devices that are out there for the specific indication of foreign-body retrieval are quite low. And the pathway for the approval for that was a 510(k) without a clinical study, so there are no underlying clinical data on the device as a foreign-body retrieval device. It just went through the normal pathway, and then the company decided that it was best not to extensively market that to avoid its use as a clot retrieval device.

DR. KU: Is the FDA aware of any device failures related to this particular device with respect to its indication for foreign-body retrieval? Because, usually, if a device fails, you're supposed to file a form with the FDA saying that the thing broke.

DR. WITTEN: Well, those would, I think the sponsor has already answered that. Those can be reported to the sponsor or to us directly, and I'm not aware of any; but, you know, there may be some. I think the sponsor is in a better position to answer that.

DR. JENSEN: How about from Europe? Was

there anything from the European --

MR. MACDONALD: Well, currently, there's been approximately three MDR's have been reported to through the MDR system, 169 devices that have been shipped. And to our knowledge, there were no clinical sequelae as a result of the MDR's. In Europe, it's through the vigilance reporting so, pretty much, every fracture that occurred during the clinical investigation because the device is CE mark, all those reported under the vigilance system. And to date, there haven't been any MDR or vigilance-type reports that have occurred outside the U.S.

DR. JAYAM-TROUTH: A question. Also, some balloon catheter problems, you know, with the balloon catheters for foreign-body retrievals?

MR. MACDONALD: The Balloon Guide Catheter actually isn't specifically required for foreign-body retrieval. In most cases, they'll use just a standard diagnostic catheter. Basically, during an interventional procedure, the coil gets misplaced. Whatever catheter they have in place, they, you know, will just go up with a microcatheter

and retriever and pull it back to that catheter.

DR. BECKER: Dr. Loftus?

DR. LOFTUS: Yes. This is a regulatory question. Perhaps, you can answer it for me. If the approval of this device for foreign-body retrieval was based on a 510(k), then may I assume that that was deemed to be substantially equivalent to some already-existing device? And if so, what device was that?

DR. WITTEN: I can't tell you specifically. The sponsor might be able to. But, yes, it was to an existing device with that.

DR. LOFTUS: So it wasn't a PMA? It was a 510(k) for foreign-body retrieval?

DR. WITTEN: Right. And I think, I don't know off-hand what specific comparison the sponsor made, but I think it's to a device that --

MR. MACDONALD: I don't know off the top of my head.

DR. WITTEN: -- with that clearance.

MR. MACDONALD: I believe it was a microvenous snare.

DR. SMITH: I'd like to respond to one other question that you raised, the question about following up with patients who had two retained fragments. Those patients are still alive, and we're still waiting for their 90-day outcomes. We haven't specifically raised in the consent form any issue to follow them up longer term, so I think it's appropriate for us, though, to make sure that they're doing well. I can say that, in a few of the cases at UCLA that were done, some of these patients have had MRI scans afterwards, so the material properties of the retained fragment itself doesn't raise a concern for MR. We haven't done specific safety studies in that, but they're not ferromagnetic. So that is another potential issue. But I think, with diligence, we need to follow-up those patients to be sure there isn't something that we're not aware of.

DR. JENSEN: What about the bench testing of the devices? Were they done in an animal model, or were they done in just on a bench top in a plastic tube or whatever?

MR. MACDONALD: Well, the specific

testing was done. For the original IDE, we actually used a similar model that was presented. We placed clots in the pharyngeal artery of the swine and then actually did attempts at clot retrieval. We didn't have any fractures or any problems in that model. Our bench testing basically looked at tip tensile, where we actually used pull forces. And the torsional testing also looked at a combination of torque and pull.

DR. JENSEN: And why do you think there's a difference between the swine model and what we're seeing in humans, in terms of the number of fractures?

DR. DUCKWILER: Well, I think that's sort of a complicated answer. One, the swine model is a straight segment; it's not curved. And in many ways, the bench models are actually better in that they reproduce the tortuosity seen in humans. Second, you know, I think that you're dealing with physicians who are quite anxious to remove the clot. And in their desire to remove the clot, they may utilize more torque than is desired with the device.

And just to follow on questions about the device that you had and the Balloon Guide Catheter. So you're absolutely right. If we consider the whole system, device and procedure-related complications at seven percent, four percent attributed to device -- I'm sorry, 3.5 percent, four cases. And then in four cases, 3.5 percent for procedure related.

In terms of the other questions you asked, vasospasm. Vasospasm can occur, at least in my experience, at the level of the Balloon Guide Catheter, but in no cases was it severe or did it cause restriction of flow. In terms of luxury perfusion, that was not specifically addressed in the protocol; but, in our cases that we performed at UCLA, we are looking at that issue and trying to relate that to outcomes and hemorrhage.

And distal emboli. The actual forms do ask you to mark down if there are recognizable distal emboli or not. That's not always possible, given the fact that the primary field that you're dealing with, say if it's in the middle cerebral territory, you may not have visualization of any of the distal

territories, so it's impossible to determine what the status is prior to your clot removal.

In some cases, you do occasionally see some collateral flow coming down towards the middle cerebral and then collateral flow from the middle cerebral to middle cerebral branches, and you do detect emboli pre-existing. But for the vast majority of cases, you cannot tell beforehand whether it's two emboli or merely one.

And in terms of dealing with distal emboli versus proximal emboli or occlusions and the size of the device, the nice aspect of the device itself is it does have multiple loops of different sizes. And the use, in-practice use device in a smaller branch entails delivering only those portions of the loops which would be accommodated by the vessel involved. So you do see the proximal vessel, the size of the proximal vessel, and you deploy the device. Then you have a loop, which is starting to flatten out, doesn't achieve its normal diameter. You no longer deploy anymore of the device, so you have the remainder of the loops within the device,

which is a nice design in that you can go further distally, and you're allowed to go M1 and M2, but it doesn't necessarily mean you deploy the entire device in an artery.

DR. JENSEN: In terms of vasospasm, you mentioned vasospasm with the guiding catheter tip, did you see any vasospasm at the site where the device had been after the clot was removed?

DR. DUCKWILER: In my experience, in those cases where we did achieve revascularization, the underlying vessel did not show vasospasm. Obviously, we couldn't tell if there's still occlusion. And at least just a partial answer to the follow-up of retained fragments and a prior question about TIMI scores, there was no worsened TIMI scores associated with failure of the device. In other words, even if there was a retained tip, that retained tip typically was at the site of occlusion and did not result in further retrograde propagation of clot and worsening of TIMI score.

