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noninferiority-type registry using the appropriate historical control.

[Slide.]

But there are some real problems with registries, when you think about it. You have heard about some of these. There is lack of standardization of the historical controls as well as the definitions of what MACE is. There have been variable inclusion and exclusion criteria used in all these different trials.

So, okay; let's say, then, what we will do is we will look at RCT2 from PercuSurge and we will enforce those exact same enrollment criteria in a registry. The problem is you can't enforce appropriate enrollment of consecutive patients with those types of angiographic and clinical characteristics.

What we have learned from past trials, especially the registries that have been tacked on to the stent-versus-stent trials or subsequent stent approvals, stents are getting better but if you look at the event rates in subsequent approvals, actually the registry event rates are usually higher than in the randomized trials.

Why? Because it is supposedly a good stent. It is the next generation. It is going to work. There is no control you have to randomize against and so physicians will

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actually stretch the boundaries in most registries and enroll higher-risk patients.

On the other hand, we have a different situation here. There is a risk in registry studies when you are talking about vein grafts and distal protection that low-risk patients would selectively be enrolled in an approval registry while high-risk patients, if you will, will be triaged to what we know is an approved effective therapy, which is PercuSurge, a 50 percent reduction in events.

I can tell you, this is already happening from another randomized vein-graft trial that we are involved in. Now that we have the PercuSurge registry ongoing and other registries of distal-protection devices, what we are seeing is that patients are only being enrolled selectively who are low risk in the randomized vein-graft trial. The high-risk patients are selectively being put into the distal-protection registries.

How about if you say, well, let's just try to do our best and then we will match. We will take the PercuSurge data and we will do the best we can to match the baseline angiography and clinical characteristics.

You have heard that, one, it is difficult. We don't know which characteristics really predict the adverse events. Two, matching, at best, is problematic. Three, the

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OPC data are not available. Despite everybody's good intentions, I have been watching as HIMA has been trying to get together for the last two years to make the stent-versus-stent equivalence data available in an OPC format.

In addition, all you have got is the PercuSurge database and you have heard it had different devices in it. It changed inclusion criteria throughout the course of the study and I don't know that that is a uniform-enough database or a large enough, robust enough, database to use as an OPC set even if we had it available.

[Slide.]

In addition, it has got to be very clear that registries have misdirected us in many situations. I just mention a few of them here in the device world. Directional coronary atherectomy, laser angioplasty, rotational atherectomy. We had United States multicenter registries, hundreds of patients, all showing improved early angiographic results, either safe or reduced early events, improved long-term results.

These devices were all more complicated to use. They were all more expensive, but the registries looked good. And their use increased and some of these got approved on the basis of registries.

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Then randomized trials were done. With DCA, with laser and with rotational atherectomy, in general, we saw increased complications. We saw no improvement in early or late outcomes in multiple randomized trials and, after an increase in these devices, they have now decreased.

On the other hand, you had other devices such as the stent where randomized trials have clearly shown the benefit and have driven appropriate usage.

[Slide.]

This was mentioned before by Debbie Hinman and I actually agree with this, that distal-protection filters are not the same as distal-occlusion balloons. While the goal is the same, and that is by retrieving emboli to decrease the incidence of periprocedural infarction and 30-day MACE, of course, the mechanisms are very different. I am not going to repeat everything that you just heard about how a filter is different than a distal-occlusion balloon.

Efficacy has not been demonstrated yet for any distal filter. Safety has not been demonstrated yet for any distal filter. Because these are not the exact same devices--I mean, it would be one thing if this was just another occlusion balloon and an aspiration catheter we were considering, but it is really a very different device.

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So I think it makes sense that the bar, if you will, should be higher than for an essentially equivalent device.

[Slide.]

Just to show you some pictures, I think you have all seen the PercuSurge GuardWire, the export aspiration catheter. No particles get through initially. Hopefully, you can aspirate most of the particles out.

The filters, which, at last count, there are at least twenty of them under development, are exciting to use because they are easier to use and they allow some perfusion during the procedure. There is no doubt that these would be clinically desirable attributes if they are effective.

[Slide.]

But when you look at what the filters look like, you can see these are very different devices. They are some sort of polyurethane or polyethylene bags with microporous material, anywhere from 80 to 150 microns, when you then have to catch the material, you have to retrieve it without it slipping out of the bag and, as you heard, at least with the present series of devices, you can lose wire position, et cetera.

[Slide.]

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Again, there are more. They all look different but they are all basically variations on the theme. Again, I think, because there is relatively less intellectual property on distal-protection devices, there are going to be a lot of these devices that may be introduced. I think they are going to be great if they can be shown to be safe and effective.

[Slide.]

In addition, if you are going to consider this topic, I would argue that thrombectomy and thromboablation devices also have the same goal as distal-protection filters as well as distal-occlusion balloons; in other words, to reduce periprocedural infarction by producing thrombectomy and thromboablation and reduce 30-day MACE.

Obviously, the mechanism is very, very different and I think that this should be considered by the FDA when considering these future pathways to reduce 30-day MACE and vein grafts.

[Slide.]

Quickly, in the last few minutes, noninferiority trial considerations. There are some disadvantages. One, they are clearly more complex. They are larger. They take longer. They are more expensive and you heard in the last, you must learn the control device.

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This kind of imparts a delay in the process in which, for example, the GuardWire would be available at selected sites but not enough sites where people are comfortable enough to use it yet to enroll in a comparative trial.

On the other hand, I think it is a good thing that people will be forced to use a new device. But there are several very important advantages. It controls for selection bias and most confounders and it provides important comparative data. Even though they are noninferiority trials, I would argue that what we have seen now with a lot of these, especially with the stent-versus-stent trials, that whether or not they fall markedly below or markedly above the bar, and this is a whole other thought, but significantly gives us pause or gives us confidence.

Noninferiority trial considerations; one thing that is clear, size does matter. So, if you consider, for example, the PercuSurge MACE rate of 10 percent at 30 days from SAFER, this is data that is generated from our statisticians. If you look here at the upper bound for new devices, this curve shows you 80 percent power. If the MACE rate at 30 days for PercuSurge is 10 percent, if you wanted it to be pretty confident that it would be within 11

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percent--in other words, a delta of 1 percent--okay, you are talking about 28,000 randomized patients.

As you can see here, it is an exponential curve that goes down and down as you increase the delta and allow more variability.

This is the 90 percent power curve and, of course, it is even greater.

[Slide.]

Since, obviously, 20,000, 30,000 patients is not going to happen, let's just focus--this is the same curve, just spread out here, from 13 percent up to 20 percent, at least where it starts getting into reasonable numbers here. What I am going to argue is that you will see one point here which is the 80 percent power curve.

