

DR. PERLER: And the status of the renal arteries? Any cases where renal artery flow was comprised acutely or long-term?

DR. MOORE: As far as the procedure is concerned, when we are all done, what we do is a completion angiogram, which includes placing the catheter above the renals, to make sure that that has not happened.

We have got verification that the renals are open when we finish and, in this series, there were no instances where the stent or the attachment graft actually covered the renal artery and obstructed it.

I think the other point that was made, when you adjust for preexisting renal insufficiency in this patient group, that that difference between the control group and the experimental group disappears.

DR. PERLER: My understanding was that the control and the experimental group were well matched, even in terms of renal insufficiencies.

I guess it is still not clear to me what the hypothesis is for the 10 percent of renal insufficiency long term among the bifurcated, stent graft, patients. Has there been, for example, any migration to compromise renal flow.

DR. ADELS: There has been no migration. There have only been two reports of migration, neither one of which -- both involve getting further from the renal artery,

not closer to it.

I think that the hypothesis is that, in the control patients they are not getting contrast. In the experimental subjects, they are getting contrast. Therefore, patients with renal insufficiency pre-operatively are more likely to have it post-operatively.

DR. CURTIS: Thank you. I think we need to move on. I am going to allow the other panel members to go ahead and make comments and ask questions. If you could limit your time to about five minutes so we can get through all this. Dr. Crittenden?

DR. CRITTENDEN: I think all the good questions have been asked, as far as I am concerned. I don't really have much to add. I will make a comment when it comes time to vote.

DR. BAILEY: Let me just follow up that last question. I guess it would be nice to see that analysis in a little more detail, because it does suggest that either the groups were slightly different in terms of the history of renal insufficiency -- I would assume that since you are talking about a causal mechanism with the contrast agent, this must have an effect only in the graft group and not in the surgical group.

At a minimum, I guess you would have an interaction there. It doesn't mitigate the fact that there

is some issue there. I guess it would be nice to see that data in a little more detail.

DR. CARICARINI: Dr. Bailey, the table reads as follows: The history of renal insufficiency had an odds ratio of 12.05 and a p value of .0001.

Also, neither of these other two things were sufficiently associated, but the p values were close to one, so we left them in the model.

If we used the control group as a risk factor, the odds ratio was .28, and the p value was .1082. In the early investigator experience, the odds ratio was 2.2 and the p value was .1025.

The really dominating factor was a prior history in that particular analysis.

Let me give you a little bit of background. What we did, we took all factors that were either in balance or, in conjunction with an advice of clinicians, we put together a list of variables that were known or suspected to be associated with renal insufficiency.

All of these variables entered the possibility of being entered into the model if they, in a screening process, were .25 or less associated with renal insufficiency.

We then retained the variable in the model in a multivariate fashion if the p value was .1 or less. That

just gives you a little idea of how we did that.

DR. BAILEY: That was about 10 times as much information as I -- all I really want is the odds for renal insufficiency in two subgroups, those without a prior history and those with a prior history.

DR. CARICARINI: Rather than giving you the odds, if I give you the proportions, would that be okay?

DR. BAILEY: That would be fine.

DR. CARICARINI: The patients with a prior history of renal insufficiency had 34.78 percent, and those without a prior history of renal insufficiency was 4.49 percent.

DR. BAILEY: I am sorry, I guess I am looking for four --

DR. CARICARINI: You want a two-by-two table?

DR. BAILEY: Yes.

DR. CARICARINI: No history, no renal insufficiency was 340. That was 95.5 percent of the people. No history, with renal insufficiency, was 16, 4.49 percent on the Roe percentage.

Those with a history of renal insufficiency, those with no renal insufficiency were 15 or Roe percent is 65.2, and those with a history of renal insufficiency and a renal insufficiency within 30 days were 8, which would be 34.78 percent.

DR. BAILEY: I am sorry, I can't process that

either. Let's go on. Let me just make a few comments on the statistical issues.

This is a very difficult arena to bring conventional things we are used to in terms of statistical comparisons.

I think I would like to thank the FDA reviewers again for their nice summary of the data. It is a very difficult thing to summarize and they did a very nice job. In particular, the statistical reviewer made some nice points.

The issue of site heterogeneity, I think, and his comment that we need to be aware of potentially how much variability there is in the performance across sites, in terms of being able to judge just how much confidence we have in these complication rates.

Probably we are over-estimating the confidence, to the extent that different people at different sites were going to have slightly different experiences.

Again, this is a very difficult thing to tease out statistically because of the very small N, diffuse distribution of the sample across a large number of samples.

I think it is still an important issue, not merely, and probably less so, for comparison with the surgical comparison, as much as just to get a better handle on the true sampling error that we are dealing with in terms

of extrapolating these results to the general population.

I have a very naive question here, but as I understand it, the way the patients were selected into the two arms -- conventional and the two arms -- was based on the anatomy, when it was suitable, within a certain overall framework of anatomical characteristics.

If it was suitable for the graft, it fell into the graft arm, and if it was not, it fell into the other group. So, in a sense, there was no overlap in the anatomical -- at least in terms of that criterion.

I may be overstating the case here but, if that is true, it seems that we need to -- as a devil's advocate you can say, well, then there is a complete confounding of the anatomy with the pair assigned.

That is the thing you would avoid with a randomized trial, which wasn't possible here. But it might be important to at least look at the surgical historical data, and if there is any way of separating out the effects of anatomy on the results of surgery, it is possible that those patients who would have gone into the stent arm here would have had better surgical results as well.

If so, there may be an over-stating of the reduction in complications. It is hard to imagine that that would be such an important variable that it would totally explain -- in fact, it may be that it is, indeed, the case

that there is no effect of anatomy on these complications.

The point that -- if I am hearing correctly, it seems that there is almost a complete confounding of anatomy.

That brings up, I guess, the general question of, to what extent has anatomy been -- not merely the anatomy of the lesion but the anatomy of the aorta, which certainly are quite different in the two arms -- has that been taken into account in these adjustment procedures.

I sense that it was, but the data that were presented did not speak directly to this.

DR. CARICARINI: Dr. Bailey, all the variables that were found to be out of balance between the control and treated groups were included in our screening for inclusion in subsequent safety and effectiveness modeling.

The only thing that consistently came through was the size of the iliac with regard to conversion and placement, which would be expected, and total aneurysm diameter, which wasn't different between the bifurcated and control groups, even though there was a small difference between the tube and control groups.

It did come out in some circumstances, but the differences between the control and treated groups, in total aneurysm diameter, wasn't all that large when we compared them.

We did put that in. Nothing outstanding really emerged from the modeling process. We kept them in as a continuous variable as well.

DR. BAILEY: So, you retained them in the model, even if they were not significant.

DR. CARICARINI: We put them in the model and screened them. If their p value with the outcome parameter was greater than .25, we did not continue to keep them in the model.

DR. BAILEY: I would suggest that it might be useful to keep them in the model, just on the general principle that even if there is a non-significant effect that you are not powered to detect, it could have some effect on the results.

There was certainly a substantial difference in the groups in the lesion size and the dimensions of the artery.

DR. CARICARINI: There was a significant difference in the dimension of the artery because the system had to have something to which to attach.

In regard to actual aneurysm length and diameter, the diameters only differed between the tube and control groups. I don't believe there was a difference in aneurysm length.

DR. ADELS: I would like Dr. Deaton to address

this. We can look at the numbers a lot, but it is important to understand what the medical effects of these differences are.

DR. DEATON: There were basically two ways that a patient would not be a candidate for the endovascular graft. One was that their proximal neck was larger than 26 or less than 15 centimeters.

In the case of the proximal neck, they had to be deemed a candidate for an infrarenal aortic clamp. I believe that 95 percent of patients had an infrarenal aortic clamp.

With regard to the distal or iliac problems, they were not candidates if they did not have a diameter of their iliac vessels big enough to take the graft. They were excluded if they had clinically evident occlusive disease.

So, someone with a six-millimeter external iliac was excluded, but they didn't have any clinical manifestations of occlusive disease, and there was no difference in ADIs, I think, between the groups.

DR. BAILEY: They were excluded from the whole study or just from the stent arm?

DR. DEATON: Excluded from the whole study. They were not a candidate for control or EGS groups.

DR. BAILEY: I am not concerned about that as much as the selection between the two arms. It sounds like that

was a fairly small effect, and that it didn't apparently, empirically relate to --

DR. DEATON: The clinical impact was avoided by excluding patients with occlusive disease, and excluding patients where it looked like surgically you would have to place the clamp in a position that is known to be high risk or different from the standard surgical repair of an infrarenal aortic aneurysm.

DR. BAILEY: I guess my only other comment, I would wonder whether one could have, in fact, done a randomized study for the delivery system question, in which case you would have a little bit stronger basis for making your inferences regarding that.

DR. KATZEN: The trial of the delivery system was the result of improvements that were suggested by investigators during the early parts of the trial.

It really focused strictly on the ability to deliver the graft in a more efficient and simple way. I think we are able to do that in a reasonably effective way in the way the trial was designed. The implant remained exactly the same.

DR. CURTIS: Thank you. Dr. Gilliam?

DR. GILLIAM: I will reserve, I think, a lot of comments to when we address the FDA questions. I think my one concern is going to direct itself toward the training of

people doing this procedure.

I think I heard several of you mention that this is a procedure that has not yet been done in any fashion, so it is a new experience.

What length of time and intensity is anticipated by the sponsor in terms of training people to do this. Do you anticipate that this procedure can be typically done in an OR setting versus a typical lab setting, once it is done?

DR. ADELS: Let me address those issues. We have an extensive training program that has been developed and is being planned.

It will include film reading and patient selection, device description and deployment techniques, follow-up evaluations of post-operative diagnostics for endoleak and AAA diameter.

There will be lectures, demonstrations and live case experience with experienced investigators. We will also be providing training for ancillary hospital personnel.

On-site clinical support will be provided for at least the first five cases that each new user does, and beyond that, if necessary. So, we do intend to provide significant clinical support for these cases.

I would like Dr. Katzen to address where the procedure can be done.

DR. KATZEN: I can't speak for the sponsor, and

maybe Lori can clarify that, but I think during the course of the trial it was demonstrated that the procedure can be safely performed in both an operating room environment or in a modified angiographic environment where appropriate support and sterile environment is created.

DR. ADELS: Certainly, the facility has to have adequate imaging and also has to be appropriate for a surgical cut down, and those are the requirements that need to be met.

As Dr. Katzen has says, this procedure has been successfully done in both the OR and an interventional suite that has been laid out for the surgical procedure, the arteriotomy.

DR. HARTZ: I would like to further dissect the two main areas that have been extensively addressed already this morning.

The first with Dr. Deaton is that of gender and the site of the femoral artery. I don't think we have discussed this quite thoroughly enough.

The mean age of the patients in this aneurysm series is 72, but clearly, the life expectation of women is 80.