DR. JENSEN: In further questioning your response to the anxiety of physicians using the

device, what is the company's plan for training to help such anxious physicians?

DR. DUCKWILER: Well, just in my personal experience, it's very difficult to reproduce the situation in a patient without having some experience in the patient. But having already had some experience and then going back to the models, I feel actually, if anything, the models reproduce the situation of humans because of the tortuosity, which is an important aspect of training using this device, which you're not capable of achieving in the animal. And so with experience and in my role as an advisor, we have worked on the models, and I think the models actually do reproduce quite well the situation and the tactile field that we see in the humans. In terms of the formalized training program, I'll let Kevin --

MR. MACDONALD: Yes, we've learned an incredible amount during the course of the investigation. We've trained 25 centers. Throughout the course of the trial, we've modified our models, our training program. It basically involves going

over the detailed results and tips and techniques that we get from physicians, like Dr. Duckwiler, on things to look out for, you know, the Balloon Guide Catheter, how to inflate that, where it should be positioned in the ICA. A lot of the training materials are reviewed by the investigators before we go out and make sure that they're comfortable with what we're saying.

The primary motive operation for going out and initiating or training a new site is we go out and we actually characterize, you know, how good are the physician's hands. I mean, have they treated, done a lot of IA cases? Have they done a lot of interventional procedures up in the neurovasculature. You know, good INR, essentially.

At that point in time, we go through the didactic session where we review the clinical results to date, discuss the tip fractures and what had happened during each one of the cases with the tip fractures, and ways to avoid it, i.e. don't overtorque the device. And then we go through the model training, where it's actually, in their angio

suite, they use all the equipment that they would use during a regular procedure, the Balloon Guide Catheter, microcatheter, microwire. We place an occlusion up into the model. They do direct vision. In fact, most cases, the INR's are better when they do it under fluoro versus direct vision. And it really mimics the actual use of the device. And short of having a proctor there, which is, you know, these are emergent procedures and it would be impossible to get somebody there in time, it seems to be the best way.

And to date, you know, some of the centers, somebody had asked about learning curves, some of the highly-skilled operators, they catch it very, very quickly. They pick up on it very quickly, and they understand the nuances of the device, and the model has been perfected to the point where, you know, it really does mimic it. It's under pressure, about 100 millimeters of mercury average pressure, so you simulate that, and just using all the equipment and understanding the prepping.

DR. SMITH: May I respond to Dr. Brott?

I like the idea of comparing as much as we can on a case control or cohort-based study with NINDS trial because I think that would give us some better understanding of safety. My guess is that if we do that, we will find a higher mortality in our group. And part of the reason I say that is, of course, as you know, it's not an angiographically-controlled trial, so we really can't match anatomy per anatomy. But I think if we really were to do cross-study comparisons, the things that we would have to control upon would be not just angiographic vessel location but would be degree of collateral flow as well, which is something that we learned, certainly, from the PROACT trial. It had been predicted by stroke neurologists far before that trial had been done. So I think there's a lot of comparisons that would be important to do, and that's one of the reasons why we would appreciate the Abbott data because that would help us in that regard.

My guess, too, though is that the NIH Stroke Scale itself, even if you did case comparisons with the same NIH Stroke Scale, same gender, same

age, etcetera, you would still find that there's a factor there that we can't control for because, in our multivariate analysis, if it's accurate or predictive of what's reality, the NIH Stroke Scale and whether or not we opened the vessel were independent factors.

So are there other things in here that we can't control for? I don't know. I would love to, also, with the IMS data, though, be able to compare because I think, as you said, that's probably a much more accurate comparison because it's angiographically controlled and there's a sicker population of patients.

DR. BROTT: I think that's a good idea, and I think the other one is a good idea, too, and I would grant you the points that you made.

DR. BECKER: I guess if there are no further questions, we'll move on to Dr. Ellenberg's discussion and presentation.

DR. ELLENBERG: Good afternoon, and I would like to summarize my thoughts prior to hearing discussion today. Many of these points will have

been talked about already throughout the day, so I may just be adding emphasis, but let me go on. I'd like to talk about the task for the Advisory Committee in terms of making a recommendation to FDA, essentially assessing the risk benefit ratio for this new indication.

What I'd like to cover are several issues: the eligibility criteria and the inferential population based on that eligibility criteria; revascularization success rate and the prediction of such; the 30 and 90-day status and prediction of such; the mortality rate and the prediction of the mortality rate; and, finally, progression. And if there's time, I'd like to talk a little bit about the logistic model approach, but I could probably just leave those comments with the sponsor.

With regard to the eligibility criteria compared to PROACT II, this has been covered extensively during the day. But, basically, there are several factors that differentiate the control group and the treatment group in PROACT II to MERCI. For one, the MERCI patients are not eligible for

thrombolytics and all the other indicators that we heard about today. Given that, is it appropriate, as we assess the risk and benefits, to use the PROACT II control group as a comparator, recognizing that this is the agreement reached between the FDA and the sponsor?

The PROACT II control group is a non-concurrent group. It's probably likely, based on what I've heard today, that the risks for that outcome in the MERCI group is going to be considerably higher than the risk for a bad outcome in the PROACT group. And, finally, in terms of the eligibility cascade and inferential population, these numbers also were mentioned in the PROACT II trials. Thirteen-thousand-plus patients were screened, of which 180 were studied. And in the PROACT II trial, the major publication gives a breakdown of how the eligibility criteria screen those patients. So we know from whence we started and where we came.

So we looked at, give or take, one percent of the PROACT subjects that were screened. In the MERCI, we looked at approximately ten percent,

and these are the numbers that we're holding before the middle application came in. But we looked at approximately ten percent; and, from what I understand from the supplemental response, we don't have data on the reasons for not being studied. So we can't tell how we came from the 1421 in a cascade down to the 121.

So the question remains at the end of the day, well, one of the questions remains, in terms of the MERCI Retriever, we're looking at 121 patients, and we need to know to whom is that result going to reflect? Is it going to reflect the 1421 patients, some other group that has been defined by the eligibility criteria? And, again, this question has been raised; but, to me, it's very important to know what we're going to do with the results from these 121 patients, now 129, and eventually 148, plus or minus some more. Who are we projecting to?