If you notice, with a delta, an upper bound of the new device, 16 percent, or a delta of approximately 6 percent, you can see that you have 80 percent power in a noninferiority trial of approximately 774 patients.

[Slide.]

What is the summary and what are my recommendations? Of course, this just represents one man's opinion. After the PercuSurge GuardWire becomes clinically available, I don't believe it will be ethically justifiable anymore, and it will practically be impossible, to complete

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saphenous-vein-graft superiority trials compared in unprotected vein grafts for new distal-filter devices.

Registry approval pathways would be undermined, I think, unacceptably so by uncontrollable selection-bias confounders and the lack of an adequate OPC database.

[Slide.]

On the other hand, if you were to do a noninferiority trial--that is, comparing a new device to the GuardWire--randomizing approximately 800 patients, which, ironically, was about the size of the SAFER trial, using a 510(k) approval pathway in case it does show equivalence, to expedite its arrival on the United State market, after, however, panel review, that this would provide important comparative efficacy data.

Now, while a delta of 6 percent is large, larger than what we have used in any other equivalence trial for approval, I would argue that the upper boundary of the events would likely be less than what would have occurred in the placebo control, so it is not going to be a dangerous device and, at the upper end of the approval bound.

So if you get, let's say, a control event rate of 15, 15.5 percent, and the device gets approved, I would argue very strongly that the marketplace will decide. If a trial has one device at 10 percent and the other 15 percent,

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interventional cardiologists now are very driven by data and evidence-based medicine and I would argue that having that device on the market would be not a big downside.

Again, stents and stent-versus-stent equivalence trial data has clearly affected which stent is being used. We have six, seven, eight stents on the market which have all been "shown equivalent" in these large 500 to 1000-patient trials. But, again, depending on where they have fallen, I think that has really affected interventionist use and I think that has actually been supported now by a lot of other data.

Within the framework of an 800-patient loose noninferiority trial, if you will, early looks can be built in, for example, at 350, at 550 patients, with the appropriate statistical penalty. If you want, you can also do an unbalanced randomization.

I think that this requirement of an equivalency trial like this, or a noninferiority trial like this, would reasonably assure public safety, is less burdensome than some other pathways that one could come up, and is fair to industry as well.

Thank you.

DR. TRACY: Thank you.

Any questions?

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Mr. Gustafson?

MR. GUSTAFSON: My name is Jim Gustafson.

[Slide.]

I am Vice President for Clinical and Regulatory Affairs for Possis Medical. We are a Minneapolis-based manufacturer of class 3 medical devices including the AngioJet, a thrombectomy catheter system, which I will get to in a second.

As for financial interest, well, I am an officer of the company so I have got oodles of stock options. But, given what has happened to NASDAQ in the last twelve months, my financial interest is mostly theoretical.

[Slide.]

Our interest in being here is the AngioJet system. It is a 4 or 5-French rheolytic catheter for mechanical removal of intravascular thrombus. It is currently on the market in the U.S. for coronary arteries and saphenous-vein grafts, peripheral arteries and AV-access grafts. It is under IDE clinical trial for ischemic stroke.

[Slide.]

This is a photograph of the AngioJet catheter tip, the LF140 model. Here you see the six retro-aiming jets of saline which I will describe in the next slide.

[Slide.]

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Another schematic of the AngioJet catheter tip. Inside the catheter is a high-pressure stainless-steel hypotube which carries pressurized saline up past this open gap, which I will get to in a second. It terminates in a loop. The loop has six holes drilled in it so pressurized saline, which leaves the pump head at about 10,000 PSI, arrives here at about 1,000 PSI, jets through these open holes across this open space back into the effluent lumen of the catheter.

Because they are under pressure when the saline jets exit those holes and cross this open space, they are moving at about 300 miles an hour. Their passage creates a localized area of low pressure via the Bernoulli effect which causes a localized vacuum which draws thrombus in from the vessel wall and the surrounding intraluminal space into this area where it is macerated by these fast-moving water jets and flushed out of the patient's body.

[Slide.]

Quickly, an example; this is an RCA, native coronary artery. Here you see, down here at the bottom of the slide, lots and lots of thrombus and junky looking stuff that would give any cardiologist pause.

[Slide.]

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After about one minute with AngioJet, the thrombus is gone and the case can go forward to definitive PTCA and stenting.

[Slide.]

The AngioJet has been the subject of significant clinical trials over the last four or five years, coronary, especially. We did a phase 1 trial in 90 patients, a phase 2 randomized trial in 350 patients using urokinase, intracoronary urokinase, infusion as our control. In addition, the VeGAS trials included over 500 patients in concomitant nonrandomized registries and it was also the subject of some peripheral arterial trials.

[Slide.]

Specifically, and I certainly won't get into the detail more than this one slide because, as you know when you do clinical trials, there is lots and lots of data, but, in the VeGAS trial, 350 patients were randomized between Angiojet and urokinase. Half the patients, approximately, were native vessels. Half the patients had saphenous-vein grafts being treated.

All of the patients had thrombus. The average thrombus area prior to treatment by angiogram was 68 square millimeters. After AngioJet, the average area was 14 square millimeters by angiogram. Just one point; distal

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embolization by angiogram after AngioJet was 3 percent and distal embolization after all treatments was still just 3 percent.

About 13 percent of all patients in the trial received ReoPro.

[Slide.]

From this data and others, the company views things this way. In thrombus-laden coronary and saphenous-vein-graft lesions, AngioJet removes the thrombus and its potential for embolization. Second, AngioJet allows same-session definitive treatment of the lesion, PDCA or stenting, as if the thrombus was not there to begin with.

So, we conclude that AngioJet is a distal-protection device for the treatment of thrombotic lesions specifically.

[Slide.]

If we look at AngioJet and compare it to some of the devices that have been discussed today, I see a distinction to be drawn. Some devices, like AngioJet, can be called active and preventive because, in the AngioJet's case, prior to definitive treatment, the AngioJet actively dislodged and removes potentially the embolic material so that it cannot embolize whereas other devices that follow the occlusion and remove model can be considered passive or

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reactive because, after definitive treatment, the vessel volume proximal to the occlusion or filter device is evacuated which removes debris that was dislodged during instrumentation.

But there isn't a period when that dislodgement is actively pursued and potentially embolic particles are deliberately gone after and tried to be removed as they are with the AngioJet.

[Slide.]

There are a couple of implications to this difference. One, just to start out with, distal protection is desirable in coronary settings other than SVGs. Certainly, native coronary vessels can be laden with thrombus as well and thrombus can embolize if you don't watch out for it or take it out first.

So, not only is it valuable in SVGs. We think it also have value in native coronaries as well. Also, as has been mentioned by some other of the presenters here a few minutes ago, different devices will have different distal-protection strategies.