In an octogenarian coronary surgery series, which is basically the same population you are talking about, the number of women in those series is approaching 50 percent,

in a few years will be 50 percent.

Does the protocol allow for the suturing of a small graft on a femoral artery akin to what we used to do with aortic balloons to allow passage of the system?

Are there plans to down-size the issue, because the whole gender issue is too intimately related with body mass index to separate them out.

Finally, along the same lines, I think the blood loss is too high, and would some sort of suturing on of a graft completely obviate the blood loss situation with these systems.

You cannot control, through just an arteriotomy, completely the blood loss, and would some modifications allow better, more efficient and safer use in women, and less blood loss.

DR. DEATON: With regard to your first question about sewing a graft onto the femoral iliac artery, that was permitted. Surgeons had discretion as to how they could perform access, and could even perform access from the iliac artery.

The incidence of abdominal aortic aneurysms is less in women. Even in control series or published national multi-center series, it is about 80 percent to 20 percent men to women ratio.

The down-sizing of the device is obviously a very

desirable goal. The device here is designed to mimic, as closely as possible, all the aspects of conventional grafts. Down-sizing is obviously a relevant application of these techniques.

The primary goal is to apply these techniques only when they can be safely applied.

DR. HARTZ: And the blood loss issue?

DR. MOORE: Let me just address the blood loss issue for a moment, and also to clarify the actual procedure in putting the device in.

We don't simply make an arteriotomy and then try to float the graft up. There is a sheath that is put in first. That sheath has a double valve system.

By using two valves in serio, you could then minimize the blood loss as you advance the device in, but some of the blood loss will be a function of the initial experience.

Also, part of the blood loss is related to conversions to open repair, when you compared the experimental and the control groups.

DR. ADELS: I would like to clarify that the median blood loss was less than 500 ccs for both experimental groups, and is much higher in the standard surgical procedure.

DR. HARTZ: So, even in those groups that had

greater than a liter of blood loss, those were probably conversions in the intent to treats?

DR. ADELS: I think we have some detailed information about patients with significant blood loss. They are looking for that and we can get back to it.

DR. HARTZ: That is all right. I just did not see the double valve system.

DR. ADELS: That is a product that has already been approved, or cleared, under a 510(k).

DR. HARTZ: The other issue, of course, is of perigraft flow. I am not sure, Dr. Moore, that I still understand the graft does not heal to the aortic intima. Is it that the hooks are too non-reactive? Is it that the graft is permeable?

We know that the whole cardiac output can get through a very small hole, and the higher the velocity, the worse the results, long term, on the aneurysm sac.

I am not concerned about collateral flow back should be biphasic and low flow, but these small defects with high velocity are very disturbing to me, and a year certainly isn't enough follow up to determine the fate of those.

So, what is happening at the actual proximal anastomotic site. What is happening that the graft isn't healing to the intima?

DR. MOORE: Well, in general, the experience has been that fabric prosthetic grafts, even when sewn in place, don't heal in the conventional sense of the word.

When we put a graft in the aorta, it is forever dependent on the suture line. If that suture line becomes incompetent, you end up with a false aneurysm. That is clearly a problem, even in conventional surgery.

The same is true in endovascular repair. There is no difference in the healing that takes place in an endovascular graft than what we see in a surgical implant.

With regard to the periprosthetic leak that takes place, when you speak of flow velocities I am not really sure we have that data.

If there is an outflow vessel, then one may have flow. If there is no outflow vessel, but an incomplete seal at that level, where you have essentially got to and from motion, I don't think that you are necessarily going to have a high flow velocity in that setting.

DR. DEATON: I just wanted to clarify, for bifurcated grafts, the attachment site, or indeterminate at 12 months, is 4.6 percent, and half of those are classified as indeterminate.

As the remaining that are classified as attachment, they are not classified as to proximal or distal, but when they are proximal, one usually knows.

At our institution, we have done 60, and we don't see any -- proximal attachment leaks are very rare. As I mentioned before, if one sees that, that usually is a reason for conversion, but those are very rare.

DR. HARTZ: That is really the main problem, is the proximal attachment leaks, because they will eventually lead to further aneurysm growth.

DR. MOORE: If they occur, they are a significant problem, but they occur very, very rarely.

DR. HARTZ: So, you think there are enough hooks that the suture line is complete and there is true exclusion, when it is properly deployed.

DR. MOORE: All the evidence that we have suggests that that exclusion, as regards the proximal attachment, is complete.

DR. HARTZ: Finally, there is no real incidence any longer, is there, of actual false aneurysm through the hook perforations?

DR. ADELS: There has never been any incidence of that.

DR. SIMMONS: I guess I just have a couple of comments. Did I understand the statistician to say, if the aneurysm was of increased size, there was an increased chance of flow and, therefore, there was an increased chance of aneurysm expansion?

DR. CARICARINI: No, that is not correct. What we -- there were too few increasers, if you will, to allow that to be modeled. What we did was, we modeled the inverse.

That is, we modeled the probability of decreasing in size by five millimeters or more. The leak was associated with the issue of size, but the probability of decreasing was less likely if a leak was present.

So, it is a rather convoluted way to look at it, but it was the only way we could evaluate this process. So, the aneurysm size was associated with a slight increase in the ability to have a leak, but was not associated with the size issue, with either a decreased ability to decrease the aneurysm, but perigraft flow was associated with a lower probability of decreasing aneurysm size.

DR. SIMMONS: It just seems like a different phenomenon. You were just saying that you don't have enough numbers to address the fact that a leak causes an increase. Is that what you were saying?

DR. CARICARINI: There were only nine cases in which there was an increase across both the tube and bifurcated series. That is really very little information on which to build these models, and the models tend to be extremely unreliable when that occurs.

What we did was to model the probability that the aneurysm would decrease in size, and determine inversely

what was associated with a decrease, or the failure to decrease.

In that particular context, the presence of perigraft flow indicated a lower chance of decreasing an aneurysm size.

DR. SIMMONS: I just think those are completely different mechanisms of something going on. I am not sure that one implies anything about the other.

Just things that I am interested in, of the dialysis patients how many of them turned out to be women, the ones that had to go to dialysis?

DR. ADELS: I don't have that information readily. It can be obtained, but I don't know of the three dialysis patients, how many were women.

DR. SIMMONS: When you were going through the people who had increase in their aneurysm size and who didn't go to surgery, it seemed like there were two -- you had one that had an increase in aneurysm size that you didn't have a leak, and that patient refused surgery, but then there were two that had an increase in aneurysm size with a leak, but didn't go to surgery or have a replacement?

DR. ADELS: None of the nine patients that we are talking about went back to surgery. Three patients were converted. Those are three additional patients above the nine with increases.

Of the nine patients with increases, seven of them have been treated either by coiling or stent and PTA, or implantation of a second endograft, and then there are two patients who have not had any treatment.

DR. SIMMONS: Those two patients have not had any treatment because?

DR. ADELS: Dr. Moore's patient is one of those who refused, and I don't know the details on the other two; I am sorry.

I just think it is interesting, though, when you said you redesigned this delivery system to improve -- what was your term -- ergonomics and efficiency, and yet the operating time increased by 35 to 40 minutes, is that correct?

DR. ADELS: Yes, that is correct. Dr. Deaton, would you like to address that, please?

DR. DEATON: I think in general, when most surgeons look at operating time, it is to correlate the problems that were encountered in the procedure, and that would correlate with ICU stay and operative length.

With the ANCURE subjects, what was seen was that the conversion rate decreased from around 10 percent to five percent, and that hospital stays went down by another day to two days, and the ICU stay was less. Overall, the patients did well.

It may be related to learning curve issues, as investigators appreciate better some of the vagaries of implanting these devices and looking for problems that previously they encountered after the procedure, in an attempt to address them at the time of the procedure.

DR. SIMMONS: I guess I am impressed by the acute and the short-term results, but as somebody who doesn't do interventional procedures -- I have to say these people are going to be sent back to me to follow these people.

Probably a lot of the people who do these procedures are never going to see them again, unless I reconsult them.

I am still a little bit concerned about what is going to happen in two years and how often these patients are going to need contrast studies with CT scans. I don't know.

I think that is very ill defined right now, what is going to happen. I think whether this thing gets approved or not is really going to depend on what the post-marketing surveillance is going to be like, and is this going to be a mandatory registry or a voluntary registry? I guess those are questions we can address later on.

DR. ADELS: Do you have a question that you would like us to address?

DR. SIMMONS: I think these are things that we

will probably address later.

DR. CURTIS: Yes, that will be coming up. Thank you. Dr. DeWeese?

DR. DE WEESE: I thought it was a very interesting application, well presented. Many questions have been asked and already covered. There are just a couple I would like to ask.

First, regarding the training requirements, I have heard vaguely, but do you have an actual outline of them that you could show us, the FDA, present it to us? You don't need to read them now.

DR. ADELS: Yes, we do.

DR. DE WEESE: Could you send it?

DR. ADELS: Yes, we could.

DR. DE WEESE: In other words, time, courses.

DR. ADELS: Right. As I said, we are planning both didactic and hands-on experience as well as proctoring, so all those things could be spelled out, and actually have been submitted with the PMA.

There is a section in the PMA, probably not in your panel pack but in the main PMA. There was an outline of the training program.

DR. DE WEESE: The second is just to get a handle on long-term follow up. You have been doing them five years, I guess.

Could you now tell me exactly how many you have seen and imaged at two, three, four and five years; the numbers.

DR. ADELS: I understand. The experience with this device just dates back -- with this specific device, dates back to the end of 1995, so it is not a five-year experience quite yet. It is about three-and-a-half to four years.

I can tell you how many patients we have at 24 months. On 24-month data, we have data for 76 EGS tube subjects and 50 bifurcated subjects and 59 controls at 24 months.

DR. DE WEESE: These are imagings that you have done?

DR. ADELS: Yes.

DR. DE WEESE: And three years?

DR. ADELS: I don't have the exact number. It is quite small.

DR. DE WEESE: This is what total now?

DR. ADELS: At two years, 76 tube subjects and 56 bifurcated subjects.

DR. DE WEESE: And how many originally?

DR. ADELS: There were 153 tube and 268 bifurcated EGS subjects were enrolled in the trial, so it is 421.

DR. DE WEESE So, 421 you started with. How many

of the ones that were done three years ago, how many of them have been back for images, the percent.

DR. ADELS: If I had a calculator, I could figure out the percentages. Seventy-six of 153, so almost half of those patients, and about 50 of the 268, so about 20 percent of those patients.

DR. DE WEESE: Why have more not been back?

DR. ADELS: They have not reached that point in the follow-up time yet. They are not eligible for that follow-up period.

DR. CURTIS: Dr. Pentecost?

DR. PENTECOST: I think it might be helpful to try to be a little bit more discriminating in the change in size of aneurysms in follow up.