Second issue, the vascularization success rate. It's already been mentioned that there were several locations that were considered in the MERCI trial, in contrast to the PROACT II trial. Looking

at the available data and the multivariate analyses that were done, many variables looked at to try and predict which patients would go on to a successful or an unsuccessful vascularization success rate.

In addition, there was unavailable data not used to predict success because the data simply was not available, such as clot density, size of the clot, the location, hypodensity, etcetera. So we have a list of variables that was available, a list of variables that was not available. But the list of variables that were available to predict success, we simply could not predict the success with the available covariates.

And this, to me, raises two questions. The first being guidance for patient selection, in terms of which patients should be selected for use with this device. Looking at this from the half-full versus half-empty glass of water, the success rate is only 50 percent, so which patients are we going to try and use this on?

And the second issue is, in looking at

this particular study, which, again, by agreement with the sponsor and FDA did not require a controlled study, looking at these particular results, we are in a situation where our comparative group is not done at the same time under the same circumstances as the MERCI group was done. And it is uncomfortable for me, as an analyst, to not have any indication as to why the success in a patient came through or did not come through when we don't have a comparative group. To me, this seems to be something we have to consider very carefully in judging how we want to make recommendations to the FDA.

Looking at the predictors of 30 and 90-day status, the secondary outcomes here were 30 and 90-day

modified Rankin and NIH Stroke score and looking at the results presented -- that wasn't supposed to happen in such a cutesy way -- looking at the results, the success of vascularization was the major indicator for what happened at 30 and 90 days.

There was one peculiarity in the results in terms of the 90-day NIH Stroke score, if one looks

at the univariate results presented by the sponsor, vascularization success is highly predictive of the 90-day outcome. But if you look at the multivariate analysis, this variable doesn't come in. There is nothing in the multivariate analysis that seems to predict 90-day NIH Stroke score, and it seems to me there must be something wrong with the approach to analysis because if it's there in the univariate and there's nothing in the multivariate, that doesn't make sense to me.

Mortality rate. In the univariate analysis, vascularization success predicted mortality. When we went to multivariate analysis where the vascularization success was competing against the whole list of variables or covariates that could predict the mortality rate, it turns out that the baseline stroke score and systolic blood pressure essentially have taken the place of vascularization success. So we see a situation here where baseline NIH Stroke score did not predict vascularization success, yet it comes back in and takes the place of the vascularization success in

predicting mortality.

And this is troublesome to me in that it doesn't quite make sense, and I think further multivariate analysis and further very simple two-by-two tables should be done to try and explain why this is happening, and that's basically what I have in this last point here.

I think we need to look at within each of the groups, those that were successful and those that were not successful. I believe that FDA needs to examine the modeling of the prediction of ultimate outcome further within those two groups. So I think this is one big major point, but I don't understand what's happening in terms of the progress of the subjects.

This table has been seen many times, and it's what we have to look at when we judge our recommendation to FDA. The revascularization success rate was 54 percent, and the mortality rate was 38 percent in the MERCI Retriever. This is compared, and it's hard to sort of separate this out in spite of the non-comparability of these two groups, this is

being compared to the control group from PROACT II; so 54 percent revascularization rate versus 18 percent, and mortality rate of 38 percent versus 27 percent.

It's very important to understand that my sense is that these groups are simply not ready to be compared. We don't know how this group might be different from this group, and, while the agreement was that this group would be used to compare against the MERCI Retriever in this application, I feel very uncomfortable using this group as a comparator, given the measure variables that have shown this group. The group for the total clinical trial versus the MERCI trial could have been tremendously different.

Sorry, that should have been bigger. We're starting here at the progression. These are the 114 patients who came into the trial for treatment. They all had baseline characteristics, and this arm goes off to successful revascularization, and this arm goes off to unsuccessful revascularization. And let me repeat my point as I close this out. We don't know what it is

about the baseline characteristics of the subjects that would lead a subject to this arm or to this arm.

The next step is for those that succeeded with a revascularization and those that didn't. They went on to that 90-day outcomes, the ultimate clinical outcome with a modified Rankin and the NIH, and it turns out that the NIH score and systolic blood pressure do predict how subjects go on once they have successful or unsuccessful or revascularization. And I find that troubling.

I'm repeating myself, but I just wanted to show it in sort of a pictorial manner. We're going down our way here, and, ultimately, clinical outcome is going to be very important, even though it's not critical in the application itself. But when we judge the success or failure and the safety risks and we report out to FDA, it seems to me that we do have to consider this sequence and understand there are things we don't understand about this sequence. We don't understand how the baseline characteristics

determine success and non-success. And further, for some reason, the success rate is overtaken by the NIH Stroke scale in predicting the ultimate clinical outcome, which to some degree one might argue with that data that it's saying that the bottom line is NIH Stroke scale when you come in and not, perhaps, the use of the MERCI Retriever.

In terms of the multivariate logistic model approach, there are inconsistencies in the analysis, unless I've mistaken something, for the variable age in predicting vascularization. In the univariate analysis, age is not a significant predictor. Yet, in the multivariate analysis, it comes up as a significant predictor and the only predictor. This is an inconsistency that I simply don't understand and I think is incorrect.

Further, in the revascularization as a predictor of 90-day NIH assess, which I already mentioned, this is highly significant on the univariate analysis, and the multivariate analysis just gets completely wiped out. There are two processes in the footnotes for the logistic

regression that says that the collinear covariates were dropped out if they're above a certain point of correlation among the covariates. While I don't disagree with that approach, I believe that the limit set was much too low in this case, and that one ought to reconsider doing this with the collinear variates in because the logistic regression could pretty well handle that.

Further, the missingness, for example referenced vessel diameter, there was a certain proportion of data that was missing, and that was never included in any of the multivariate analysis. And, finally, I would like to see the supplemental data rerun for MCA only. Thank you.

DR. BECKER: Thank you, Dr. Ellenberg. Does anybody have any questions for Dr. Ellenberg? Okay. Well, I think, if nobody has any questions for Dr. Ellenberg, we'll move on to the general discussion portion of the panel's deliberations. And just to remind everybody that they're able to ask the sponsor or the FDA questions at any time. So I'm going to open it up, and if anybody has any general

comments or questions that they'd like to put forth at this time, please go ahead. We'll get this started by asking Mr. Balo to --

MR. BALO: From an industry perspective, being an industry representative, as we heard today, we know there's been a lot of questions from the panel members, and I wish the panel members to consider this. When the industry is dealing with the FDA, they're working cooperatively to come up with a study they feel will basically be representative of what the device will be doing out in the field.