Finally, because of that, approved indications may have to use terms that have been defined carefully to reflect the differences in device design and distal-protection strategy.

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[Slide.]

Specifically, some implications are these, and some of these have already been covered by previous speakers. Patient selection; in the AngioJet trials, the VeGAS trials, thrombus was always present. 100 percent of our patients had angiographically evident thrombus. In the SAFER trial that was discussed this morning, something less than 50 percent of all patients treated had angiographically evidence thrombus.

On the other hand, the trial discussed this morning, all the patients were SVG patients; with the AngioJet trial, only half were SVG patients. So patient selection becomes important.

Endpoints can be considered important. Some of the important endpoints for the AngioJet VeGAS trial were angiographic because, before you use the AngioJet, you can see thrombus. After you use the AngioJet, the thrombus is gone and you can't see it anymore. So angiographic endpoints become important.

In other cases where you are simply passably or reactively dealing with any embolic particle, most of the endpoints that are of greatest importance are clinical.

Finally, as Dr. Stone just mentioned, controls, or the selection of controls can be important. If there is a

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new distal-protection device with a particular strategy that is going to be offered in IDE clinical trial, should the control be another device with the same distal-protection strategy as the control or should it be another distal-protection device with a different strategy for providing protection as the control or, as in the case of the SAFER trial, should there be no distal protection offered as a control and simply be only one of the two arms of the study providing an active treatment.

[Slide.]

In summary, we think that any FDA guidance that is eventually developed for clinical trials of distal-protection devices should accommodate these and other implications of device design and treatment strategy to assure that the resulting clinical science properly serves and informs both practitioners and the public.

I thank the panel for its attention.

DR. TRACY: Thank you.

Any questions?

Mr. Mezger?

MR. MEZGER: Again, my name is Jerry Mezger.

[Slide.]

I am President of EndiCOR Medical which, I guess, makes me somewhat conflicted as well, but I want to share

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with you some thoughts about a trial that we have going on right now. We are a little bit of an unusual and unique situation in that we are in the middle of a randomized trial for vein grafts.

[Slide.]

EndiCOR has developed what we call the excisor catheter system. That is a mechanical thrombectomy device that is designed to remove thrombus and grumous from native arteries as well as saphenous-vein grafts. So, it is essentially a mechanically assisted aspiration device.

Its purpose is somewhat similar to the Possis device, prevention of distal embolization and, therefore, following the model of the distal-protection devices, the design of the trial is there to try to reduce the incidence of MACE.

[Slide.]

So, for the X-TRACT trial we designed a protocol that we think is extremely similar to PercuSurge's SAFER trial and have many similarities to the Possit trial as well with the control arm to PTCA and stents and vein grafts and native arteries. The primary endpoint, again, is 30-day MACE.

We had confidence in designing the trial the way we did because of the data that we collected for the X-Sizer

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in our phase 1 study as well as international studies which show 30-day MACE similar to the published PercuSurge study results. And so we completed phase I last year. We started our phase I randomized trial in May, 2000.

[Slide.]

As the sponsor, I have to admit to a certain level of anxiety to the fact that we were blinded to the results. But that is the fact of doing a randomized trial these days. But we are getting site feedback which is positive so far, very easy to use. It is apparent that we are reducing distal embolization but, of course, we will find out how the randomized trial goes and what the actual results will be at the end of the trial.

But we have to admit to a growing concern about how the trial is going. Vein-graft trials are historically slow. We know that. We expect that we will complete our 800-patient trial by the end of this calendar, so that will be about a year and a half to do that trial.

But our concern is really that enrollment will become even slower as these new alternate treatment modalities become available.

[Slide.]

That concern is based upon the fact that we are seeing, at our really key sites the big hospital centers

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that we are counting on for enrollment of saphenous-vein-graft patients--we are seeing very low screening rates. We are seeing patients being dropped out for the purpose of protecting their well-being and we are seeing a strong correlation in these enrollment rates with the availability of distal-protection devices at some of these sites.

As Gregg Stone mentioned, they have multiple registries going on. Some sites have three or more registries going on for distal-protection devices. That is becoming a real problem for us.

Another problem for us is a concern that we are seeing a biased lesion selection in these randomized patients. It appears, in some instances, that, for the X-TRACT trial, we are only getting patients that were the low-risk patients that they put into our trial but didn't put into the distal-protection studies. So that gives us a concern that our control arm may have a low MACE rate.

[Slide.]

So my message today is that randomization against PTCA and stenting is considered unacceptable by some cardiologists today. We are concerned that distal-protection-device availability may bias the conduct of our trial in that we are only going to get the low-risk vein graft patients. So, in the post-PercuSurge era, the

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question we have is that are our historical MACE rates the only valid standard for comparison.

Furthermore, as the panel considers recommendations for future trial designs, I ask that the panel bear in mind that we have a trial ongoing right now. It is a randomized trial and we would hate to see that upset.

Thanks.

DR. TRACY: Thank you. Any questions?

Is there anyone else in the audience who wishes to speak on this topic?

DR. O'NEILL: Good afternoon. My name is Dr. William O'Neill. I am the Director of Cardiology at William Beaumont Hospital in Royal Oak, Michigan. I believe that Mike Crevina paid for my airline ticket here. Otherwise, I have no other conflicts to disclose.

I think many of the panel here have watched this field evolve over the last twenty years. I would remind the panel that the balloon angioplasty was approved as device, the mainstay of the interventional cardiology without a randomized trial being done. If a randomized trial had been done in the early inception of angioplasty with a 60 percent success rate and about a 10 percent rate of emergency

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bypass, it is really unlikely that balloon angioplasty would have ever been approved.

The reason that I wanted to take a few minutes to come up to the panel is because I would like to tell you what it is like practicing in a large volume environment right now in vein-graft interventions. These patients are the walking wounded. They are ten years older. Their ejection fraction is lower, much higher complication rate.

I think all of us, obviously, are interested in having new devices become expeditiously approved. When I go to Europe, I come back depressed because these people have access to these devices much quicker than we do. In fact, many of these devices have already been approved and I would ask you whether or not the Europeans really are harming their patients more than we are.

It is going to be very, very difficult for us to do randomized trials. I think, in fact, as everybody here has alluded to, it is going to be unethical for us to do randomized trials of the comparison standard right now because of the high rate of complications that occurs and because of the impossibility for us to really identify prospectively which patients are going to be high risk.

I think that what the panel has to really strongly consider is either using registries or noninferiority

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trials. It is going to be really very, very difficult for us to continue with these randomized trials. From a practitioner standpoint, I would like to have new devices available that makes them safer for us.

In the SAFER trial, there still is a 9 percent rate of complications. It is not 0 percent, so this device is not infallible. It still can be improved upon and the question is how are we going to get these new devices available in a more timely fashion.