You basically break it down in three groups, which is a decrease in size, no change or an increase. You say that no change is less than five millimeters.

One of the reasons for that is because of measurement error. But the difference between five and six millimeters, which makes you an increase in size, is only one millimeter.

I think it would be very helpful to have the raw data, to say that everybody that is less than five millimeters, are some ones, some twos, some threes, some fours, or are they all five millimeters.

Half the patients are in this no change category in the bifurcated subjects, 67 out of 135, 50 percent.

I cannot be certain that 50 percent of the patients, at one year, don't have a five-millimeter increase in size in their aneurysm.

Since the size of the aneurysm was a little bit less than five centimeters, that is a 10 percent change. So, I think we need to see the raw data, rather than just broken out into three categories of decrease in size, no change or increase.

Secondly, I think that the perigraft flow clearly is a major issue. It is troubling that the core laboratory and your investigators had a two-fold difference in measuring this.

I think you are also going to need to be more discriminating in how you image these patients for perigraft flow.

It is referred to as a contrast CT scan afterwards. That could be a contrast CT scan, where someone is given 50 ccs of contrast and scanned an hour later, or it could be a patient who has a power injection, large volume of contrast, helical CT, a much more refined type of examination to assess that.

DR. ADELS: Do you want to continue, or should I address some of your issues?

DR. PENTECOST: Why don't you go ahead.

DR. ADELS: I just want to say that we have submitted the results. There is a discrepancy between the investigator and the core laboratory. We recognize that. We intend to work on that through the training program.

We also see, with the ANCURE data -- and this is something that is under review by FDA -- that the agreement is getting better in the ANCURE subjects between the investigators and the core lab.

Dr. Caricarini has some numbers. The five millimeter increase, I must tell you, our original analysis was going to be three millimeters. FDA asked us to increase that difference to five, which we did. Dr. Caricarini has some more information on this.

DR. CARICARINI: Yes, in the actual PMA we did provide the mean and the ranges of the sizes at discharge at six months and at 12 months.

The mean at discharge for the tube was 48.9, and at 12 months it was 44.1. So, the average decreased by approximately four to five millimeters.

For the bifurcated, the average size at discharge was 52.3, and by 12 months, it was 46.2. The ranges of those were quite broad, roughly 30 to 75 millimeters.

DR. BAILEY: I think the point was that by analyzing the change as opposed to the trichotomous

variable, you might be able to better ascertain some of the relationships that were being asked about earlier, in terms of the associations and implications.

DR. ADELS: I would point out that also, in the PMA, we do present the mean change for the patients who have no change.

The mean change for the patients who have no change at 12 months on the bifurcated subjects is -5.9, and for the two patients it is -.15. That would certainly indicate that they are not all up there at the +5 as well.

DR. PENTECOST: I think it would also help, between the core lab and the investigators, if you codified the type of CT scan more carefully, that you are doing.

DR. MOORE: On the core lab, because the core lab's mandate was to be as sensitive as possible, and because these are subjective readings of radiographs, there were occasions where, say, a high quality contrast CT was negative for perigraft flow, but that the core lab read an ultrasound -- which in other work has been shown to be sensitive but not as specific -- as positive, and therefore, it was counted as perigraft flow.

The investigator, particularly experienced investigators, would record it as not perigraft flow because they thought it was a false positive ultrasound.

So, there is some -- the core lab is

ultrasensitive. Then there is the issue of experience improving the investigators.

Another important thing to note, I think, is the fact that any aneurysm enlargement was always picked up by the investigator without the assistance of the core lab. So, no clinically significant events were missed by investigators.

DR. PENTECOST: I don't think prospectively any of us would have anticipated this much operator difference. One way to reduce the operator difference is to present both sets of people a coded set of images, rather than something wildly different ones.

I think that is something you should work on, to try to pick up the most sensitive way you can to look for perigraft flow, and then educate different groups of operators about how to interpret those images.

My last comment is about -- you talk about operative time but not fluoroscopy time. Did you all make any effort to look at radiation from these, since this is a new procedure and this has been an issue with some interventional procedures in the past.

DR. ADELS: We don't have data, and it was not presented in the PMA. We actually did collect fluoroscopy time on the case report forms, and it could be analyzed, but it hasn't been at this point.

DR. PENTECOST: That is all I have.

DR. CURTIS: Dr. Sethi?

DR. SETHI: A couple of comments and a couple of questions. Like Dr. Bailey, I am disappointed that a randomized trial was not done in this case.

I think, as a retiring member of this panel, we have worked very hard over the past few years, to ask the sponsors to provide controlled trials in the devices.

I would urge the panel and the agency to insist, whenever possible, to have the randomized trials for the devices.

I think, just because of difference in control -- and I will mention the questions I have got -- it is difficult to compare the results between the control and the device.

The basic clinical characteristics are similar. If you look at the anatomy of the neck and the distance between the femoral artery and the aneurysm, in the control patient the neck is bigger and the neck is smaller.

Those patients are technically difficult to do, and those patients tend to have a higher complication rate. So, some of your complications could be because of that.

DR. MOORE: I think it is important to point out that, while the necks were shorter in the control group, that there was a neck present, and that that did permit

infrarenal clamping.

It was not the same situation as when we are dealing with a perirenal aneurysm that might require a suprarenal clamping or encroachment upon the renals.

So, true enough, the necks were longer in the experimental group, but they were not absent in the control series.

DR. SETHI: I think it is a question of semantics here, but wouldn't you agree that the patients are tougher to do when the necks are pretty small and you are next to the femoral artery?

DR. MOORE: As long as there is enough room for me to place a clamp immediately below the lowest renal artery and have adequate room to sew, obviously, one likes long necks in any event, but I don't think it really jeopardizes the outcome of the surgical procedure.

DR. SETHI: That might be the difference between an experienced surgeon like you and some of the younger surgeons in the community doing this operation.

My second question is, if you look at the size of the aneurysm, it looks like about 40 percent of the patients have an aneurysm size about four centimeters, and some of them are even -- three, four and five are about three centimeters.

My question is, because you can do this procedure

easily now, and there is a less morbidity and the patient can go home the next day, have you seen the difference in practice that you are doing the smaller aneurysms now over the period of time?

Have your indications for intervention become more liberal because the procedure is available now.

DR. MOORE: I think that becomes an issue for individual surgical judgement and I think there are some surgeons and recurring physicians, who would insist that the aneurysm, all other factors being equal, would be in excess of five, maybe even six centimeters, before they will refer the case to us.

I think there are some surgeons who may be more aggressive even in conventional operations, and operate on patients with aneurysms less than five.

From a personal perspective, five has been, and continues to be, my cut-off point. I suspect that most of the investigators -- although certainly not all -- would agree with that.

DR. SETHI: Can you tell us the number of patients, break down the number of patients who had an aneurysm size less than five, say four? Do you have that data available?

DR. ADELS: It is a small group that is below five.

DR. SETHI: Forty percent according to what I see. Plus, if you include the five percent less than four, it is 45 percent of the patients have aneurysms about four centimeters, which I think is not accepted clinical practice in this country.

DR. KATZEN: Actually, I think it is lesser percentage below four, and not 40 percent.

DR. SETHI: It is five percent below four, and 40 percent between four and five.

DR. KATZEN: I think at least within the trial, among the size indications, the patient had to be a surgical candidate.

I think that some of the variation reflects surgical preference within the community. If you look at the distribution of the control group, there is also a number of smaller aneurysms in the control group as well. I think that reflects operator preference and recommendations for patients.

DR. ADELS: There is not a difference between the control and the experimental group. So, it is not as though we are treating smaller aneurysms with these devices.

DR. SETHI: The control is only 88 patients. How can you compare 88 patients with 500 patients. That is what the trouble, I think, in what this uncontrolled trial is.

How can you compare -- is 88 the sample size to

compare the size of aneurysm?

DR. CARICARINI: There were 111 controls.

DR. ADELS: Only 88 with one-year follow up.

DR. SETHI: I think that is the basic flaw in this study. It is an uncontrolled study, it is a non-randomized trial.

The second difficulty I am having is that, even when you change to your new mode of delivery system, I think you have unfortunately at that time to randomize between two delivery systems. Is there any thought that you would do it?

DR. CARICARINI: I think the issue of randomization was felt not to really be appropriate, since it was simply a device delivery modification, to improve delivery of an implant that was virtually identical to the original trial.

DR. SETHI: How many patients had impending rupture in whom you used the device. It doesn't say that? Do you have any data?

DR. ADELS: None of the patients had impending ruptures. All of these were elective procedures. None of these patients were emergent or near-emergent procedures.

DR. SETHI: So, none of the patients had a back pain, they were all elective patient.

DR. ADELS: They were all elective patients.

DR. SETHI: I think we need to considering that in the labeling, when it comes to that.

Do you have any data on the incidence of complication at one year or two years? I think, if I remember correctly, about 10 percent of the patients had some kind of a procedure done afterwards, stent placed -- I was just wondering what happens over the period of time.

We know the nature and history of stents. They tend to have problems. Do you have any data on that?

DR. DEATON: All the patients that had stents placed, they never had any re-intervention and they never had any problem with reduced limb flow or thrombosis to date.

DR. SETHI: But you are not doing any kind of a questionnaire to find out whether they have got any symptoms because of --

DR. DEATON: They continue to have a physical exam and anco brachial indices measured at the time of physical exam, and they continue to have the abdominal radiographs that are in the protocol.

DR. SETHI: Nothing further, thank you.

DR. CURTIS: Do either the industry or consumer representatives want to make any comments?

MR. DACEY: Yes, there is a consumer perspective I would like to bring to this. Number one, the long-term

patient follow up, I think, is absolutely essential.

To just continue to add to the body of knowledge, I think, is absolutely vital, speaking from the patient perspective.

That segues into my favorite issue, which is what do we tell the patients. We have an aging population, what was it, 72 is the age of the patients.

These demographics are changing rapidly. The socioeconomic demographic is changing rapidly. The informed consent issues that you refer to, doctor, are changing.

More and more people are jumping on the web site to get their medical information even before they go into the doctor's office.

At the same time, at the other end of the spectrum, there are people who may not have functional literacy above the fifth-grade level.

This information, at the time of their personal intervention, has to be conveyed to them in ways that they can understand it.

You have got this huge wide variety of information you convey to patients. I don't know how that is going to be done.

It is curious, because patients are being told, on a regular basis, in order to gain a high level of confidence in the institutions and in the practitioners, to ask a

question like, how many of these have you done, doctor, or how many of these have been performed at this institution.

Something as new as this, I am not sure it is very comforting if the answer is two or three. Somehow the patients have to understand the newness of it and, on patient selection, what some of the criteria are.

I think the gender issue is extremely important. So, I will go back to what will the patients be told, and I am not sure you have to answer that now. I think that is an issue that is going to come up over time.