If you think about it, the industry has told us today that the population they went after, basically, was a more severe population than the population they're being compared to. Secondly, they said that their adverse event rate, which we've heard Dr. Smith talk about, is about seven percent. And if you compare it to when he talked about tPA, he had mentioned if he was providing that information to his patient, he would basically say they would have a six percent rate with a three percent rate of mortality if they did use the tPA.

So taking it into consideration and also looking at the success rate, and I'm not a statistician, so I can't comment on what Dr. Ellenberg says, but I would think that we should take into consideration does this provide to an interventional neurologist or radiologist the opportunity to offer to me, as a patient, another form of maybe removing a clot that I won't be available for if this wasn't allowed in the marketplace.

I think one of the keys that we have to understand is, from an industry perspective, there's risk in everything we do. You're not going to go out there and have a procedure that's basically risk-free. And I think I would really like to encourage the panel. I mean, if there are conditions, and it sounds like there are some panel members that do have some concerns that, you know, this device could provide and will provide some value to patients, and if there are some conditions that you think should be added on, I would encourage the panel to really deliberate that seriously before they vote. Thank

you.

MS. WELLS: There's one thing that I noticed, coming from an engineering background. I was looking at the bench testing and, specifically, in one of the points, it says it should be noted that you said the retriever does not require rotation of the device to ensnare the thrombus. And specifically, in the instructions for use, it details twisting or rotating the device. That was one of the questions that I had and wondered about the safety of that.

DR. BECKER: Does someone want to answer that question?

MR. MACDONALD: Just want to clarify in the instructions for use, torqueing is required. We require, just before you deploy the device, to rotate two counterclockwise, and then, once it's deployed in the clot, five clockwise, and that's it. The maximum number of torques, so it's incorrect.

MS. WELLS: Okay.

DR. KU: Well, we've heard a lot of the information, and it seems like it's, at least to me,

it's boiling down to --

MS. SCUDIERO: Excuse me. Could you go back until we call you back up for questions, unless they have specific questions for you. Thank you.

DR. KU: It seems like some of the data is showing that if there is revascularization, the patients seem to do well. And that, overall, if the device doesn't succeed in revascularization, there seems to be a higher risk of bad things happening. The overall numbers seem to be somewhat equivocal with the PROACT data, as far as overall morbidity and mortality. So it seems to me that this device may offer patients sort of a difficult choice if it's approved. It's a device that, if it works, then you wind up doing better. And if it doesn't work, you wind up doing a lot worse. And that's often a clinical question that we face when we talk to patients with strokes because a lot of patients have an all-or-none type of approach to their disease. They'd rather be either completely intact or completely out of it. So part of it is a philosophical question, and I think that's something

that we have to consider.

DR. BECKER: Comments from at the end of the table?

DR. JAYAM-TROUTH: Yes. Essentially, I think, from the perspective of whether this works and whether this does revascularize, I think you're showing it does revascularize. So from the FDA angle, that was all that we are looking at. You know, does it revascularize? Yes, the percentage is pretty good. I think it does do a revascularization, but does it help the patient? That is where, you know, I have my own concerns because the outcome that, even though it is secondary, doesn't show that it is any better than the PROACT II.

So the question comes why is it, I mean, you know, as it relates to what Dr. Ellenberg presented, it kind of raises a question: why are there some different types of data that we are getting? You know, we're getting, on the one hand, you know, we are saying that it does not relate to the NIH Stroke Scale, but then, when the outcome data comes of mortality and morbidity, we're saying, yes,

it's related to the NIH Stroke Scale. Then, you know, why is revascularization successful, you know, in some areas and some points? And when the patient is revascularized, why does not that become the major determination of outcome.

So I think I have my own questions on that, but if I am asked does the device work? Yes, it does work, but does it help the patient? There's where my question comes.

DR. ELLENBERG: No further comment at this time.

DR. HAINES: Well, just to reinforce, on the safety issue, issues that Dr. Brott and Dr. Ku and Dr. Ellenberg have brought up, there does appear to be an excess of mortality in the patients who are not successfully revascularized. Unfortunately, the PROACT data doesn't break down those who spontaneously recanalized and those who didn't and their differential mortality. But if the numbers in the MERCI trial were applied to the PROACT group, there would be only half as many deaths. If the numbers in MERCI were applied to PROACT, there would

be twice as many deaths in the placebo group, as are reported.

So it appears, to me, that there is an excess mortality in the unsuccessfully-treated patients, as others have suggested. And I think that raises the safety issue.

DR. BECKER: I guess I would just echo the number of the thoughts that have already been stated in that there's no question that the device actually will revascularize a vessel. There's a big question as to whether or not it's effective in improving clinical outcome, and I also believe that there are some issues regarding safety, as well. And Dr. Jensen had brought up the issues about the predicate device, and it's unclear to me, at this point, what the predicate device is and what the safety there was. So it's unclear what comparisons are being made.

DR. JENSEN: I think the way the FDA and the company designed the study, the question is whether or not the device revascularizes, and it does. The safety issue, if you look at it as a 3.5

percent intracranial complication rate and you compare that, and it's hard to compare it to anything, but let's say we would compare it to, say, balloon angioplasty for vasospasm, which is a device that you're placing in the vessel and inflating, so similar to placing a device that you're then pulling, it's probably a similar complication rate, about two percent. I do continue to have some concerns about the fracture rate of the device and the fact that, even after retooling it, you still had fractures. And it's still unclear to me, even with the education that you've given to the physicians not to torque the device that you're still having fractures, there isn't something intrinsic in the device. And I would like to see either further bench testing of the new model and employment of your training program to ensure that physicians are not overtorqueing the device. And I would also want to see continued collection of data of all patients that have any sort of fracture, regardless of whether or not it comes to a serious adverse event, so that you can look for some sort of trend with the device.

DR. MARLER: Well, over the years I've been working in stroke research, I've learned a lot of respect for the brain and the disease of stroke and how frustrating it can be. Unfortunately, there have been numerous examples of extremely well-done Phase II studies, as you've done here, looking at various surrogates, or even not looking at surrogates, that haven't really panned out when really compared with a concurrent control. I'm really concerned that this could go either way, just because so often historical controls just really don't seem to pan out, and I could name trial after trial where that has occurred.

