly?

DR. WAHR: I think that I would agree with Dr. Laskey that all of us have a gestalt that the more diffusely diseased vessels are more likely to embolize. That would be my opinion also. That said, we saw no reflow cases occasionally in patients with very discrete, short lesions. So, it is more complicated than just that, and I don't know the answer, you know, as to how to predict them.

DR. BAIM: I think that those discrete lesions were also in RCT-II. It is just that in addition there were these more diffuse lesions.

I want to come back to this learning curve issue because this, as a new device, really had us in the position of pulling ourselves up by our boot straps. We were learning the tips and tricks of how to use this device as a group even as the trial was starting, and we had a number of conference calls, pooling experience for investigators that led to the gradual evolution of clear "do's" and "don't's" with this device that were taking place during the learning curve phase. So, I would say that if one is looking at taking new operators following the approval of this device and getting them proficient in its use, they are going to benefit from all of those "do's" and "don't's" learned during the trial and not have to surmount that part of their learning curve.

Secondly, the device that they would be using, the GuardWire-Plus and the EZ-Flator device, is ten times better in terms of ease of use than the original two-syringe model and the original guardwire. So, that is a reasonable level of training to get operators used to the unique characteristics of the device and, secondly, to the need for coordinated activity of the operator who is at the groin and the operator who is manipulating the proximal adapter on this device.

DR. CRITTENDEN: A question for Dr. Kuntz, did you ever look at a time since the original operation to see if there was a difference in MACE? Did that seem to make a difference?

DR. KUNTZ: We were just discussing whether we even captured that data. I think we do have it, we have not analyzed, as Dr. Laskey brought up, the age of the vein graft with respect to the complication rate. I can tell you that the majority of these cases were greater than six or seven years old, and we have seen a gradation when we look at fresh vein grafts, a few years compared to the old ones. I don't know if we will be able to get the gradation in the group that we have in this trial, but it is certainly a good point and we are going to evaluate that.

DR. CRITTENDEN: And a question for the FDA, what is a high rate of device malfunction? I don't know, myself,

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what a high rate is. Could someone just briefly discuss what their ideas or opinions are about a high rate of device malfunction?

DR. DILLARD: Jim Dillard, FDA. I think our perception, Dr. Crittenden, is that when you see sort of overall rates where it could be as high as about 30 percent -- I think that is really what we saw here -- that is not small. I mean, a third is not small. So, perhaps saying that it is a high rate or a relatively high rate -- those descriptors may be a little more difficult here but even in a clinical trial if you talk about 30 percent where they may or may not, as we have heard, have a clinical impact but they certainly have something associated with the product not functioning in the 100 percent rate, that is something where we start becoming a little concerned. I think, obviously, if there is clinical impact we are more concerned than if there is not. But, I think 30 percent, to us, seemed like relatively that could be a little bit high.

MS. HINMAN: I might respond to that. We certainly saw more malfunctions associated with the first generation device, the GuardWire-1 which was the two-step syringe, and that was a series paired to occlusion volume and, recognizing that the goal here in the trial was not only to assess treatment of a severe disease scenario, we also wanted to make sure that we weren't complicating the

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trial outcome by a device that was perhaps too difficult or too early in its iteration. Therefore, through a series of conference calls that Dr. Baim just alluded to, during the course of the trial we gathered feedback from the investigators as to their chief concerns or issues with the first generation device, and with our engineering group we were able to modify the inflation/deflation setup. We still maintained the principle of design, that being a volume metric control so that within the device itself we were able to control the actual inflation of the occlusion balloon based on a vessel size diameter. That was keyed into the dial mechanism. So, what that did in actuality in the last 144 or so cases that were able to benefit from the second generation device was that it reduced sort of back-end handling because it was more facile and it was more ergonomic, and it was certainly a device that was more like what commercial devices are at present on the market. So, that is what we chose to do.