DR. ADELS: Just to address your concern a little bit, we are working on patient labeling with the FDA. The purpose of that labeling is to summarize the results of the clinical trials in a very lay format to make sure that the patient can understand it.

The IFU includes a summary of the clinical trial that hopefully he or she can help translate to the patient.

MR. DACEY: I appreciate that, but I also suggest that we have a velocity of change taking place, where maybe the older patient doesn't have the science-based questions to ask, but their son or grandchildren, who access the internet on a regular basis, have got not only the knowledge, but how to use that knowledge. So, they become an influence in the decision-making process.

MR. JARVIS: A couple of questions here. One on

the heparin here, and the usage. Was there actually some type of protocol within the protocol that says you are going to give so much heparin?

DR. ADELS: The instructions for use actually say -- let me get to the specific page here, but the instructions for use actually recommend the administration of 5,000 units of heparin prior to the initiation of the procedure. So, it is in the instructions.

MR. JARVIS: Then they would just kind of follow the institutional procedure after that?

DR. ADELS: Right.

MR. JARVIS: The blood loss, did you see that you had a higher blood loss at the beginning? I think Dr. Katzen brought up, when this trial started, that there was no intervascular device out there. Did you see a higher blood loss at the beginning, kind of a learning curve, versus the end?

DR. CARICARINI: There was a small change with physician experience in blood loss with both the tube and bifurcated patients.

It was not significant for the tube patients, but was close. It was significant for the bifurcated patients, but it turned out to be about 100 ml, the median difference turned out to be about 100 ml.

MR. JARVIS: Was there any difference between the

old delivery system and the new delivery system as far as blood loss?

DR. ADELS: Again, a very small difference, about 100 mls.

MR. JARVIS: The renal insufficiency that was kind of attributed to contrast load, did the people who had insufficiency have longer procedure times and a much higher contrast load than the others?

DR. ADELS: There was no correlation there. I think it was more correlated to pre-operative history of renal insufficiency.

MR. JARVIS: Then as far as complications in general, with any new technology, you see with a higher comfort level, people get a little bit more aggressive, different patients are enrolled.

Do you see that maybe your complications went up in the latter part of the study versus the early part of the study, where you were probably a little bit more conservative where you were maybe a little bit more conservative about the patients you enrolled?

DR. CARICARINI: Actually, I think there might be a slight reduction in the total IDE composite rate with physician experience. We did not see that.

MR. JARVIS: This was a collaborative effort of interventional radiologists and vascular surgeons together?

DR. ADELS: In some centers, that was the case. In some centers it was just the surgeon.

DR. CURTIS: I just want to make a couple of comments myself. Looking over the data we have seen here today, I think there is no question that it is preferable for a patient today to have an interventional procedure like this than to go through an open repair of an abdominal aortic aneurysm.

We have seen information on shorter recovery times and shorter ICU stays and all of that. The long-term unknown issues are going to be things like the endoleaks and what do they mean.

I am also wondering about long-term need for interventions. There are some stents placed early on. What we don't know is whether or not these patients are going to wind up needing more interventions in the future. That is why we are going to have to do long-term follow up, and we are going to have to make some recommendations about the means of doing that.

I did have a comment about what Dr. Sethi said. The issue about intervening earlier or on smaller aneurysms, I think that is going to be a real issue.

Since we don't know whether these endoleaks or changes in aneurysm size, we don't know what happens at five-year follow up, because there isn't any five-year

follow up yet.

If patients like this are going to more often require stents, more often require more interventions later on that we don't know about yet, I am a little bit concerned about people getting access to this device and going, gee, this is great; I don't have to do an open surgical procedure, so I am going to go ahead and put it in all my patients with three-and-a-half centimeter aneurysms.

With an open surgical procedure, there is naturally a little bit more -- I think everybody gets pushed a little bit more to waiting for them to get larger, because there is serious morbidity and mortality associated with it.

I know that we are going to be talking about the labeling shortly here. We talk about aneurysm, or there is mention of it, and there is no mention of aneurysm size.

I am a little bit concerned there, that if we leave it that vague, that there would be an enthusiasm for using this broadly.

We risk later on finding out that, gee, there is a fairly high incidence of requiring further procedures that maybe in retrospect you don't want to get that graft in that early and that you might want to delay.

I don't know if there is a specific answer for that, but I do -- you know, once you put it on the market, people can use it for whatever size they want, and there is

going to be, I think, a lot more liberal use of it than you may anticipate at this point.

DR. MOORE: I think that was a very real concern. Once again, I think there are several controlling factors that will keep it from being over-utilized in the majority of cases.

One is the knowledge of the natural history of aneurysms that are small, and that is that the likelihood of that rupturing over a reasonable period of time -- maybe even the patient's life expectancy -- is going to be quite low.

Therefore, the likelihood of a patient with a small aneurysm being referred for this, I think, is going to be controlled at that level.

The other issue, like it or not, are the insurance companies, the third party payers. We have to justify all the time the indications for why we are doing a procedure.

If I were to go to one of my third party payers in Los Angeles and say I want to do a three-centimeter aneurysm, you can imagine what kind of answer I am going to get. So, I think it will be controlled at two levels.

DR. CURTIS: I just have a couple of quick comments. You use heparin during the procedure. Is there any need for, or recommendation for long-term anticoagulation?

DR. ADELS: No, there is not.

DR. CURTIS: Another issue is going to come up with contraindications. What happens if you can't deploy this thing or there is a complication during the deployment.

I didn't hear there was a lot of problem with that during the clinical trial, but should this be deployed or used in a patient who cannot have surgery; for example, as a contraindication for general anesthesia or some reason why they shouldn't be operated on.

DR. MOORE: I think that is a difficult question. Again, we have not looked at the high risk group of patients, and that is what you are talking about right now.

The only comments that we can make are those that are surgical candidates, because that is where we have data.

Clearly, if you have a high risk patient that is not a candidate for open repair, and you get stuck halfway and have to convert, that is obviously going to be one of the major risks.

I think one would have to stand back and then ask the question, if the patient is that high risk, does he need his aneurysm repaired at all, and should we be doing anything.

There again, clinical judgement becomes an important issue.

DR. CURTIS: Dr. Hartz had one other issue she

wanted to raise.

DR. HARTZ: The issue I had forgotten to discuss is whether there is always a surgeon present or available for these procedures or, if not, does the interventionist have hospital privileges to perform groin cut-downs, vascular surgery, by their hospital before they are admitted into the training course. The liability issue would be outstanding if they did not.

DR. ADELS: There is always a surgeon present at these procedures.

DR. HARTZ: Is that going to be part of the requirement for the procedure being done?

DR. ADELS: Yes.

DR. CURTIS: Dr. Roberts, did you have any other questions?

DR. ROBERTS: Oh, a few. You didn't expect me to be totally quiet. This may lead into some of the labeling things.

In terms of contraindications, I know that in your exclusion criteria you said that patients with evidence of thromboathrometous projections -- I don't know exactly how you defined that -- into the lumen were being excluded.

Given the fact that you had a fairly high thromboembolic rate with this device -- eight percent with the ANCURE and three to 3.5 percent with the EGS, versus

less than one percent with an open procedure --

DR. ADELS: Are you referring to thromboembolism or graft thrombosis?

DR. ROBERTS: It says thromboembolism in the chart. I don't know exactly what you mean by that. It is on page -- well, it is page 6 of my packet.

It says embolism-lower extremity ischemia. I don't know what you mean by that, but it says that it is 7.9 percent in the ANCURE, 3.9 percent in the EGS tube, 3 percent in the bifurcated and .9 percent in the control group.

I am assuming anyway that this means thromboembolism. If that is the case, I would think you -- that is in patients that are already excluded, or perhaps the ones who presumably already had a lot of junk sitting in their aorta were already excluded.

I assume that one would want to continue -- this should be a contraindication, perhaps, to placing the device?

DR. ADELS: Perhaps.

DR. ROBERTS: The other thing is regarding aneurysms that have an etiology other than atherosclerotic disease -- i.e., mycotic aneurysms, inflammatory aneurysms -- I assume those were not enrolled in this study. I assume they should perhaps be contraindications as well?

DR. ADELS: Or at least a precaution. They haven't been studied.

DR. ROBERTS: I don't know. I would be sort of moved to think that maybe mycotic aneurysms, if you think they might be mycotic, they ought not to be treated this way.

DR. MOORE: I would agree that certainly mycotic aneurysms, presumably, there is an underlying bacterial etiology and should be excluded.

On the other hand, I would like to have the option of treating an inflammatory aneurysm with this device. It is going to make the procedure much easier than an open repair.

DR. ROBERTS: Of course, since you didn't study these patients, we don't really know whether that is the right thing to do. At least we ought to have a warning that we don't know about it.

DR. ADELS: Absolutely.

DR. ROBERTS: The other thing that I did want to bring up, one is this business of heparin. I would just suggest that somebody look at that. I looked again after you said it was there, and I can't find it. Maybe it is there. It needs to be clear.

The other question was, you said you weren't treating these patients with anticoagulation. What about

anti-platelet agents, aspirin, other kinds of anti-platelet agents. Were they being treated that way?

DR. ADELS: There is no recommendation for that, no, and there was no requirement for that in the protocol. I am sure some of these patients were being treated for other conditions, because a lot of them had cardiovascular disease, but not specifically for this device.

DR. CURTIS: Finally, I would like to follow up just a little bit on two issues. One was, in terms of the renal insufficiency, do you have an amount of contrast that was given per patient?

Do you have those numbers, so that you know that patients perhaps that had renal insufficiency did, in fact, get a large amount of contrast? Do you know how much contrast was given?

Certainly it is in the bifurcated group that seems to have most of the problem, which obviously is a more complicated deployment procedure, presumably got more contrast.

Do you have any idea of how much contrast these patients got?

DR. ADELS: No. We could get that data, but I don't think there is a direct correlation between the amount of contrast and renal insufficiency.

Again, I think the main correlation is between

pre-operative renal insufficiency and post-operative.

DR. CURTIS: Granted that, but then the question is, in terms of adding the insult of contrast on top of that, whether or not that should be evaluated.

Finally, one last thing, I would like to follow up a little bit on what Mike Pentecost said. I think it is important, particularly when we are talking about the need for good imaging modalities and being able to see what you are doing, the question of radiation exposure to these patients, if you have any idea what the dose of radiation these patients got was, the amount of radiation exposure at least in terms of time -- you may not have a dose, per se.

Also, did anybody evaluate these patients looking for radiation changes. Were there any radiation burns, were there any other kinds of radiation.

That would tie in a little bit to what the radiation times and exposures were.

DR. KATZEN: In terms of radiation injuries, I don't believe that there were any noted, and no physical changes of radiation exposure.

DR. CURTIS: Was it looked for?

DR. KATZEN: Only to the extent that they all have physical examinations periodically. I don't know that there was a specific line item on the CRF for that.