The other thing that I would finally ask the panel to consider is not only the efficacy but also the mode of failure of these devices and the method by which they fail and the complication rate of failure. Dr. Wahr told you that when the PercuSurge device doesn't cross, a 70 percent complication rate occurs.

So I think it is very critical for this panel, with all of these new gadgets, not only looking at the overall success rate but also how these devices fail, how often they fail, how often they can't be delivered, is going to be very, very important in assessing the marketability of these on a long-term basis.

Thank you.

DR. TRACY: Any questions? Thank you.

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Is there anybody else in the audience who wishes to discuss this topic?

MR. KIM: Good afternoon. My name is Stu Kim and I am a regulatory attorney with the law firm of McKenna and Cuneo in Washington, D.C. Our law firm represents several clients. We manufacture proximal protection devices. Although, this may go beyond the scope of this afternoon's discussion, I would like the panel to briefly identify any issues unique to the clinical-trial design of proximal-protection devices for SVGs.

Thank you.

DR. TRACY: Thank you.

Any other members of the audience wishing to speak?

If not, then we will close the open public hearing and move on to the FDA presentation.

FDA Presentation: Questions for the Panel

DR. ZUCKERMAN: Good afternoon.

[Slide.]

My name is Dr. Bram Zuckerman. I am a medical officer with the Food and Drug Administration, Cardiovascular Devices Branch.

[Slide.]

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Coronary-artery bypass-graft surgery, or CABG, is not a permanent fix for patients with ischemic heart disease. The CABG procedure is not a permanent fix because there is one, either continued progression of native disease and two, progressive attrition of saphenous-vein-graft patency.

In fact, saphenous-vein graft attrition is approximately 7 percent during the first week even with aspirin therapy, 15 to 20 percent during the first year, 1 to 2 percent from years 1 to 6, and 4 percent per year from 6 to 10 years after surgery.

Deterioration of native vessel in graft lumens after surgery has resulted in an increasing need for repeat revascularization procedures. Surgical reoperation is associated with a higher mortality and morbidity than the initial procedure. Hence, percutaneous treatment of symptomatic venous-graft disease is often a preferred initial treatment strategy.

Unlike native coronary-artery disease due to fibrous or calcified plaques, vein-graft narrowings often contain thrombotic and degenerative material that is easily disrupted by catheter-based therapies. The dislodgement of material downstream during a saphenous-vein-graft procedure is associated with a relatively high incidence of death and

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myocardial infarction when compared to percutaneous treatment of other lesion subsets.

It has been hypothesized that distal protection may significantly reduce complication rates by collection of dislodged material that would otherwise embolize downstream during the interventional procedure.

[Slide.]

Over the last fifteen years, a fairly wide range of procedure success in complication rates has been reported in the SVG literature. Part of the variability can be explained by assessment of graft age, lesion length and thrombus burden. Risk is increased with older grafts, longer lesions, and grafts with a larger thrombus burden.

Other key factors that lead to a high probability of distal embolization of material with resulting no reflow, myocardial infarction, death or emergent CABG remain incompletely understood.

[Slide.]

The agency acknowledges that development of safe and effective distal-protection devices for use in diseased saphenous-vein grafts is currently an important research area in interventional cardiology. For this reason, the agency is seeking panel input on several key questions regarding study design in this field. Panel responses will

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be used to help develop a guidance document for distal-protection devices.

[Slide.]

The panel questions will deal with choice of control group, study endpoints and study protocol issues.

[Slide.]

Please note, in several of the questions that follow, a composite endpoint of major adverse cardiac events or MACE is used. MACE is defined by death, Q-wave or non-Q-wave myocardial infarction, emergent bypass surgery, or repeat target-vessel revascularization.

[Slide.]

We will switch now to the panel questions. We will start with the questions regarding the control group. Question 1a; Given our understanding of vein-graft disease, please discuss the need for a randomized-trial design when evaluating a new distal-protection device for saphenous-vein-graft use. When is a randomized trial necessary to insure comparison to an appropriate control group?

[Slide.]

Question 1b; Please discuss whether adequate trials can be designed with historical controls or objective performance criteria for assessment of this technology.

[Slide.]

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Question 1c; If a randomized trial is warranted, please discuss whether the control arm should incorporate use of an approved distal-protection device. If so, please discuss use of an equivalence hypothesis rather than a superiority hypothesis for this study.

[Slide.]

Moving to study endpoints, Question 2. Please discuss use of the 30-day MACE rate as the primary endpoint in a saphenous-vein-graft distal-protection device trial. Please discuss whether use of this composite endpoint captures important clinical events. Please discuss whether an in-hospital or 14-day MACE rate would be acceptable as a primary endpoint. Please discuss any alternatives to MACE that would be important to consider.

[Slide.]

Question 3; Please discuss what secondary endpoints should be emphasized in a saphenous-vein graft distal-protection-device trial. For example, should a pathological description of the type and amount of debris removed by the device be included?

[Slide.]

Question 4; Please comment on appropriate entry criteria for a saphenous-vein-graft trial that is intended to evaluate a new distal-protection device. Please discuss

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any specific patient populations that should be excluded or studied separately.

[Slide.]

The final question; Please comment on use of adjunctive antithrombotic medications. Please discuss, for example, whether glycoprotein IIb-IIIa drug use should be left to operator discretion or be prospectively outlined in the protocol.

DR. TRACY: Thank you.

Open Committee Discussion

DR. TRACY: At this point, we will move to the open committee discussion. I would like to suggest to the panel members that we follow the outline of the particular questions and focus our discussions on the questions as we move along here.

So we will go back to question No. 1, control group; given our current understanding of vein-graft disease, please discuss the need for a randomized-trial design when evaluating new distal-protection devices for SVG use. When is a randomized trial necessary to insure comparison to an appropriate control group?

Comments from the panel?

DR. CRITTENDEN: I think it is always necessary.

We have all been here when we have sat at a panel when there

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hasn't been a randomized trial and we are sitting here agonizing over what to do because the company spent a lot of money things and there are kind of iffy results, and we just don't know what the right thing to do is. So my bias would be we always need to have one.

DR. VETROVEC: Can I ask a question of the FDA, and that is where does the "rule of three" play in this? Can you help me understand that?

MR. DILLARD: Let me just ask for one clarification. By the "rule of three," you mean the third-of-a-kind device that would otherwise have been approved by the agency? Let me try to just quickly review that because we have had some changes between the Safe Medical Devices Act of 1990 and the Food and Drug Administration Modernization Act, or FDAMA, of 1997.