One of the first trials done in stroke that was a randomized, controlled, concurrent controlled trial was the ECIC bypass, in which surgeons worked very hard and documented very well revascularization, but they couldn't demonstrate any relation to clinical outcome, and that was very frustrating at the time. There have been numerous examples since then in different types of stroke treatments, and I think we're all looking for ways to

make things simpler and to reduce the investment we have to put in to developing treatment for this, apparently, ridiculously simple disease. I mean, it's just a blood clot, and you have to take it out. But it seems to defeat a lot of our efforts. I think we don't really understand all the vascular biology that goes on acutely and how simple manipulations, either pharmacological or mechanical, can interact in the process in both negative and positive ways.

And so I just don't have any way to know whether, if this device were put in use, you'd be helping people or hurting them. I think both possibilities exist because of the lack of really good data to compare to. And I think historical controls, I mean, the NINDS data, probably most of it is ten years old now. I would guess PROACT II data is aging pretty rapidly, and stroke treatment is changing, almost certainly, year-by-year, if not month-by-month.

So it's going to be very difficult.

DR. LOFTUS: I'm going to say something

completely different because I am satisfied, you know, to the extent of my knowledge, that my questions regarding trial design and my questions regarding safety were answered in the interchange that we had. And I have learned here, you know, a lot about regulatory matters, and I am sensitive to the fact that a regulatory decision was made in the design of this trial to design it in this 510(k) fashion.

But, to me, whether or not this device is to be considered substantially equivalent to removal of a foreign body depends on the pathophysiology of the lesion involved. To Dr. Smith's credit, we had this discussion, and he gave me an honest and forthright answer in that there is a mixed population in this trial, some of whom have an artery-to-artery embolus and others of whom, most likely, have local stenosis with an associated thrombus.

I would say that, for an artery-to-artery embolus, as opposed to a foreign body, this is an equivalent use of the device, to me, clearly. I have more question when you talk about a

focal stenosis in the middle cerebral artery, for example, with a thrombus, which, to Dr. Smith's credit, he said it could not be ascertained prior to treatment or prior to the institution of protocol in most of these patients. To me, that is more likely to be a change in the intended use than it is a substantially equivalent use of an existing device. I realize that's the regulatory question.

But, to me, the litmus test to that a little bit is the fact that some patients, although we don't know which pathophysiological group also received intra-arterial thrombolysis, which one would not do after retrieval of an iatrogenic foreign body, I would assume. So I have my concerns, just regarding the design, how this fits with the current, how this pathophysiology fits with the current application.

DR. DERDEYN: My thoughts, basically, are that the primary issue here, in terms of how this application is set up, is really we're either looking at this as safety and efficacy for clot removal, which is the 510(k) application, for which we see

this is quite effective and I think reasonably safe, although definitely some issues that I'll touch on in a minute, versus the other theme that's coming up over and over here which is that clot removal really isn't a procedure so much as a disease process, which is acute stroke. And the safety and efficacy of this device for the treatment of acute stroke needs a randomized trial.

So coming back to the 510(k), and I think that's where a lot of the comments are coming from and my primary reservations are, but coming back to the 510(k) avenue that we're looking at here, I think there is good data that it's effective at clot removal. There are definitely safety issues regarding the tip detachment that are not completely worked out. There's a number of instances in the complications where, simply, the device is placed and you pull on it and it detaches. And I don't know if some of that was with the older technology, but it is a problem.

As a consequence, too, I think there is going to have to be some testing of MR compatibility.

To say that you've done MR's in these patients is not enough to say that it's actually safe. Nitinol is generally fairly compatible, but they're platinum, and the way that the metal is worked can lead to that, so that should be tested. And I think, in summary, this is an extremely compelling, exciting Phase II study. That's it.

DR. DIAZ: I have a, perhaps, ambivalent appreciation of the process. What we're really asked to look at today is the issue of safety and efficacy of the equipment to remove a clot from the vessel. And the definitions that we are given for safety are the parameters of perforation, dissection, and embolization. That's it. If we fit our criteria to just those things, the procedure is efficacious in removing clot at a very high percentage rate, as compared to a non-contemporaneous control, and the procedure is safe when it pertains only to the assessment of perforation, dissection, and embolization. So if we fit our analysis to those things alone, then the questions have been answered.

My problem with this is that we have the

analogy of looking at what piece of the elephant. If we are the group of blind people looking at the elephant, are we looking at the tail? Are we looking at the tusks? Are we looking at the legs, the trunk, or the body? These three could be just the tail and the toes, and we are missing the big part of the elephant, which is what we are all concerned at this table.

Is safety limited to perforation, dissection, and embolization? In my mind, as a clinician, it's not because I have to deal with a process, with a dynamic process of evolution, which is really what stroke is. By removing a clot, we are not just acting as when we remove a piece of a catheter, which is a foreign object, or a piece of PVA, which may or may not occlude the vessel. That can be done without really triggering the cascade that follows an embolus or that follows a thrombus.

And so to look at it from a very narrow perspective, I think we've answered a question. But in my mind, I think the safety parameters were too narrow. There were too many variables among the

groups. The n, the power in the groups is too small to answer to my satisfaction any of the safety issues that I need to be comfortable with when talking to my patients about doing one or another thing. I would be very concerned that approving something like this would carry with it the imprimatur of an FDA label of quality, when, in fact, the questions that, to me, are important have not been answered.

DR. BROTT: I would agree with what Dr. Diaz said. My concerns are safety and learning more about what happens. You know, I agree with Dr. Smith completely that to cite the NINDS tPA placebo patients that were very bad with a median Stroke Scale score of 18 may not be comparable to your population with the median Stroke Scale score of 19. But the procedure itself takes sick people, in this case with a mortality of 40 percent, and they undergo a procedure that lasts two hours, and it's beginning four hours after the stroke has begun, which is about the time it takes to fly to LA, that the patient in that circumstance may be more vulnerable to safety issues that aren't there at 90 minutes or not there

at two hours because, after all, the brain has been injured for four hours.

And so I think there may be some variables that the device and the procedure are up against that don't really relate directly to this device. But I think that that series of questions needs addressing in more detail than we've got today.

DR. BECKER: Dr. Witten, any comments?

DR. WITTEN: No.