I don't know about the actual fluoroscopy time.

As I mentioned, when Dr. Pentecost asked earlier, that data probably could be presented to the panel, but I don't think we have it available.

DR. CURTIS: Any other member of the panel have any questions or comments they want to make, because the next step will be getting into the questions.

DR. PERLER: I just want to make one comment as a follow up to Dr. Sethi, and no disrespect to my statistical colleagues, and certainly acknowledging the scientific purity of a randomized, prospective trial, I personally don't fault the sponsor for not conducting a randomized prospective trial, with the exception of ANCURE versus the predecessor.

I think I can understand the difficulty in doing a randomized prospective trial with this technology. Frankly, just speaking for myself, I don't put that much weight on the conventional control surgical group, and I am not that concerned about whether they were perfectly or not perfectly matched.

I think this is a technology, a device, that has to be judged on its own merits. We know the outcomes of conventional surgical repair of abdominal aortic aneurysmal disease.

This is a device, I think, that should stand on its own merits. It has its own risks and potential long-

term considerations and concerns. That is an issue to me.

My major question, really, is probably for the FDA, in terms of legally, what sort of control does the agency have in terms of access of practitioners to the technology, once approved, and requirements for follow up.

I have seen so many studies over the years that have come before this panel where X percentage of patients is supposed to come back for routine follow up, and the number is always much, much lower.

The typical answer is, when patients are doing well, they don't want to come back and so forth.

What power does the FDA have to require routine imaging and, even considering the difference in imaging results at these excellent centers when compared to an independent core lab, is it your plan to have these follow up studies looked at, at least for a few years, in a central, objective laboratory, understanding that the people looking at these images, perhaps, are less likely to be as sensitive in looking for leaks and some of the other complications.

DR. ADELS: I don't think it would be practical for us, in general distribution, to have every patient who is treated with this device have their film sent to a core laboratory.

I think it would be logistically almost impossible

for us to control that, although we can continue to have, if the FDA feels it is necessary, core laboratory evaluation of the patient data set that we have in the trial today.

Again, I think that it is important to note that when there was an increase in aneurysm size or anything substantial for the patient, that the investigators were very able to notice that before the core lab did, and act appropriately.

I also think it is important to realize that, while I think we are all jumping to the conclusion that the core lab is always right, the possibility exists, certainly, that the core lab is over-reading in some cases.

We will be training physicians, as part of our training program, about how to evaluate these follow-up procedures, and training them in the same techniques that the core lab used.

Again, the core lab was very conservative. If they saw anything even on an ultrasound that was of very good quality that they thought might be a leak, they reported it as such, and we included it as such.

DR. CURTIS: Did you want to make any comments about post-market approval and surveillance and what the FDA could do about what Dr. Perler was talking about?

DR. SAPIRSTEIN: These devices will be subject to tracking. Certainly the new regulations of FDAMA requires

that a reporting of adverse events must be made by all users of devices, not just the sponsor.

The end user, even the institution which purchases the device must report any adverse events. So, we have that.

Unfortunately, with MDR reporting, most of the reports come from the sponsor and less than 10 percent come from the users or operators.

As far as post-market surveillance, there are -- the Office of Science and Biometrics is trying to develop a more response method of following up these patients.

It is very difficult if patients do not return for follow up. But after all, even the standard of care now days for surgical treatment of aneurysms require routine follow up for the patient on an annual basis. I assume this will be maintained with this technique.

DR. HARTZ: Dr. Moore just mentioned that he would like to use this device in a patient with an inflammatory aneurysm.

In my mind, that would more likely be a patient who is less than 50 years old. On the indications, there is a suggestion not to use this device in a patient less than 50.

Indeed, those will be the patients who will need multiple interventions throughout their life. I am

wondering why that inclusion of less than 50 was place there.

DR. CURTIS: That was a suggestion by FDA. It is not a suggestion by the sponsor.

DR. STUHLMULLER: If I can make one comment, the law makes a distinction between marketing a device based on its intended use, and that the FDA does not regulate the practice of medicine.

In response to Dr. Perler's question earlier, the FDA cannot restrict the use of a device for off label use. What the panel's job is today here to do is determine whether the device is safe and effective based on its intended use.

If a physician, in the routine practice of medicine, decides to use it off label, that is a medical decision in his judgement.

DR. PERLER: I guess my concern is that we can only make a judgement about safety and efficacy based upon a one-year follow up, for the most part.

Following up on Dr. Mannick's presentation with respect to a Lifeline Foundation registry, it is not clear to me how that registry is going to be maintained if there are not any sort of codified restrictions or directions in terms of getting that data, to see how these patients are doing long term.

I realize that we can't regulate who puts them in or who is putting them in, but I guess my question is, is there any way legally to require that patients who have had these things put in have that data -- or at least the fact that they have had one of these devices put in be captured and registered someplace.

DR. STUHLMULLER: If the panel, for example, were to make a recommendation of approvable with conditions, one of your conditions would be to require that the study cohort be followed for an additional period of time, and you can have the option to specify that time, and what you would like evaluated at a given point in time.

DR. CURTIS: As far as follow up, the labeling does recommend that the patients be followed annually and that patients with perigraft flow be followed every six months.

So, there is a strong recommendation in the labeling in terms of required follow up. I don't know that either the agency or the sponsor can completely enforce that. It is up to the patient and their individual physician.

DR. SETHI: One question here. On your page 21, there is about 16 percent incidence of arterial trauma. What is the definition of that?

DR. MOORE: I guess I can give you some examples.

For example, if one is accessing the femoral artery and, during the course of passing the sheath or the device, the femoral artery becomes separately, ordinarily one makes an arteriotomy and just may complete the arteriotomy and do an artery revision, so that the suture repair of that would be considered arterial trauma.

DR. CURTIS: We will break now. We will reconvene at 1:00 o'clock.

DR. STUHMULLER: As a procedural note for the panel members, I would like to remind them that there can be no discussion of the files during lunch.

DR. CURTIS: And there is a table set aside for us in the restaurant.

[Whereupon, at 11:58 a.m., the meeting was recessed, to reconvene at 1:00 p.m., that same day.]

**A F T E R N O O N   S E S S I O N** (1:01 p.m.)

DR. CURTIS: We are going to go on to the FDA questions for the panel. You might want to put the first one up if we can.

As we are getting started here, did anyone among the panel have anything else they wanted to ask the company? If they do, let's do it now, and if they don't, we can ask them to step back. Any other issues that you thought about.

If not, we would like to thank the company representatives and ask them to step back now.

Okay, we will go through the questions for the panel and there will be an opportunity for any other comments from the public, just before we have a vote on this.

The first question we have been asked to consider is, do the data presented permit assessment of the safety and effectiveness of this device.

Any member of the panel who wants to comment on this is free to. It is not whether it does or does not, it is whether we have the data to make an assessment of this. I will ask the lead reviewers to step in here.

DR. ROBERTS: My feeling is that yes, at least for the short-term results, but I think that, as has been expressed this morning, that there is considerable concern

regarding the perigraft leaking problem, and the long-term effect of the leakage on the size of the aneurysm and the potential for rupture over time.

DR. PERLER: I would concur with that, and also emphasize that there is really much less experience with this device in women.

DR. CURTIS: Okay, so, there seems to be a general consensus that we have enough data to be able to assess the device.

DR. DE WEESE: One other thing. I would like to actually see and review with the panel the requirements for people who are going to be doing the procedures. They say it is in the PMA. I have not seen it.

DR. CURTIS: All right, number two. Does the following indications for use statement adequately define an appropriate population for use based on the population presented.

It says, the ANCURE bifurcated system is indicated for the endovascular treatment of grade II infrarenal abdominal aorta aneurysms.

The ANCURE tube system is indicated for the endovascular treatment of grade I infrarenal abdominal aortic aneurysms.

This would be a good point for anybody to make any comments about indications, including types of aneurysms, if

we want to get into that.

DR. GILLIAM: That it has not been adequately studied in inflammatory aneurysms and mycotic aneurysms. So, the safety cannot be assessed in that group.

DR. CURTIS: Would we want to recommend that the indication be atherosclerotic abdominal aortic aneurysms, or is that too specific?

DR. HARTZ: Did we come to a consensus regarding size? That ties in with atherosclerosis here.

DR. CURTIS: That is right. We are trying to reach a consensus right now.

DR. SETHI: Under contraindications, under warnings. It is pretty broad indications that look pretty good to me.

DR. CURTIS: So, you would prefer to see the indications remain broad, but then have as a precaution the fact that it hasn't been studied in certain types of aneurysms.

DR. SETHI: That is what I would suggest that we do.

DR. CURTIS: So, leave then indications as stated but then have a precaution later on. I had been concerned before about the issue of size of the aneurysm. I was reassured by some of the comments made about that issue. At this point I don't see a need to put an exact size down

there. Does anyone feel strongly otherwise?

Then the panel in general feels comfortable with the indications as listed?

DR. SETHI: Yes.

DR. CRITTENDEN: You know, in the panel pack and in the labeling there is no definition what a grade II and grade I infrarenal aneurysms are.

I know that there is a paper with the definitions in it, but I just wonder whether or not that ought to be added, just for clarity.

DR. CURTIS: That is a good point. Okay, number three. Is the proposed contraindication section appropriate. Are there any other contraindications for the use of this device.

Do not use this device in patients with a sensitivity or allergy to the device materials, and they are listed there. Any other contraindications that you can think of?

DR. SETHI: One of the contraindications is symptomatic aneurysms. We don't have the data on that, and I think that is a different group of patients, patients with impending ruptures, rapidly growing aneurysms. Those are different patients and they should be excluded.

DR. CURTIS: Is that a contraindication or a warning or a precaution?

DR. SETHI: I think it is a contraindication.

DR. CRITTENDEN: I think for impending rupture or leaking I would agree, but for rapidly expanding, I am not sure.

DR. PERLER: I think one of the issues is, with a symptomatic patient, there might not be time to do a workup to assess whether this is the approach that can be taken.

DR. HARTZ: It would not hurt just to simply reiterate under contraindications, do not use this device in patients with suprarenal aneurysms or impending rupture.

DR. CRITTENDEN: Symptomatic.

DR. HARTZ: Symptomatic and impending, I don't think, are the same thing, but do not use this device in patients with impending or ruptured aneurysms.

DR. SETHI: And precaution should be used in symptomatic aneurysms because we don't have the data on those.

DR. CURTIS: Question number four gets into information to include in the labeling, and asking if we have suggestions regarding wording and/or placement and there are a number of different issues there. Let's go with the first two.

The incidence and types of endoleaks associated with the system is the first topic. The question is whether or not it would be meaningful and useful to include

information about those endoleaks.

DR. PERLER: I think the findings in the study should be explicitly stated in the labeling, as well as a statement to the effect that the long-term risk of that has not been established one way or the other.