Both of those gave us different provisions, when you are talking about that particular piece. It specifically was focussed on PMA products, not 510(k)-kinds of devices. We heard this morning, just at least from the FDA's perspective, that the particular PercuSurge product, we believe the 510(k) pathway is the most appropriate pathway at this point when we talk about the indication we talked about this morning.

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That doesn't mean, necessarily, or a priori, it is going to be applied or even can be applied equivalently across all distal-protection devices. That really is something that we look at both technological and indications for use, and we make a comparison. Some may or may not be found equivalent if this particular product moves forward.

So the "rule of three" specifically applies to PMA products because in the PMA situation, it is almost as if, when we approve a PMA and it is not "is if," there are additional protections associated with the sponsor of a PMA device and the data that is in the PMA. It remains confidential.

In 1990, the passage of the Safe Medical Devices Act made the FDA consider whether or not, when we had multiple approvals of a similar kind of product, at what point in time could that data be more broadly used for additional products.

We never clarified that between 1990 and 1997. So that was never fully implemented. In 1997, we did have a change with FDAMA which, really, gave us a little bit different vantage point as to how we should look at data that the FDA approves through a PMA application.

Right now, it is considered--it is sort of a change in terminology, but it is the "six year" rule which

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is six years after PMA approval of a product, could the data become more broadly available to be used by the agency or other outside parties. That, likewise, has yet to be clarified by our Office of Chief Counsel as well as, I think, really understood by not only the agency but the industry alike.

We have put out--well, I won't say it is out yet, but let me just say we have the intention to put out a draft guidance that helps clarify what the agency's position is. We will have other comments from industry. At some point in time, we plan on clarifying that.

So, right now, it is not a "three of a kind" rule. It is a six-year rule and the two main pieces are at what point in time does it become an effect. Is it proactively, once we clarify it, or does it actually reach back to some point in time? I think that is going to be the main piece for us to consider. When we clarify that, we will bring you that clarification for your consideration.

So the real answer you are looking for is that right now neither one of those particular provisions are going to help us out here.

DR. DOMANSKI: In terms of randomized trials, it seems to me to very difficult to abrogate judgment completely in terms of what the FDA is willing to accept.

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Clearly--I think, clearly, if a device is new in terms of its design--in terms of its concepts, certainly, but also in terms of its design, then one would have some enthusiasm, or at least I would have some enthusiasm, for a controlled trial.

I think the other situation is somebody who simply moves a marker to a different place on their cath where that clearly doesn't need a randomized trial. So there is a spectrum of change and somewhere along that spectrum, the judgment has to be made that this is sufficiently different so we don't feel comfortable with it.

I am not sure you can make a general rule. I don't think it is all the time, but I think, for new concepts and new engineering designs, I would be nervous about saying you can deal with historical controls partly because it is clear that placebo rates and rates with standard treatment change over time.

DR. TRACY: I think one of the issues I suspect we will address a little bit more in some of the subsequent questions is what is the definition of the appropriate control group because there are so many different types of devices that we have just heard about with filters and some kind of turbojet thing and who knows what design will come up in the future.

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Against what standard are they being compared? Do they all go back to the current--the device we were talking about this morning or where does the equivalence of the device stop between the different designs, and if they are found to have such fundamentally different designs, against what control group.

It seems as though going back to a control group where no distal device is being used would be inappropriate given the clear superiority that we seem to have seen on today's presentations. So I am not sure what the answer to that is and I think that Dr. Domanski was alluding to that you may have to be a little bit creative to define what the appropriate contro group is.

But I think it is going to be a little difficult. I don't know if anybody has any more concrete thoughts on that than I do.

DR. KRUCOFF: I think, to some degree, we have to recognize that there is sort of a life-cycle issue here where the answer to this question of when a randomized clinical controlled trial is appropriate may vary. I think as we birth a new indication, that then the devices within that indication first have to be sectioned into those that are fundamentally similar or those that are different.

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Obviously, what we have seen today, I think, would, even to the lay person, qualify as many different groups potentially within the same indication. As long as we are working, as has been repeated stated through the day, in a patient population who are vulnerable and who are frail, that means we have a patient population in whom the practical logistics of doing a clinical trial are actually enhanced because the endpoint density is higher and a randomized clinical trial remains relatively reasonable and feasible as long as fundamental attention is given to how to design the trial.

I think, as we get further into the life cycle of devices within this indication, presuming that distal protection actually reduces the complications in these patients, and the standard of care becomes distal protection, that then the issue of the lower endpoint density makes the logistics of a randomized clinical trial more difficult.

However, by that point, in the life cycle of devices in this indication, we will have more historical data. Ideally, by that phase, we could see the use of a randomized clinical trial less important than the use of an OPC or some sort of historical control in which a registry is used up front.

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The one thing I haven't heard at all today is, and potentially in which, as the accrual of these patients takes a longer time, post-marketing surveillance could systematically be built in in addition to registries in order to create a sort of next part of the life cycle of how devices eventuate in this indication.

But I think, at the beginning of a new indication such as this one, where, really, I think we are looking at a broad array of device designs, that a randomized clinical trial--and I would like to come back later when we get to the control population to discuss that--but I think, basically, at this point, the randomized clinical trial for devices that are fundamentally different in a new indication would seem like a basic requirement.

DR. TRACY: So, then, I think, in summary, we pretty much feel that randomized controlled studies are appropriate and desirable recognizing the difficulty in deciding what that appropriate control group is and the variability in the different devices that we have heard presented to us this afternoon.

We will move on to 1b, then. Please discuss whether adequate trials can be designed with historic controls or objective performance criteria for assessment of this technology.

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I think you just heard us say that not until there is more information.

MR. DILLARD: I think we had it there in case the answer to 1a wasn't so definitive. So thank you.

DR. TRACY: All right. We will move on to 1c, then. If a randomized trial is warranted, please discuss whether the control arm should incorporate use of an approved distal-protection device. If so, please discuss use of an equivalence hypothesis rather than a superiority hypothesis for this study.

DR. DOMANSKI: I think what you compare it to should be the standard of practice rather than specifying a particular device. There may be other devices that operate on a somewhat different principle at the time that they are trying to approve something, so I am not sure I would say distal-protection device. But it ought to be against standard of care at the time.

DR. TRACY: Which is probably going to be different in about two-and-a-half, three, four months than it is right now. I guess it is a slippery thing.

DR. KRUCOFF: I think that is okay. I think that is normal and I think that, in a field, again, where multiple life cycles are eventuating as they are in this area, that, basically, turning to your investigators or a

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steering committee and then sitting down with the results of that discussion and discussing what the FDA--what a protocol design would be.

What we have talked about today is the elegant data for distal protection and how profoundly it reduced clinical endpoints in the population of sites who are involved in the SAFER study. What that doesn't touch on is the hundreds of operators of sites who are still out there doing vein-graft stenting or intervention with no distal protection at all because they didn't participate in the SAFER study and they won't be educated in a given time frame.