DR. BECKER: With that, I think we'll take a ten-minute break, and we'll come back for the FDA and sponsor summations. So if we could be back here at 20 after.

(Whereupon, the foregoing matter went off the record at 3:13 p.m. and went back on the record at 3:25 p.m.)

DR. BECKER: Could we begin, please? Okay. It's now 3:25, and we're going to proceed with the FDA and sponsor summations. Dr. Schlosser, I was wondering if you or anybody else from the FDA would like to speak at this time? No? Okay. So I guess

we'll see if there's any further words that the sponsor would like to have.

DR. SMITH: I just wanted to say that I greatly appreciate the discussion that's come forth today. These are all questions that I think all of us, as scientists, clinicians, and interventionalists, if I were one, deal with each day. We don't have any further comments. Thank you.

DR. BECKER: Thank you, Dr. Smith, and Concentric Medical. So I think, at this time, we can begin to focus on the discussion of the FDA questions, and the questions, I think, have been distributed outside and all the panel members have a copy in front of them. So we'll go through the questions one-by-one. I think there's already been a lot of discussion on a number of these points, so, especially with regards to question one, maybe we can consider it as a single question instead of three parts.

MS. SCUDIERO: Do you want to project this? Oh, it's already -- there we go.

DR. BECKER: So the question has to do

with the results to the MERCI trial with regards to serious events, efficacy of clot removal, and hemorrhage. And I think we'll go around the table and have anybody make any further comments on these subject matters, and we'll give Dr. Witten a summation. Dr. Ku?

DR. KU: Okay. With respect to question number one, because it's so difficult comparing the patients in the two groups, I don't think I have adequate information to determine whether the data supports the safety of the device or is against the safety of device.

DR. BECKER: Ms. Wells?

DR. JAYAM-TROUTH: I guess I concur.

DR. HAINES: I think, just to reiterate, I think there is concern that there is excess, there may be excess mortality in the patients who are not successfully treated, and the absence of an appropriate control group just makes it impossible to make the judgment about safety for this device.

DR. BECKER: I have nothing more to add to that. Dr. Jensen?

DR. JENSEN: Nothing more to add.

DR. MARLER: Nothing to add.

DR. LOFTUS: Let me just briefly read the notes I wrote in here last night when I read this because I truly have not modified this opinion, notwithstanding the fact that we did this exercise today in any material way. Does the data support the safe use of the device in removal of clots? I said that it did. Once the redesign and assembly had been done and the instructions for use had been so modified, I thought that it did. Whether there's a safety concern in the proposed population, I did not think there was. And the answer to number C was also no. I was not materially concerned about that.

Regarding question number two, was this adequate to demonstrate that you could revascularize --

MS. SCUDIERO: We're only doing question one.

DR. BECKER: Just question one right now.

DR. LOFTUS: Oh, I'm sorry. No problem.

DR. DERDEYN: No more comments.

DR. DIAZ: My concern continues to be the one of inability to make a decision based on the information provided because there is no concurrent control study. I am not satisfied the question was answered.

DR. BROTT: I concur.

DR. BECKER: So Dr. Witten, I think that, with regards to the question of whether the data supports the safe use of the device in the removal of clots in the neurovasculature and whether there are safety concerns with the device and whether we're concerned about the risk of intracerebral hemorrhage, I think that, if I understand the panel correctly, I think that we don't feel there's enough of a comparison group to be sure of any of those issues.

DR. WITTEN: Thank you.

DR. BECKER: So question two has to do with the efficacy end point in the trial, which was successful revascularization defined as achieving a TIMI II or III flow. The trial showed a 52 percent revascularization rate in the intent-to-treat population, and a 47 percent serious adverse event-

free risk revascularization rate, which was statistically significant compared to the spontaneous revascularization rate of 18 percent seen in the placebo group of PROACT II and greater than the goal of 30 percent set forth by the IDE and the FDA and the company in their discussions.

So the question is is this adequate to demonstrate efficacy of the device in restoring flow in occluded vessels within the neurovasculature? Why don't we start with Dr. Brott?

DR. BROTT: I would state that I agree with the trial results that show a 52 percent revascularization rate. I disagree with the terminology of 47 percent serious adverse event-free revascularization rate because of the overall mortality of 40 percent and the mortality in the revascularization group of 25 percent.

DR. BECKER: Dr. Diaz?

DR. DIAZ: I would limit myself to saying that the mechanics of removing the clot and being able to successfully revascularize the area were achieved, but not go beyond that.

DR. DERDEYN: And I would say the same thing a bit differently and say, yes, this is adequate to demonstrate efficacy of the device in restoring flow.

DR. LOFTUS: Yes, yes, my answer is exactly the same. With the question posed here, the device is clearly, in my mind, adequate to restore flow in these vessels.

DR. BECKER: Dr. Marler?

DR. MARLER: This is difficult for me. I guess it restored blood flow in some of the vessels, I just disagree with the implications of the term "efficacy."

DR. BECKER: Dr. Jensen?

DR. JENSEN: The device was capable of restoring flow.

DR. BECKER: I think there's no question that the device can restore blood flow?

DR. HAINES: I would concur with that.

DR. BECKER: Dr. Ellenberg, do you have any comments to add?

DR. ELLENBERG: Can I pass and come back?

DR. BECKER: Sure.

DR. ELLENBERG: Thank you.

DR. JAYAM-TROUTH: I think it definitely showed, I think, in answer to that question, it showed successful revascularization.

DR. KU: I agree. The device does what it was designed to do.

MR. BALO: It does restore blood flow.

DR. BECKER: Ms. Wells, do you have anything to add?

MS. WELLS: I agree.

DR. BECKER: Okay.

DR. ELLENBERG: Since this is not a voting situation, perhaps you'll allow me a little latitude here in asking a question before I respond either way. If we were presented data that showed that the PROACT II control groups spontaneous revascularization in a group that was as comparable as possible and only for MCA, a group that was as comparable as possible to the MERCI Retriever study. I'm saying if. If the rate were some rate X percent, and the rate in the group from the PROACT

study was also X percent, would all of the people who said that efficacy has been determined have given the same answer?

That's what's troubling me. We don't have a comparison group, and we have, through history, since the start of clinical trials, comparative trials, seen many examples where what is obvious and in practice when tested in a controlled environment turned out not to be efficacious. We've seen this repeatedly. FDA is well aware of this issue, and it's the reason that the goal standard is a randomized controlled clinical trial for showing efficacy, safety, any sort of comparison.