DR. CRITTENDEN: And just one final comment, as a surgeon with a fair amount of experience with redos, I know that looking at angiograms and looking at the graft in the operating room there is a big difference in what you see. I am not sure even quantitative angiography is going to be able to do it. I am not surprised that you can't find characteristics or morphologic pictures on the angiogram to

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really make a difference because the two just are completely divergent in my view. That is all.

MS. HINMAN: Could I comment just briefly on that? Then Dr. Wahr would like to add something. With respect to what Dr. Kuntz described in terms of how we came to identify this RTC-1 group, at PercuSurge we were blinded through the entire trial to the outcome of either the control group or the treatment group. Of course, we were watching the enrollment quite closely and our interest was to not prolong the trial unnecessarily, as a small start-up company. So, we began reviewing the screening logs with vigor and, to our dismay, we were not encountering the level of enrollment that prior review of hospital treatment logs would have indicated. In talking with some of the investigators, and Dr. Wahr included, we began to ask, well, what kind of patients were we losing? So, I will let Dr. Wahr speak to that, but we solely made the change from the standpoint of wanting to verify that the commercial device that was studied that had the bulk of the clinical data would be evaluated on a patient cohort that was typical and reflected interventional cardiology today.

DR. WAHR: In terms of ways to get a better handle on the morphology of these grafts, IVUS is a good suggestion, however, one of the things that we have found is that it is very easy to dislodge this friable material from

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the graft and one of the critical moments is literally crossing the stenosis initially. In that regard, a very low profile device is desirable.

I would be a little hesitant to routinely IVUS these grafts, particularly initially, to define the morphology because of the profile of the device and potential for embolizations. So, while that might be nice, I think it would be difficult.

DR. TRACY: In the interest of time, I think we will move on to Dr. Domanski.

DR. DOMANSKI: You know, I would like to pursue briefly the whole buisness of CPK elevation as a surrogate marker. I guess I am reasoning simply and maybe you can help me with it. It seems to me that this trial is clearly not powered to look for mortality, yet it shows, you know, a pretty strong tend, obviously, in the direction of improving mortality despite being, no doubt, very low powered, and you can tell us later maybe wqhat the power was and what your estimates were. But, I guess if the device is to be useful in helping one out, it has to prevent embolization that results in damage, that results, in fact, in CPK elevation. Now, I guess for the CPK elevation to be an appropriate surrogate marker it needs to, in fact, have some causal relationship to mortality, not just an association. I mean, if the position is different, by the way, than when I walked

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into the room thinking -- if the position is that people who have more extensive coronary disease and, thus, a higher mortality are simply more likely to have an elevation but there is not a causal relationship then, in fact, there is little equity in this as a surrogate endpoint and, therefore, in your study. So, I guess what I would like to hear is a little bit more education for me about why CPK elevation and, therefore, preventing microemboli is really a reasonable thing. So, maybe you could help me out a little bit because I certainly walked in thinking it was.

DR. KUNTZ: I can address that issue. You are absolutely right, I mean this is a highly debated area. As a matter of fact, we have spent day-long sessions on this in the American Heart Association and others about these issues. I can tell you my perspective on this. That is, in the native coronary device arena I think the level of atherosclerosis is probably largely the driving force between a relationship between those patients who have an incidental CPK elevation and their incidence of death three or four years later.

DR. DOMANSKI: Could I ask you right there whether what you are saying is that, in effect, the competing risk is the extent of atherosclerosis?

DR. KUNTZ: Right, the confounder. Right. It is both the relationship between atherosclerosis and the

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possibility of having peri-procedural enzyme elevation. On pure theory, lowering the CPK as associated with the procedure isn't going to affect the atherosclerotic component of the patient dying later on.