DR. CURTIS: I clearly think that information about endoleaks ought to be included. You have got to explain that to people and say how many, and what we know so far, and what we don't know yet.

DR. PERLER: And that this mandates a requirement for long-term follow up. We can sort of decide later what that constitutes ideally.

DR. CURTIS: Okay, due to the lack of long-term data, the device should not be used in healthy young patients under the age of 50.

DR. PERLER: I think I would take that out. I think we ought not to be stating specific ages. Fifty, to me, is almost childhood. That is for the eyes of the practitioner, and it is physiologic age and not chronologic, obviously, but I am not sure that statement needs to stay in there.

DR. CURTIS: Due to the lack of long-term data, we don't know what is going to happen in all kinds of patient populations.

DR. SIMMONS: Did you want to take the age out,

and healthy young patients?

DR. HARTZ: No, just take the whole thing out.

DR. CURTIS: Take that whole section out.

DR. HARTZ: If somebody has got an aneurysm and they are young, they are not healthy.

DR. GILLIAM: I move we scratch that sentence.

DR. CURTIS: Take that sentence out all together. Let me ask, we had brought up the issue about women before, that there have not been that many women who have been studied.

There has got to be something in here about that, along the lines of, you know, that the number of women studied was small or that they have a higher risk of needing an open repair. There has got to be some information about that in the labeling.

The third part of this question is, the acute symptoms that may be expected if rupture occurs.

I personally think that if you are a vascular surgeon, you know what that is and you don't need it listed in the labeling for a product like this.

DR. ROBERTS: I think that might come in, not so much in terms of the warnings, but in terms of whether or not there is some type of patient education material that should be developed, that patients should have, so that they are the ones that ought to realize what the warning signs

and symptoms are, so that they can get in to get medical attention.

DR. CURTIS: That is a good point, but in terms of physician education, I don't think it is necessary.

Okay, a warning regarding the use of patients with impending rupture. There seemed to be some consensus to make that more of a contraindication.

There has got to be some information in there saying that it has not been studied, and we don't know what the results would be in that sort of situation.

DR. SETHI: It should be taken out and put in the contraindication.

DR. PERLER: I am not sure it should be an absolute contraindication. I can see a patient being electively scheduled for repair, with all the imaging done, who may then become symptomatic a day or two prior to the procedure, but be absolutely stable hemodynamically.

I am not sure that that discomfort should be a contraindication to proceeding as planned, acknowledging that there may be a conversion to an open procedure.

I think certainly a statement with respect to concerns about impending rupture, but I don't think impending rupture, or symptoms, should be an absolute contraindication in a properly selected patient. I think it ought to be in the hands of the practitioner.

DR. CURTIS: I agree with that approach. Tony, did you want to say something?

DR. SIMMONS: Did you decide you were going to put something in the contraindications about -- what did you decide before, I guess is what I am asking.

DR. CURTIS: There was some talk about making impending rupture be a contraindication. I tend to think that is a little bit strong, too.

I agree with Dr. Perler, that that wouldn't be your ideal patient, but that there could be a situation in which that could come up.

In that case, there should be more of a warning or a precaution, that you have to have the imaging studies done, and that usually in that sort of a situation you won't have the time to do it, and that there have been no patients studied under those circumstances.

If the physician knows all of those things and still says, well, this is the way I want to go because I have got some good reasons, there is nothing that absolutely says you can't do it that way.

It is just the likelihood of success, if you don't have the imaging and all that, it is going to be very hard to get that to be as good of a result, I would think.

DR. SETHI: There is no data. How can we say all these things we are saying when there is no data. If this

is a patient with a pending rupture and if it ruptures, the possibility of death is very high.

I think this is a device which we don't have the long-term results. Even suggesting that it be used in such a high risk patient, I think we should be careful.

DR. GILLIAM: I think that, you know, as a warning it should exist, but I wouldn't put it as a contraindication, because we don't know.

For all we know, this procedure may be better than doing an open procedure for someone with an acute rupture impending. We don't know that it is not better.

DR. CRITTENDEN: We don't have data to support that.

DR. GILLIAM: Either way.

DR. CRITTENDEN: The labeling is going to be inaccurate in that regard, if we have that on the label. I would like to hear from the FDA, to hear what they have to say about it.

I wouldn't have a problem with this being an off-label use, that if you looked at the use of this nationwide a year from now, that a lot of people are doing it because they found what you are saying. I don't know if we have enough data to say it ought to be labeled this way, that we approve of it.

DR. GILLIAM: What I mean is not to label that you

can use it that way, but label it as a warning that it has not been studied in patients with impending rupture and there is no data to support its use, but not to list it as a contraindication, which would say that you have data that suggests somehow that using it would be the wrong thing to do.

DR. CURTIS: A contraindication means in all cases you are not going to do it, like giving anticoagulations to somebody who has got active intracerebral bleeding. You do not do that ever. That is what a contraindication is.

DR. GILLIAM: We don't know that this is necessarily a bad thing. We don't have the data for it. So, I would like to say it as a warning, that there is no data for this population.

DR. CURTIS: We certainly don't say to put it in the indications either.

DR. PERLER: I have a bit of a problem even with the terminology, impending rupture. I am not sure what that means.

I would prefer to think of asymptomatic aneurysms, symptomatic aneurysms and leaking aneurysms. I mean, an aneurysm that goes from four to six to eight centimeters over two months is an impending rupture in my mind, but that patient may be completely asymptomatic.

I am just not sure what is meant by impending

rupture, and if you don't know what that means, I don't know how you consider it a contraindication to the use.

DR. ROBERTS: Maybe what we could do is say, if the patient cannot undergo the appropriate imaging studies - - which would mean that presumably they are in a position where you really think they are going to rupture and you want to get them to the OR and get something done before they do something, if you can't do the appropriate imaging studies, maybe that should be a contraindication, and that would take care of a lot of it.

It would sort of answer your question, Bruce, as you have somebody who has actually been imaged, is all ready to go and now starts having some symptoms, but you might want to go ahead and do it, but you have already got the images.

DR. CURTIS: I think those are the sorts of issues that can be worked out, too. Maybe if symptomatic is a better word than impending rupture, that would be the way to go and the FDA can hash out some of those details.

Any other comments on that? The next subject there was the non-specific relationship between endoleaks, aneurysm growth and rupture, should information be included on that.

DR. PERLER: I think this study showed that a perigraft leak, or at least the interpretation of the data,

in terms of how the patients were cared for, is that of perigraft leak and aneurysm expansion, is a very worrisome finding, which probably should stimulate some intervention. I think that clearly should be stated with some wording.

Secondly, again, as I said earlier, I think the fact that persistent aneurysm size, no change in aneurysm size with or without a perigraft leak is something that is unknown, and that should be also so stated, that really, the natural history, when aneurysms don't shrink, that we simply don't know what that means.

There may be leaks that are not being picked up, or they may be just intermittent leaks that just weren't there. I think they are two issues that ought to be explicitly stated.

DR. CURTIS: Okay, then the last subject, a warning regarding the use in patients for whom antiplatelet, anticoagulation therapy or thrombolytic drugs are contraindicated.

From what I heard, all we need is some heparin during the procedure. I don't know that that is a real issue that needs to be stated, since there is no long-term need for anticoagulation. That seems to be unnecessary.

Number five, what follow-up imaging schedule regarding observations for leaks and aneurysm growth should be recommended, if any, in the labeling.

DR. PENTECOST: I think there has to be some schedule and also some codification of the types of examination.

I don't know what the core lab saw and what they didn't see and what was useful in finding all these endoleaks and what wasn't, but someone needs to investigate that, and that needs to be spelled out clearly by the FDA.

I think the fact that -- contrary to what the sponsor, I think, thinks, I don't think there were probably any false positive endoleaks.

I think if they saw what they thought was a leak on ultrasound or CT, that is a leak. So, I think that we need to look in a very discerning way at that, and use our most sensitive imaging studies to measure that.

DR. CRITTENDEN: Are we satisfied enough that we know the best way to specify that?

DR. PENTECOST: I am not.

DR. CRITTENDEN: That is the problem. I don't know if we have to state specifically what it is. It sounded attractive when you were giving your presentation about doing spiral CTs and all that, but I really don't know.

DR. PENTECOST: I don't know what the core lab saw. Maybe they saw leaks on small doses of contrast and delayed scans. I don't know that. I would just be

guessing.

DR. CURTIS: How often should patients be scanned or imaged in some way?

DR. PENTECOST: I don't think we know, unless we see the data, the raw data.

DR. CRITTENDEN: Can we ask the FDA to talk to the core lab or do we need to be more specific? The core lab probably knows more than anybody else what the best imaging modalities are and their frequency.

It was briefly stated that six months for perigraft leaks and then to follow up the aneurysms a yearly study.

DR. CURTIS: I thought that sounded reasonable. Someone where there is a potential problem, such as an endoleak, and we don't know what it is going to mean long term, then every six months would be appropriate.

Then people who don't have that, probably, can be imaged once a year. That is a relatively simple recommendation to make.

In terms of the imaging study, I wouldn't know which is the best. It sounds like ultrasound is not the ideal, obviously, but I would be happy to defer that.

DR. ROBERTS: I guess one of the things -- again, we really need to look probably at the raw data, in terms of particularly whether or not there were not leaks, and then

later on there were leaks.

I think that one of the things that would be very important is if, in fact, we can show that an aneurysm is treated, there is no leak, it is stable or it gets smaller and it stays that way for a year or so, then maybe it is not worth studying these patients over and over and over again.

On the other hand, perhaps with the patients who have a scan where the aneurysm doesn't get smaller, then maybe they need to be in a different type of protocol for scanning.

Those that are obviously getting bigger or that there is an endoleak on, then probably they would have to be followed still more closely.

I would think certainly the ones that are increasing in size, that probably every six months it is something that ought to be done.

I think what we really need to get a better handle on because, honestly, I am not sure we heard it today, is exactly how many patients do we have that supposedly we are fine, but then six months later or a year later, started having a leak. If that is happening, then we have got to scan all the patients.

DR. PERLER: I think we asked that question and we didn't get numbers, but I think it was stated that there were patients who, at one follow up point, had no leak and

then subsequently did.

Secondly, there was at least one case that I recall, in reviewing this, that we didn't talk about this morning, where there was device migration. I think it was attributed to shrinkage of the aneurysm.

So, indeed, if shrinkage of the aneurysm is a potential cause of graft migration, and if one of the outcomes is aneurysm shrinkage, I think for both of those reasons I would have a problem stratifying a follow up protocol.

I think there ought to be a standard follow up imaging protocol, irrespective of what the patient looks like today or a year from now.

DR. DE WEESE: I would recommend that we say they should have imaging at least yearly, and at least each six months if they have endoleaks, enlargement or other things you may want to add.