So, clearly, we're seeing the number 18 percent, and we're seeing the number 52 percent, 48 percent, whatever it is, and we're impressed because, logically, this seems to work and the data for the MERCI study seems to be showing that it's working. But I keep on coming back, in my own mind, to ask the question, "Working for whom?" Who's this group that it's working for and compared to what other data? So

I have to say that I believe that the efficacy, as defined here in isolation without comparison, has not been shown.

DR. BECKER: So to summarize the panel's answer, I think that the majority of the panel feels the device was able to restore blood flow as defined, although Dr. Ellenberg raises the point that the standard by which we're judging the restoration of blood flow was a fixed standard from the PROACT study and may not be the right comparative group. Dr. Marler also raises the concern that the definition of efficacy is probably the wrong one, in just that the restoration of blood flow should not be what we judge this device by.

So now we move on to question three. The MERCI trial was designed using successful revascularization as a surrogate end point from improved clinical outcome. Although not the primary end point, the sponsor collected 30 and 90-day clinical outcomes, the NIH Stroke Scale score and the modified Rankin score, for patients enrolled in the study. Please comment on whether you believe the

results observed, i.e. the trend toward improved clinical outcome in patients where revascularization was successful, supports the surrogate outcome measure.

Actually, why don't we start with you, Dr. Haines?

DR. HAINES: Well, I think this gets to the crux of the problem and the reason that there's been so much discussion. The fact of the matter is I don't think anyone is comfortable using this surrogate as the primary measure of safety and efficacy for this device, as evidenced by the collection of far more data about clinical outcomes than about the technical success of the procedure.

The net effect of approving this device through this mechanism when there is no existing clot removal device against which to compare it will be to have the device approved for what is, essentially, the treatment of stroke on a narrow technical criterion of re-opening a blood vessel. And I think if we do that with all of the questions raised, we will not be meeting our obligation to protect the

public. So I don't think that the data presented really allow us to use this surrogate as an appropriate measure for determining safety and efficacy.

DR. BECKER: Dr. Ellenberg?

DR. ELLENBERG: My answer to number three is no.

DR. JAYAM-TROUTH: I agree. I think this is where the problem is, and I haven't seen it showing safety, and the outcome I do not support.

DR. KU: I'm going to agree with the first comments. Although, as a caveat, the other thing that comes across to my mind clinically is that, very often, I have patients that I will do a IA thrombolysis on and the clot doesn't dissolve, and this device may be very interesting, potentially valuable for me as an option to do mechanical treatment. Now, whether that's done as an approved device or as off-label use, you know, if I need it, I'll probably use it.

DR. BECKER: Ms. Wells?

MS. WELLS: I agree with Dr. Haines.

DR. BECKER: Mr. Balo?

MR. BALO: I agree with Dr. Ku. I really do think that you've got to look how does this device really fit in with the tools you have today to treat various patients that you can't treat today, and if Dr. Ku says that if there is a patient where a clot can't be treated with a thrombolytic drug and if you could use this mechanical device to sort of help the patient, I think you should consider that when you talk about this device.

DR. BECKER: Dr. Jensen?

DR. JENSEN: Well, I agree with Dr. Ku with the caveat that having an approved device may also tie my hands.

DR. MARLER: I agree with Dr. Haines.

DR. LOFTUS: I do not believe that revascularization imaging criteria can be extrapolated to predict clinical outcome.

DR. DERDEYN: Okay. I disagree. I think successful revascularization is a good clinical outcome. Those patients did very well, and I think this is very compelling data, Phase II data, that

this is going to be something that works. The unanswered question is the control group issue of the patients in whom flow is not restored who did so poorly, and I think that's really, that's the safety thing and that's what a randomized trial is going to address. So, yes, successful revascularization is a good end point for improved clinical outcome, but the unanswered question is the inverse of that, in terms of the unsuccessfully revascularized, did you do some harm there?

DR. DIAZ: Having been involved in a number of revascularization trials, I cannot agree with the predicate that showing blood flow is sufficient to show return of function or prevention of neurological deficits. The fact that we may use a device, such as this one, to treat the isolated patient as an end-of-the-road measure is not really the answer that we are being asked to come up with today. The answer is is this safe for the patients? Does it provide clinical improvement? And does it meet the criteria that we have been given?

Given the fact that this study does not

have a concurrent control, I cannot answer that question in the affirmative. I believe this does not prove, to my satisfaction, that it is effective, safe, or clinically beneficial.

DR. BROTT: Well, I actually agree with Dr. Haines, Dr. Ku, and Dr. Derdeyn. I think we'd all agree that successful reperfusion at 30 minutes into a stroke is likely to be an excellent surrogate outcome. I think we'd also agree that successful revascularization at 48 hours is not likely to be an effective surrogate clinical outcome. So the question here is somewhat oversimplified. We're asking is revascularization a successful surrogate outcome when treatment is completed at six hours because that's the requirement of this protocol. And I think the evidence that's been presented today is that at six hours at the time of the last angiogram, we do not have evidence to show that this is an appropriate surrogate outcome.

DR. BECKER: So I think, in summary, the panel feels that, while there may be a hint toward efficacy and revascularization, certainly the data

that's presented here does not prove that. And I think just to make a clarification is that the company was not asked to prove that. They were only asked to prove that their device was safe and able to revascularize the vessel. So I think that, overall, the panel feels that we're a bit uneasy with the fact that they weren't asked for clinical outcomes and to power study to show a benefit to the device with a concurrent control group.

And I guess we'll move on to question four. One aspect of the agency's review of a new product is to assess the adequacy of the product's labeling. The labeling must give appropriate instructions for use to the treating physician. Given results of the MERCI trial, does the indication for use adequately define the patient population that should be treated with the Concentric Retriever? Specifically, should the population be limited in terms of the time between symptom onset to initiation of treatment, location of the occlusions that can be treated, the severity of the strokes at baseline, or treatment with the retriever only when a patient is

not a candidate for other approved treatments, such as IV tPA?

I'm going to add in the second point to the question, so we can address it all as one. Are there any additional warnings or contraindications that should be added to the labeling, specifically with reference to adverse events seen in the MERCI trial?

And why don't we start with Dr. Brott again?

DR. BROTT: I don't think that the data that we've had the opportunity to review and that's been presented to us today would allow us to provide safe labeling for this device.