On the other hand, there is no question that when you have a cardiac enzyme elevation there is death to the myocardium. That in and of itself is something that we should try to preserve. Now, in the case of coronary arteries this might be less of an issue in patients with normal LV function and more of an issue in patients with advanced LV function because small chips at the heart are something that puts them over the threshold by which they will have LV dysfunction, and the LV dysfunction will increase the risk of death through heart failure.

It is our position that in vein graft disease the cardiac enzyme elevations are probably more profound in their relationship between myocardial infarction and LV dysfunction than in native coronary.

DR. DOMANSKI: In fact, a larger infarction.

DR. KUNTZ: Right.

DR. DOMANSKI: Relative to the remaining function.

DR. KUNTZ: Absolutely correct, right. But these patients are generally those that have multi-vessel disease and, in fact, have multiple low motion abnormalities on LV imaging studies, suggesting that their reserve for having

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further damage to their heart may not put them into the position of having an effect of optimal survival. So, in the continuum of looking at the effect of cardiac enzymes as a measure of cardiac infarction, I think it has more of an impact on vein graft disease to justify this as an endpoint, I think more profoundly than for coronary disease cases.

On the other hand, in looking at the connection between cardiac enzyme elevations and death, there is clearly going to be a connection through things like LV dysfunction and arrhythmias. But the majority of connection seen previously in IIb/IIIa trials, I think, has been confounded by atherosclerosis. As a matter of fact, I think this has now been agreed upon by many of the investigators of IIb/IIIa in recent papers, that any life-saving value to IIb inhibitors might be on other things, issues of atherosclerotic mechanisms. Again, it may be somewhat speculative but the shift has been away from this relationship of CKs.

Nevertheless, the common factor of frequent distal embolization occurring vein graft procedures, the patients who are at high risk of dying in hospital after receiving a vein graft and the measurement of cardiac enzyme elevations is a true paradigm which I think we all share as interventional cardiologists, and a reduction of that myocardial infarction and reduction of immediate risk of

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death and reduction of LV dysfunction I think would carry the day with respect to this being a legitimate endpoint in this arena. The alternative is to measure mortality or to measure things like changes in LV dysfunction, which might require a sample size I think on the order of five to ten times higher than what we have up front here.

So, I think one of the issues might be the labeling would be associated with the fact that this device does, in fact, reduce the incidence of myocardial infarction which, in and of itself, might be a valid label. In the case of the vein graft patient with LV dysfunction, it might portend into an increased risk of mortality.

DR. DOMANSKI: Well, that is certainly a clear discussion of that subject. Can you talk a little bit about the power calculations for mortality? I mean, you must have done that on the back of an envelope somewhere.

DR. KUNTZ: Right, I can do it even on the back of a business card; it is going to be extremely low. If we are looking at mortality rates that we can measure over time in this trial, which would be a six-month to one-year follow up -- I think patients are out to one and a half years -- we would expect rates normally we see in trials such as this to have a mortality rate of about two percent per year. So, a 50 percent reduction would be bringing it down to one percent. If we just looked at the typical power

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calculations done on binomial distribution for bringing something down from two percent to one percent, I can tell you that those sample sizes are going to be in the 5000 to 20,000 patient range. The power would be probably about ten percent or less.

DR. DOMANSKI: If you had had this kind of a change -- I mean, if you just looked at the percent change, it is a massive percent change actually in death. It doesn't quite reach statistical significance at the 0.05 level. How many patients would you have needed to demonstrate this much of a difference?

DR. KUNTZ: Well, if you extrapolate --

DR. DOMANSKI: About three times really.

DR. KUNTZ: Right. If you extrapolate from those estimates, assuming that they are fixed, it is probably just another couple of hundred of patients and we would have crossed the p value. But we would have to assume that there are actually random variables. So, we would have to determine what the distribution is from, and my guess is that practically speaking, with 80 or 90 percent power there is no difference. I am just, again, thinking off the top of my head -- probably two to three times our sample size to continue this further.

DR. DOMANSKI: Well, I must say as a comment that the way I sort of put this together because, you know, we

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