We are still talking about thousands of patients undergoing angioplasty of vein grafts who will be injured. I think that, as we do clinical trials in the meantime, that it is quite reasonable to let that moving target move and, for each trial, in the real practicalities of when are you planning it, when are you going to begin.

The ethics of patient enrollment, the best people to ask are your investigators. If investigators feel that a new device, a distal-protection filter, for instance, randomized one-to-one against no distal protection actually helps them use a more advanced device in half the patients, that is 50 percent more than they are doing right now.

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There is an equipoise point here that--we have been through this with IIb-IIIa's as well. Do you do it against an active control or do you do it against placebo. I think, there, the standard of practice is best voiced by the gentlemen and ladies going the procedures for whom no access to distal protection versus a trial that randomizes a distal-protection device to half of their patients may be a significant plus.

On the other hand, if all your investigators tell you, "We won't randomize patients unless you let us use a PercuSurge or a distal device," then it would seem pretty reasonable that would be the way to plan your clinical trial.

I think the key question is when do you go with superiority or equivalence. I think if, out of your investigators, you anticipate 75 percent of your cases being randomized and sites practice against placebo, against no distal protection, you would clearly burden yourself, I think, more with a superiority agenda whereas, if you were to engage a group of investigators in whom 75 or 80 percent were committed to using a distal-protection device, I think you would have more reason to design a trial around an equivalence hypothesis.

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So I think part of it, really, depends on the actual community of practice at the time you do the trial and who they are willing to enroll under what circumstances as you design the trial.

DR. DeMETS: I would like to speak to the second half of that question, assuming that you have decided to do a randomized controlled trial with an active control arm. I would like to at least purport the idea that we shouldn't choose between an either/or; that is, equivalence or superiority.

It is somewhat an artificial dichotomy. I think you should do a trial powered for a certain size difference and use a confidence interval when you are done. That confidence interval will tell you whether you have a superiority trial or an equivalence trial or neither.

So I think we have said it is one or the other and I think that is not, necessarily, a useful way to think about this. The delta that you would specify for a superiority trial and the delta for a noninferiority trial don't have to be the same. I recognize that. But, ideally, they shouldn't be too different.

If you can sort of make those as close together as you can do or afford, then I would argue, use a confidence

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interval when you are done and you can sort out where you are.

MR. DILLARD: Could I ask a follow-up question to that, Dr. DeMets? Of course, one of the things--and I understand your point--one of the things we are faced with is trying to appropriately size the study, obviously, before we begin. When we are working with a company, it can be rather embarrassing, from our perspective, if we come back and we tell them, after they have done their 600-patient trial, "We're sorry; you need another 600 patients," they generally don't receive that very well.

How would you balance our need to work very interactively with the sponsors to try to come up with a reasonable number prior to the study beginning if we don't really, a priori, decide whether or not we have a superiority or a noninferiority type of trial?

DR. DeMETS: I think the question is what delta are you looking for and what delta do you need to rule out? Ideally, the delta you are looking for should be the same size delta that you would like to rule out. So the answer is the same, ideally.

Now, you may not be able to get there in a practical sense, but you shouldn't be too far away. So I

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think that, if you do the design right up front, you won't be in that dilemma.

DR. TRACY: Just a comment. It sounds like we think that an appropriate control would be standard of practice. However, the concern I have is what the statistical implications would be if you have two different standards of practice in the centers that are involved in the study. One center has a distal-occlusion device at hand, one does not.

How many patients do you need to enroll and how many substudies are you actually going to end up? It may be the best that we can do but how does that play into the statistical analysis of the study?

DR. KRUCOFF: There, I think, with all the clarity and fuzziness of a power calculation, you end up in about the same shoes. You would have to anticipate ahead of time approximately what percentage of distal protection would be used and approximately what might not, if you really think that is going to influence your outcome, and base your endpoint on the arithmetic of those two denominators.

I think, with that, you do take on, in the same way, again, we do with a good number of devices trials where, for instance, we allow IIb-IIIa's to simply be used or not at operator discretion.

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You can look at those, or plan prospectively. For example, a subgroup of secondary or tertiary looks and, ultimately, to make sure they are randomized equivalently. But, ultimately, I think for a power calculation, you would take the higher endpoint expected without distal protection, the lower endpoint expected with distal protection and the average number of patients that you expect, based on your sites and your investigators for the use of these things in each.

DR. TRACY: Any other comments?

DR. VETROVEC: I guess the one concern that could happen is that the development of a trial of 800 patients for vein grafts will take some finite amount of time and the baseline and what the investigators are telling a company may change over that time. So the standard will change a lot and that might make it very difficult in terms of continuing a study to its end if all the investigators, initially, don't have distal-protection devices and then, halfway through the study, most of them do.

It could become cumbersome, so I think, going back to what Rick talked about, I think some concept of how you do this flexibly, with some flexibility from the outset, would make some sense to me. I think this is going to be a

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moving target. It is not the typical study that is going to be done in three months.

DR. TRACY: Dr. Laskey, a comment?

DR. LASKEY: Just maybe a follow up to all of this. I think, ultimately, there has to be some standardization and uniformity in the trials. What I am concerned about is similar, if I may be so bold, to describe what is going on in the heart-failure experience which is the same group of investigators doing the same types of studies and cranking the stuff through and getting the same, almost the same kinds of results.

We may wind up with a bias series of studies here in which some of the studies with, for example, distal-protection-device control arms are being done by a group of investigators who are highly experienced with it, who have had a good track record with it and then using that in the control arm may give a series of results of X.

Then, to try and pool or compare those results in a trial in which the standard of care is not that experienced, or the investigators are not that experienced, I think this does tend to bias trial outcomes. I would be concerned that there is the potential for that unless we agree upon some more uniformity within the industry, if you will.

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But to centralize control of these studies in the hands of those who are most experienced in the high-volume centers--some of these problems were alluded to earlier on some of Gregg Stone's slides and I think they speak powerfully to what is going on right now about selection bias and how you funnel patients from one study to another.

With the best of intentions, you are going to wind up with different results. This is a very, very real issue so we need to at least--end of soap box here--we need to achieve some more uniformity in the trial design and, perhaps, flexibility, too.

But we cannot have the series of results in the hands of the experienced few and then generalizing that to the unwashed masses who then have to deal with this.

DR. TRACY: I think that is a variety of comments coming to the conclusion that, as flawed as it is, the standard of practice is probably the standard against which to compare a new device but that the standard of practice is different in different centers and there should be caution made not to have that standard determined by the highest level but should include different levels of technology in the studies.