This way, leave it up to the clinician. If he wants to get them every three months, once it has expanded a lot in one month, then he ought to have the choice. Why don't we say at least yearly and at least six months.

DR. GILLIAM: I think we may find out data from a follow up that that may not be necessary. I think I would caution to say that we require mandatory imaging at any interval, because at this point we don't have the data to

suggest that that would be beneficial or even recommended, and once the long-term data becomes available -- we may want to require that they do certain things with the study cohort to later provide that data.

It may be at this point, to be able to say that these people should be evaluated, maybe, and leave it as an open ended question.

I am not sure I know enough now to say, to the company or be able to write in a recommendation on the label, they should be followed yearly when, in fact, they may require to be followed every six months or every three months, even, to be safe. On the other hand, it may not be required to be followed at all.

DR. PENTECOST: Early on, it would be better to have too much data and ratchet back, rather than trying to start this later.

DR. CURTIS: The labeling can always be changed later on. We may find out that you do yearly imaging and after the first two years if you haven't seen anything, years three, four and five don't give us any more information.

Once we know that, then you can change the recommended follow up schedule to go along with that. Any other comments about the imaging schedule?

DR. SIMMONS: You have to have two groups, one,

the group that nothing is going on and you haven't identified everything. In the protocol, they study those people every six months. But if they discovered a leak, they studied them every three months.

I guess that makes me uncomfortable that we don't even know enough about this device to feel comfortable making recommendations about follow up. That makes me nervous.

I would say we should err on the side of suggesting to the clinician that we don't know, and that if patients get one of these devices, every six months, and every three months if there is a problem and the thing is leaking.

I think we should at least make some recommendation and not defer that to let somebody else do it later on.

DR. CURTIS: I agree. What I am hearing is three to six months if there is a problem identified or a potential problem, and six months to a year if we just think everything is going great.

DR. SETHI: A lot of study has been done in these patients. I think every six months, if there is a leak or an expansion of the aneurysm more than five millimeter, and if there is no leak, then maybe once a year, and then in three or four years we will know more about it and we will see if

we have to do it.

DR. CURTIS: Most of the panel members seem to going along the six months to one year kind of framework, as a more or less consensus.

DR. PERLER: The radiologists on the panel know more about this than me. Clearly, ultrasound and CT probably are more sensitive or specific for various things. It would seem to me not unreasonable to expect an ultrasound every six months and a CT once a year.

So, at least once a year you are getting both tests, and every six months you are getting ultrasound to look at aneurysm size, very non-invasive, relatively inexpensive. I just throw that out for discussion.

DR. PENTECOST: We are just guessing though.

DR. PERLER: We are guessing.

DR. PENTECOST: If the core labs have real data about this, someone should look at that, and make recommendations based on what we have already seen in these hundreds of patients, because we are just guessing.

Ultrasound in a lot of these patients may not be feasible, because of body habits and other things like that. Again, I think we must have the data and the core lab results, and we just need to look at it.

DR. CURTIS: If the application is approvable with conditions, that could be one of the conditions, is to look

at that core lab information and make a determination about that. Do we have any other suggestions for the labeling?

DR. SIMMONS: You were going to make a comment about the women?

DR. CURTIS: Yes.

DR. SIMMONS: Do you want to make a statement in there or let FDA make it?

DR. CURTIS: I think I already made that point, that there has to be a statement in there, that there have been very few women studied and that the incidence of having to go to an open repair was higher. I think that is important information for a physician to have, and important information for a patient to know, so they don't have an unrealistic expectation about what their chances are of getting through with just the interventional technique alone if they are women.

Any issues about anatomy or tortuosity that ought to be brought up? I know in some cases it made it more difficult, but I can't personally think of some way to put that, that would make sense.

DR. SETHI: I don't know how to put it in.

DR. CURTIS: Right, I don't either.

DR. PENTECOST: I think it has to be addressed with the training, I think.

DR. ROBERTS: The tortuosity? It may be something

in a warning, just like small arteries need to be evaluated so that you know you are going to have problems. The same may be true with tortuosity.

The one issue that I have is that, you know, I think that it would be a good idea for there to be something in terms of what would be an appropriate pre-evaluation for these patients, so that people have an idea of what they ought to be doing to look at these patients ahead of time.

DR. CURTIS: I agree. I had raised the issue before about patients who have a contraindication to major vascular surgery.

If you get in there and you are doing this procedure and, for some reason, it gets stuck or whatever, you have bleeding, if that patient can't be converted to an open surgical procedure, that is a very serious issue.

There may be some situations where you go into that with your eyes open and you say, I know this patient is high risk and I really can't, but it is the only thing I could do.

Perhaps some sort of a precaution or warning in there to say that patients who are not candidates for surgery, you ought to think very carefully about whether you want to use this procedure.

DR. SETHI: I think that could be the warning. Some of these patients are old, and you know, doing a PTC in

a patient who has no other alternative, you just do it, because they are going to die otherwise. It is okay to have a warning on that.

DR. CURTIS: Any other labeling issues? Okay, let's go to number seven. Are there any other issues of safety or effectiveness not adequately covered in the labeling, which need to be addressed in further investigations before or after device approval.

We have mentioned the long-term follow up and we know that clearly. I think that is actually going to come up in number eight. Is there anything besides the long-term follow up issues?

Okay, let's go to number eight. The long-term safety and effectiveness of endovascular grafts has not been established. The FDA has identified the following long-term issues that could be addressed through a post-market study on the original cohort, identifying the risk factors associated with rupture, the risk factors associated with surgical conversion, clinical relevant device integrity issues, and adverse event rates associated with the device and/or procedure.

Then it mentions that the manufacturer is participating in the development of a registry intended to address these issues.

So, what we need to do now is discuss post-market

study for endovascular devices and the treatment of abdominal aortic aneurysms.

What kind of post-market study is indicated here, that we want to recommend, and the sorts of things that should be looked at in a post-market study.

DR. CRITTENDEN: It seems to me that there are two issues. One is the study group, the original cohort, tracking them down, and then the other is the registry issue.

Looking at the post-marketing or study cohort, another bullet point I would like to add would be to look at the adjunctive endovascular stents or embolization, in terms of how it affects the natural history after the graft is placed, to see whether or not more stents or less stents or whatever affects these applications.

In terms of the registry, that is going to be difficult to do because you can't legislate it without full participation, and I am not sure how valid the data is going to be. We ought to make it as a recommendation. It is nice to have it, whatever it is going to mean.

DR. CURTIS: Recommendation for registry follow up of the original cohort of whoever gets this put in for a period of time.

DR. CRITTENDEN: Are you going to count the number of adjunctive endovascular interventions, so if they get

embolized pre or post placement, I would like to track that. If they get stents on the limbs, that ought to be tracked. It probably is, but it is not stated here on these bullet points, so I just wanted to add that.

DR. CURTIS: Do we agree in general with the bullet points that were listed, about this being included in the post-market study.

Risk factors associated with rupture, yes, you would want to know what those are. So far, the risk looks like it is low, but whatever the finite risk is, what factors are associated with that would be important.

Risk factors associated with surgical conversion, of course. We have already identified female gender as one of them, knowing what the risk of a patient is.

DR. PERLER: Risk factors associated with rupture is important. I don't know if you are going to be able to identify all the ruptures if you have sort of a voluntary registry.

A lot of old patients drop dead outside the hospital and they are written off cardiac events, and patients with ruptured aneurysms who are written off as cardiac deaths.

Unless there is some formalized post-marketing surveillance of all the patients who had these put in, or study patients, or patients who in practice have them put

in, I am not even sure you are going to be able to identify the true late rupture rate among patients who have had this device used to treat their aneurysm. If they drop dead at 85 outside --

DR. GILLIAM: You could always have a select group of people followed, the original cohort but in addition, if the statisticians determine what kind of numbers would be necessary to look at this later on.

I think it would be a pipe dream to believe that we could have a registry to get every single implant tracked and followed. I just don't see that happening.

I don't think there is any way in the world, if this was approved for general use, that most of the physician implanters would ever get all their people put on the registry, so they would be followed as intensely as it would be to get the data that we need.

I think your point is well taken, that if someone just drops dead, the death certificate is going to be signed and they are going to be gone and you are not going to have any clue as to what the status of the graft was.

I think that if we are going to do a post-market study, we should get help from the FDA and statisticians to figure out how many people we need to follow up long term, and intensively look at that group to make recommendations, but certainly include the original cohort.

DR. CURTIS: Would it be sufficient to study the original cohort over a longer follow up period, with the imaging studies and clinical follow up as we suggested.

DR. GILLIAM: I don't know. I would defer to the statisticians.

DR. CURTIS: We have a statistician here.

DR. BAILEY: Obviously, more is better. I think that requires a little bit more thought.

DR. CURTIS: In terms of calculating how many patients, that sort of thing; is that what you are talking about?

DR. BAILEY: You need to know what confidence you want to have for the rupture rate. I would think if you had regular follow up, and then someone drops dead, at least you have the data for what was going on in the meantime. At least the death rate we have.

DR. CURTIS: So, what we would be looking for is incidence of late rupture, incidence of aneurysm expansion over time, need for stents or other interventions, thrombosis of the grafts, those sorts of things, all of which so far, in short term follow up, appear to be relatively infrequent.

So, if that holds true, you need a fairly large number of patients to pick up that sort of thing. You know, we can't sit here and make calculations off the tops of our

heads as to how many patients would be necessary.

You can kind of define what kinds of rates would be -- sometimes one way to handle it would be to think of the sorts of rates that would be unacceptable.

I am not so sure what the answers to some of those things are. For example, let's say that 20 percent of the patients end up needing an open surgical repair five years later. Is that so bad.

They have all avoided having an open surgical procedure day one, and you have postponed a major operation for later on.

Just the fact that they had to have it, I don't think, is necessarily so bad. What you are trying to avoid is death related to the aneurysm, most importantly, and then major morbidity related to that.

DR. BAILEY: I think the right answer is that it is the maximum that you can afford to study. You have to ask what kind of follow up because there is different costs for different levels of follow up. What does it cost to just register the patient in a cohort.

DR. CURTIS: Not very much, but on the other hand, how much information do you get out of it.

DR. BAILEY: Then you can see whether they are dead or alive and then it goes up from there.

DR. STUHLMULLER: As a point of clarification, a

couple of things. First of all, the term post-market, from a regulatory point of view, implies that there is already a device approved.

You should not take this question as an effort by the FDA to lead the panel into a decision.

Second of all, relative to this device, if you have specific issues that you would like to see in terms of clinical data, that could potentially be done as a condition of approval, if you were to make a recommendation of approvable with conditions.

So, it is a very important distinction in terms of post-market versus a condition of approval, and post-market would include, for example, as you heard earlier, there is a group that wants to do a registry study, and that is separate from -- that would be separate from FDA.

DR. PENTECOST: It is not clear to me that we want to have more post-market study and analysis, and we are going to do this through the registry. I think those are disconnected.