DR. BECKER: Dr. Diaz?

DR. DIAZ: I would agree with that. I don't think we can come up to making up a label when we don't believe that the data we were given is sufficient.

DR. DERDEYN: Yes, I agree. There's not enough information to know for certain, and it gets, again, to the problems of having an approved device

that, essentially, ties our hands in some ways of pursuing other treatments.

DR. LOFTUS: Well, I disagree somewhat. I believe that this device is to be approved as substantially equivalent -- I keep saying this, I know -- but substantially equivalent to a device approved to remove foreign bodies, then that labeling should reflect that the indications here would be the removal of similarly-defined foreign bodies, i.e. an embolic clot from a distant source, and not for the more broad indication of the treatment of stroke patients.

DR. MARLER: Well, I agree with Dr. Brott.

DR. JENSEN: That's a toughie. If it's going to be approved, then I want to give some sort of guidance, but it's difficult to know what, given the patient population, so I agree with Dr. Derdeyn there.

In terms of warning or contraindications, I think there should be a warning as to detachment of the end of the device in not only a torque situation but just

in a retraction even without torqueing.

DR. BECKER: I would say that the data showed or at least hinted to the fact that patients who are revascularized did well, those who were not revascularized did not do well. And so it will be important to be able to predict who is more likely to be revascularized, yet the multivariate analysis gave us no indication of that. So the data from the study really doesn't help us predict who's going to respond to this procedure, so I don't think there's anything we can include in the labeling to suggest that.

DR. HAINES: I think Dr. Brott and Dr. Becker have said it very well.

DR. ELLENBERG: I concur with Dr. Brott and Dr. Becker. I concur.

DR. JAYAM-TROUTH: I think I, too, have to raise, you know, some questions there. Although, you know, when you are attached, as Dr. Ku was pointing out, you have a patient within three to six hours who doesn't fit into the IV tPA, the question comes in is there something that you can offer a patient. Now, there's nothing that shows that, you

know, yes, this outcome is going to be better, but there's always something that we are scratching for. Is there something new that is there, is something out there?

But, to me, I mean, there should be more information. There should be something more telling as exactly which patients will benefit from this. I think those answers will not come unless we get the double-label study. I know that if the clot does go away, if you do manage to remove the clot, they do do better. But how many patients will we get those clots removed? Which kinds of patients will it be? We need better answers before we can address the labeling issue.

DR. KU: I don't think we have the information to decide what is the appropriate labeling, as far as what is the appropriate patient population. If the device is approved, however, I believe that appropriate physician training should be a component of access to this particular device because I think it's a device that potentially has use. However, it's a double-edged sword. It can do

what it's designed to do; and if it's used inappropriately, it can cause problems, also.

MS. WELLS: I agree with Dr. Ku and Dr. Jensen.

MR. BALO: No comment.

DR. BECKER: So Dr. Witten, I think that the panel sees a potential role for this device, and many of the physicians who actually perform these procedures look like they have it in their armamentarium. But the concern is, if the device is approved for the removal of a clot, it may lead to a slippery slope of when the device is used, the training of the physicians using it, and, as some members have raised, concerns about legal issues surrounding the use of the device or other therapies instead of the device. I think the issue raised about physician training with regards to torque and device use are appropriate, and that would need to be a part of the labeling.

So I think now that the panel has addressed the four FDA questions, we can take a few minutes to go around the table so each of the

panelists can give their summary comments on Concentric Medical MERCI Retriever K03-3736, intended for the use and the treatment of ischemic stroke. And we're going to actually start with Dr. Loftus.

DR. LOFTUS: And I'll start by saying I really have nothing further to add than what I've already said.

DR. BECKER: Dr. Marler? Why don't we just come on down this way.

DR. MARLER: I have nothing to add.

DR. JENSEN: I think it's pretty much all been said. I would like to have one on my shelf in case I need to use it, though.

MR. BALO: I agree with Dr. Jensen.

DR. BECKER: Yes, I don't have anything to add either. Dr. Haines?

DR. HAINES: No, I have nothing to add.

DR. ELLENBERG: Nothing.

DR. JAYAM-TROUTH: Nothing.

DR. BECKER: Dr. Ku?

DR. KU: I agree with Dr. Jensen.

MS. WELLS: Nothing to add.

MR. BALO: As I said, I agree with Dr. Jensen and Dr. Ku. I still think this will probably be available for patients in that uneasy area between three and six hours, where it could be used in conjunction with another therapy to help the patient.

DR. BECKER: Dr. Derdeyn?

DR. DERDEYN: Yes, I think this device has enormous potential, and I think this data is very exciting and shows real feasibility and a lot that it will work. And I suspect in a randomized trial, it would definitely, very likely, show benefit. I, too, am very interested in using it off-label as it is. And then just one last little thought of mine in that regard. Some of the comments earlier about the FDA and randomization issues, I come from a very conservative institution that, were this device to be approved, we would probably not have a lot of buy-in for using it among our stroke neurology community, given the absence of randomized control data. And we would be eager in participating in such a trial, you know, a year down the road if it were approved or in terms of within an FDA framework.

DR. DIAZ: From my perspective, I believe the device has potential, but it's use should now be limited only to the off-label use until a randomized control study has been completed.

DR. BECKER: Dr. Brott?

DR. BROTT: I would agree with that, but I'd like to add that the team that put this together is an outstanding team. They've put together 25 of the best centers in the United States. They already have just a gold mine in terms of information to guide the planning of whatever trial may follow this one. And specifically, we didn't really hear about TIMI II versus TIMI III today. We didn't really see any of the angiograms. We didn't see the hemorrhages, in terms of the ECASS classification of hemorrhage.

I think that there are a number of things that these investigators are aware of that they can use in planning so that not only for their planning they've got that information but for the community because I certainly agree with them that IV tPA, even IV tPA can combine with IA tPA or any of the new-

generation agents. They are not likely to be the answer, and that's why I think that they've got a great, their data is great at this point, and I think they've got the potential to move the field forward and advance the care of stroke patients.

DR. BECKER: Thank you. Thank you, panel, for your participation. Dr. Witten, do you have any comments to make at this time?

DR. WITTEN: No, I'd like to thank the panel and the sponsor and the FDA presenters.

DR. BECKER: All right. This concludes the meeting. Thank you very much.

(Whereupon, the foregoing matter was concluded at 3:54 p.m.)

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