DR. DOMANSKI: I think that is a slippery slope, though, to put it quite that way, frankly. I really do. It

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is very hard, in a clinical trial, to account for incompetence. It is important not to try and start doing that. We have that problem all the time as we design trials and NHLBI.

It is true that somebody may not be as good as somebody else, but what you are really asking is what the device can do in competent hands. We are really rarely faced with a thing where there is some uniquely skilled set of hands in the world. I don't think that is true in the interventional world. I think there are good people and then are ones who are weaker.

I wouldn't worry too much about the truly unwashed masses, though. I think, in good hands--so I would be very careful. I think that is a slippery slope.

DR. TRACY: I didn't meant to imply that it should be put in every hospital across the country, but that there are different standards of practice in different centers. Until other centers are facile in the newer devices, there will always be differences in standard of care in different centers.

DR. DOMANSKI: I am not sure, though, that it is fair to say that if you have centers operating at different levels of technology that it is appropriate to put them in the lesser places. I guess I wouldn't sign on to that. I

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think the people who are practicing the best standard of care are the ones to whom these newer devices should be--in whose hands they should be tested.

If it turns out that there is such a one small eclectic group of people--I don't think that is true in the interventional world, though. I think competence is pretty widely distributed.

DR. LASKEY: Well, no. The volume-outcome relationship exists in every single technical procedure and there are most of the industrial approaches to quality assurance, as well. The more you do, the better the machine works. So I think that tremendous credit should be given to those investigators in this trial who didn't do thirty-four or forty cases who pulled it off and were committed and all of that.

But, still, there is a volume-outcome relationship in our profession which has been described universally. The more you do, the better you are. When that comes to science, as opposed to clinical matters, I think it is even more important to take that into account.

DR. DOMANSKI: Yes; but the world is replete with high-volume places, and there is an asymptote phenomenon. We are not talking about somebody doing forty cases a year but whether there is a real difference between somebody

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doing 300 and 362. I think there is probably not that kind of linear relationship, as a matter of fact, among the high-volume operators.

DR. TRACY: But even, still, the issue will become complicated. I think we are going to have to close on this particular question. The issue will always be complicated because the standard will be different, even in the high-volume centers. As more devices become available, the standard in one may be device X. The standard in another center may be device Y.

That just has to be taken into account. We just have to deal with the fact that the standard of practice, even at high volumes or expert centers, will be different, one from another.

DR. LASKEY: Hence the moving target to arrive at an acceptable endpoint and complication rate. This is really a moving target and changes from year to year in our business.

DR. TRACY: Unless somebody has a burning issue, we will move on to question No. 1, the study endpoints. Please discuss use of the 30-day MACE rate as the primary endpoint in the SVG distal-protection-device trial. Please discuss whether use of this composite endpoint captures important clinical events. Please discuss whether an in-

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hospital or 14-day MACE rate would be acceptable as a primary endpoint. Please discuss any alternatives to MACE that would be important to consider.

One thing that certainly--maybe not endpoints but one thing I am still concerned about from earlier this morning is our lack of definition of what the high-risk vessels are. We have to come to grips with that somehow better than we have.

I don't know whether that is appropriate to bring up here again but I will because I do think that that, in the study design, has to be emphasized somewhere.

DR. KRUCOFF: I think that 30-day MACE is a very appropriate endpoint. I would be concerned about 14-day for a variety of reasons. But I also think longer than 30-day from at least any concept I can think of or heard discussed with regard to distal-embolic protection, that, by thirty days, the vast majority of what we would be after ought to be claimable.

DR. TRACY: The composite endpoint that has been discussed earlier. Are we happy with the three times CPK rise as being the definition of infarct? Is that something we should consider or leave that open to different trials? It would be nice if it were standardized so that if, at some

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point, there were an historic control, that we would at least know what we were comparing things to.

DR. DOMANSKI: Don't you think, right now, though, by setting a threshold of three times or five times--I mean, trying for this panel to set that, you go beyond what we know about the subject.

DR. TRACY: Probably, yes. But I think that the data should be available as to the outcomes at the different CPK levels until we understand that better.

DR. AZIZ: Hopefully, by the time the treponin becomes much more acceptable--I think that is a much more sensitive--if you really want to start picking up injury, they we should really look at that.

DR. VETROVEC: The other thing is that, practically speaking, the sponsors are almost surely going to take the less stringent criteria to try to show a difference more readily. So it is unlikely somebody is going to take five times. They are more likely to take three times to show a difference.

DR. TRACY: Any alternatives to MACE that would be important to consider? I'm sorry; Dr. Laskey?

DR. LASKEY: Just to back up for a second. It is clear that we are talking about a safety endpoint here or do we need to distinguish that from the efficacy endpoint.

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MACE is the safety endpoint. So, yes, it is true, based on this morning's data, that we are doing less harm. Are we doing more good? Do we need to put that into the equation? Should we translate the other interventional endpoints such as target-vessel failure or need for repeat procedure, that sort of thing, which obviously widens this past thirty days, which I am not in favor of doing because that is impossible.

But I think we need to recognize that this is simply a safety endpoint--this is not an efficacy endpoint--and that we need to balance the doing less harm against the need to demonstrate doing more good, particularly in saphenous-vein-graft patients, particularly with the high-risk population that they are for recurrent disease, need for repeat procedures, the relationship between the stents we put in at the end of the procedure and the likelihood of them coming back. All of this needs to be--

DR. KRUCOFF: But, Warren, don't you think there is an over--I mean, with distal-embolic protection, to me, that is sort of like cardiopulmonary perfusion during bypass surgery. It is not actually the intervention at the site. it is sort of the protection of the myocardium while you do the intervention at the site.

It seems to me that a lot of the repeat revascularization issues may have more to do with what do we

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do at the site than with the distal-embolization protection, which is why it seemed to me that this was a pretty reasonable way to go, actually, as an efficacy endpoint.

MR. DILLARD: I just wanted to make a comment in that this has been a very complex area for us, and we have generally viewed, in many of these technologies, MACE as being the catch-all endpoint. We really use it as safety and effectiveness although there are some other secondary measures that we look at that help clarify both safety and effectiveness as we are doing the real overall clinical evaluation and the overall risk-benefit evaluation.

So we targeted this and asked the question specifically that way because we have used it as the primary endpoint which captures both safety and effectiveness events. Any suggestions would be great here. I am not saying that is completely appropriate, but that is certainly what we would be asking you to comment on.

DR. TRACY: I think it is interesting that the device design changed in this study as a result of their being a number of device failures noted. I think it is important to track that and have that reported as part of the endpoint of the study.

As many people have indicated on the panel already, this device still does have a relatively high

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number of device failures and probably will undergo different iterations. So I think part of the endpoint would be to look at device failure and need for device redesign.

Any other comments on that? We will move on to question No. 3, please discuss what secondary endpoints should be emphasized in an SVG distal-protection-device trial. For example, should a pathological description of the type and amount of debris removed by the device be included?

That would be a little difficult with the different types of devices that might handle the debris differently. It might get pulverized or the nature of it changed in the acquiring of it. So I am not sure that would be reasonable.

DR. DeMETS: It is perhaps stating the obvious, but I would think that one of the secondary outcomes you would look at would be the components of MACE, not that you would expect significance but you would certainly like to know that they are going more or less in the same direction or, if they are not, exactly how does that look.

DR. KRUCOFF: I would also put here what, Cindy, you were starting to mention that, to me, this is where some of the technical elements that I would hope would be collected of however you want to characterize it broadly,

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ease of device use, device failure, secondary interventions because of the device.

This is, to me, where the technology evolution of these devices, as they are actually applied in human use, might be most straightforward to pick up because not all of them generate MACE outcomes. If you dislodge the system or whatever, you may manage to recross the lesion and finish the procedure but, ultimately, if you do that a hundred times or a thousand times, you would worry about the patient population.

MR. DILLARD: Could I actually just ask one clarification? One of the things that was mentioned this morning that I thought was interesting was that much of the effect in this particular area may be on the quality of life of the patients--that is at least what I heard from a couple of people this morning--and that the real clinical outcome, in terms of mortality, perhaps we will never size the trials appropriately to get there.

Are there any other--just as I am thinking about it, are there any other quality-of-life particular issues in this patient population or any others that we should be looking at, since that seemed to be one of the main points this morning?

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DR. TRACY: That is, actually, an excellent point since it is probably not, in many of these cases, going to be survival, long-term survival, that is impacted. I would never say don't collect quality-of-life information. I think that is very useful information.

DR. DeMETS: While it is useful and while we are trying to make people's symptoms better, I think that is going to really be difficult to assess. You have to assume that the physician doing the procedure is doing it because there is a clinical indication that he or she perceives that will benefit the patient to do it.

If that judgment is poor, it doesn't necessarily mean that the device is a failure.

DR. KRUCOFF: Just as a brief illustration of the complexity, if using a distal-embolization-protection device means I make an 8-French arteriotomy or larger, and I leave a bigger bruise in a person's groin but they have a day-and-a-half shorter length of stay in hospital as opposed to just doing a stent or a 6-French guide and sealing the groin in some way.

I think, in the spirit of all of us, quality of life is a huge issue but the complexity of basing device approval on it would take a lot of guidance.

DR. TRACY: Comments?

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DR. LASKEY: You hate to relegate this to postmarketing ascertainment. I think it belongs somewhere. I have been alluding to that all day, but requirements for repeat procedures in recurrent angina may not be intimately, in a one-to-one way, related to a catchment device or protection device, but it is part of this procedure.

If this procedure becomes the standard of care in the vast majority of patients with vein-graft interventions, then it is important to have this information to compare it to either historic controls with all the weaknesses or to confirm controls.

But I strongly feel that a procedure whose indication is not to prevent death but to improve symptoms should somehow have symptom outcome response somewhere in the list of outcome variables.

DR. TRACY: Question No. 4; please comment on appropriate entry criteria for an SVG trial that is intended to evaluate a new distal-protection device. Please discuss any specific patient population that should be excluded or studied separately. I think we had basically felt this morning that any SVG disease would be reasonable to include in a study like this so, unless there are other thoughts or particular exclusions that anybody has--

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DR. VETROVEC: Maybe issues regarding subtotal with huge clot volumes that may not be applicable to distal protection and may be more applicable to other devices. So that was, certainly, I think, true in the SAFER trial. It had to be an open vessel and so forth. So I think some thought about the issue, about volume of clot that might be present and relative flow at the outset might be important in that decision.

DR. TRACY: Question No. 5; please comment on use of adjunctive antithrombotic medications. Please discuss, for example, whether glycoprotein IIb-IIIa drug use should be left to the operator discretion or be prospectively outlined in the protocol.

DR. KLOCKE: The interventionist could probably answer the question. I am not sure that it is practical to prospectively outline them at this point. So the strategy of stratifying the randomization form seems to me an appropriate alternative.

DR. KRUCOFF: I would agree. I think this is another heterogeneous standard-of-care sort of issue where the prospective plan, in my opinion, should focus more on the structure of the analysis and/or the randomization stratification than on inclusion or exclusion or mandating

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until or unless the actual interaction of the device and the drug becomes part of the proposal.

DR. TRACY: I think there is consensus on that on the panel.

DR. LASKEY: I just had one afterthought to No. 4. The diabetics just stand out all the time as being a different risk, not just long-term but short-term. So I just wonder whether they should be broken out, studied separately, stratified, some way of looking at them differently because they are quite different in terms of their acute and long-term outcomes.

DR. TRACY: I guess that concludes the FDA panel questions. I am not sure how to answer Mr. Kim's query regarding the proximal-protection device under investigation but I think it is clear that some type of randomized controlled trial would be appropriate for that. I don't know what the specifics of the devices were but I don't think that a distal-occlusion device would be an appropriate control for that.

DR. AZIZ: Can the gentleman who asked this question about proximal-protection devices--do you what that is?

DR. TRACY: Mr. Kim, are you still available to come to the microphone?

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MR. KIM: I have to admit this was a last-minute request by several of our clients. They saw the meeting announcement and then they suggested that I at least try to pose the question. Specifically, I have no idea what they are looking for but I guess they are looking for some type of guidance since they are developing products that they would like to get into clinical trials.

They have been monitoring your discussions with distal-protection devices and they would like to see if there are any other consideration that they should have in mind as they design--

DR. AZIZ: But what do you mean by a proximal-protection device?

MR. KIM: I wish I could explain more.

DR. AZIZ: How can we answer the question?

DR. KRUCOFF: When Mr. Kim first came out, what I thought I heard--maybe I was mistaken and maybe it was in the light of the previous presentations, was whether what I would actually consider more thromboablation or atherectomy devices belonged in the distal-embolization protection category or not.

I don't know if that is now what is being asked.

MR. KIM: That is what I had thought. But, again, I am not entirely 100 percent sure.

[--- Unable To Translate Box ---]

DR. KRUCOFF: If that is what is being asked, are we going to respond to that?

DR. TRACY: I think since we don't have a good understanding of what is being asked, there is probably not much point in going into any further detail.

MR. KIM: I appreciate the panel's time.

DR. TRACY: Thank you. That will end the open session which I would like to now adjourn. The next portion of this meeting is going to be closed to the public so anybody who is not involved in the closed session, I would ask you to please leave the room.

We will now take a 15-minute break.

[Whereupon, at 3:20 p.m., the meeting was adjourned.]
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