DR. CRITTENDEN: Those are two separate issues, I think. One is what Lifeline wants to do over and above what we deem as being a condition or ask the FDA to do in terms of post-marketing study.

I think they are two separate issues. Now, there may be cross over in terms of logging the registry.

DR. PENTECOST: I wouldn't use the registry as a substitute for your own post-market surveillance of these. That is what I am trying to say.

DR. STUHLMULLER: FDA has post-market mechanisms in place which are separate from the conditions of approval, which are separate from what another organization would do, as far as a registry goes.

DR. SIMMONS: Conditions of approval, is that like we can only make conditions of approval based on the cohort that has already been established, or can you have new patients entered into it as far as a condition of approval.

DR. STUHLMULLER: It can be both. It has been done as both.

DR. CURTIS: I would say, a condition for approval sounds to me like, well, you have got to fulfill these conditions before you can get approval; is that not true?

DR. STUHLMULLER: Yes, there is an agreement that they are going to -- if you have a condition of approval that says you think the original study cohort needs to continue to be followed, and you need to collect X amount of information at these time points, then that would be in the letter that would go out, and then the company is obligated to do that as a condition of approval.

DR. CURTIS: But they would have to complete that follow up before they got approval.

DR. STUHLMULLER: No, that is a condition of approval and it would be done after the device -- as one of the conditions to legally market the device.

DR. CURTIS: But they could get the approval to market the device now, as long as they continued to collect that follow up data.

DR. STUHLMULLER: That is identified as a condition of the approval, yes, that would be right.

DR. SETHI: But you can't put in new patients, can you? Are you saying you are going to put new patients in the post-market approval?

DR. STUHLMULLER: No, as a condition of approval, we have at times requested that the sponsor collect information on new patients. That has been done. That information is probably available in terms of letters.

DR. CURTIS: I guess in some respects it is accomplishing the same thing. You can market it now, but you have got to get us this data.

The difference between the two ways of saying it, it sounds like to me, is that the post-market study means it is marketed, it is approved, go ahead and do it and get us this data later on.

The condition of approval would mean that if that data was not coming back, the approval could be withdrawn.

DR. STUHLMULLER: Theoretically, that is correct.

DR. CURTIS: Practically speaking?

DR. STUHMULLER: I am not prepared to answer that question.

DR. SAPIRSTEIN: If you approve something here, you have approved it for the data with which you have been provided, and any additional study that is required is for additional labeling changes.

A surveillance registry is something entirely different, something like what Lifeline wants to carry out. This is an entirely new technology. It is completely new, and we have data up to one year, and we don't know anything further about it. A registry seems like an appropriate way to follow this up.

DR. CURTIS: I think the registry sounds like it is something that is going to go ahead, and that is very important.

I think in addition, what we want to recommend is that hopefully for much, if not all, of the original cohort, that there be follow-up imaging studies and follow up on these patients, to see what the longer-term outcome is, not just up to one year out.

DR. GILLIAM: I think that is important, but there are certain populations where we really do not have enough of an original cohort, that we may want the sponsor to really focus on some post-market data; specifically women.

It may very well be that there is a requirement for additional people, not just in a registry, but to evaluate them in a more intensive manner than just following them, and maybe ultimately acquiring the data on other types of aneurysms, inflammatory or mycotic or whatever.

Those are the sorts of things that I think you could get from a post-market study that we don't have now. It may not be the type of information that we would, say, today disapprove the device, but we could approve the device with a condition that the company starts to investigate its use in these populations.

DR. PENTECOST: From my understanding earlier, are we supposed to mandate a Lifeline registry?

DR. CURTIS: I don't think we can.

DR. PENTECOST: We are not privy to the information from it, so how is this relevant to what we are talking about.

DR. GILLIAM: We don't have to maintain that it be in Lifeline, but we can state that as a condition of approval, that the sponsor, with the FDA, acquire information, post-approval, post-market, not necessarily through that mechanism.

DR. PENTECOST: From any registry, any registry, another source?

DR. GILLIAM: Through mechanisms that the FDA has

already set up, or approves through the company.

DR. PERLER: In Dr. Whittemore's second proposal - - suggestion -- from the Vascular Society is that all procedures performed with the endovascular grafts should be entered into a national registry. I think certainly this panel can support and endorse that recommendation.

How it actually effectively is carried out I think is another issue, but I certainly have no problem with both of those proposals.

DR. CURTIS: I kind of see that maybe this is two separate issues. I think that certainly the panel can recommend or endorse the idea that there be a registry for endovascular grafting procedures. I think that is fine.

I think the issue with regard to this product is whether or not there should be post-marketing surveillance of a group.

My feeling is that patients that are already enrolled in a study are probably appropriate patients to do a sort of longer-term cohort study on.

You already have those patients that are already involved in the study. I don't disagree that, maybe if it is possible to get more information on women, that would be helpful and certainly might allow labeling changes that maybe we want to strongly say that, at this time, this may not be an appropriate device for women.

So, if the company wants it to be used, or feels that they want it marketed for women, then they need to get some more information on that, before we feel as comfortable about having it placed in women.

I would also suggest that there might be some other aspects that, in terms of a condition, would be important.

I feel very strongly that there should be some kind of patient brochure that clearly outlines in wording that, hopefully, most patients can understand, about what we know and what we don't know about this.

The patients should realize that they need to have imaging studies at least on a yearly basis, and maybe more depending on what it looks like, and that there is the possibility of leakage and that we don't really know what that means in terms of rupture.

So, the patients not only hear it from their physician, but actually have a piece of paper in front of them that helps them to understand it, and that they can refer to at home and hopefully educate themselves about it.

The other thing that I would suggest -- and I don't know whether this needs to be a condition or not -- but I think it may be very important that there be more of a physician education material as well, so that we are not dependent on physicians reading the label which, I hate to

say, we probably can't count on all that much.

At least there is some kind of education that is provided with the device, so that the physician has that as well.

Perhaps, like I say, some of the things that might be put into it is, how to get out of problems if you are having problems.

That might be another appropriate thing to do. I don't know whether that falls exactly into this thing with conditions, but if it does, that would be one of my recommendations.

DR. STUHELMULLER: I think in terms of keeping the discussion focused on the current PMA, the term "post-market" implies that there is a device already approved.

I think the issue you should stay focused on is, is there additional information that you want from the study cohort, and what do you think is reasonable information that you would ask the sponsor to acquire, and not depend on any other outside organization to do that.

DR. CURTIS: I think we will want to strongly require appropriate training for physicians and strongly endorse the idea of the registry, and that that ought to be carried out. There is absolutely no reason not to.

In terms of conditions for approval, you are right; it has to do with the device that we are talking

about.

DR. SIMMONS: I would just say that this is a brand-new device. We don't even feel comfortable about making recommendations for follow up for the first year after this thing is approved.

That certainly is a condition for approval, not just a recommendation or post-marketing surveillance, which is virtually voluntary, but at least as a condition of approval, that they should be required to enroll a certain number of women to be followed for three to five years, just to show that this thing really is safe in women.

Maybe it doesn't have to be a large number, 100 women or 150 women to be enrolled and followed, at least as well as the current cohort, and then continued follow up of the current cohort for the first five years with imaging done at least every six months for the next two to three years.

That would be at least a minimum, I would think, that would be required as a condition for approval.

DR. PERLER: Will those imaging studies be assessed at a core lab? The reason I ask is that I suspect that a lot of patients treated in this trial probably came to these various centers from far away specifically for this technology.

It may be very difficult to get these patients

back to the investigational sites for follow up, which might require they are going to be studied in their community hospitals.

We have already seen there is a discrepancy in reading the imaging studies at the investigational sites versus a central lab.

I suspect there may be an even greater discrepancy if we rely on a whole host of other uncontrolled centers.

I think we need to think about in terms of where these imaging studies are going to be assessed in that small cohort.

DR. SETHI: Another problem is, if you dye in these patients, these older patients, you are really putting them into unnecessary risk, at least some of these patients.

DR. SIMMONS: We are going to recommend follow up on these patients whether they are in the cohort and being studied -- I mean, you are going to recommend follow up if you just turn them loose and let their doctors follow them up.

DR. SETHI: But every six months --

DR. SIMMONS: You are talking about every six months anyway, at least for the first year. I wouldn't vote for anything less than that. I mean, what would you recommend?

You brought up the question. What do you

recommend that we do?

DR. PERLER: I agree with your suggestions. I think that the images, the CTs or the ultrasounds or whatever is decided is the most valuable should be assessed in a central objective core laboratory facility, to get that data. I have no problem with what you have recommended.

DR. CRITTENDEN: So, if I understand it correctly, then every patient in the study cohort, for the next five years, is going to get yearly or twice yearly studies. Then those are going to be forwarded to the core lab?

DR. PERLER: I would think at least yearly. I think that is not unreasonable. This is a new device.

DR. CRITTENDEN: I just want to make that clear, so that everybody knows what we are voting for, when it comes down to that.

DR. CURTIS: Well, we will have to make a specific recommendation. Any other comments before we close discussion?

All right, at this time I would like to ask if any member of the company would like to make any last minute statement.

DR. ADELS: We would just like to thank the panel for their deliberation, and we look forward to your decision.

DR. CURTIS: Anybody from the FDA want to make a

comment?

MS. MOYNAHAN: Just to clarify, that the reason we brought up the Lifeline registry was simply to let you know that there was this registry available, and that they were developing a protocol for following patients for long term, and that protocol is available for you to see if you were interested.

DR. CURTIS: And we actually need to have an open public hearing at this point, which would mean that if anybody in the audience, from the public wants to make a comment at this time, it is possible.

**AGENDA ITEM: Open Public Hearing.**

MS. COLE: My name is Patricia Cole. I am an interventional radiologist at Yale University, and I represent the Society for Cardiovascular and Interventional Radiology today.

Evaluation of the endovascular graft therapies has involved investigators from vascular surgery, interventional radiology, as well as cardiology.

We have heard from both panelists and presenters today about the concern and need for long-term follow up, and the Lifeline Foundation registry was mentioned as a mechanism for that type of follow up.

As a representative of the Professional Society of

Interventional Radiology, I would simply like to urge the panel and FDA and industry to support a multidisciplinary approach to long-term follow up, with all members of the endovascular graft professional arena participating fully and jointly, to optimize the evaluation of the long-term benefits of these new devices. Thank you.

DR. CURTIS: Anyone else?

**AGENDA ITEM: Committee Deliberations and Vote.**

DR. CURTIS: Okay, now we actually get to the point of needing to make a motion either for approval or disapproval. Dr. Stuhlmuller will read the possibilities here.

DR. STUHLMULLER: The panel recommendation options for premarket approval applications. The medical device amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the agency.

The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable available public information.

Safety is defined in the Act as reasonable assurance, based on valid scientific evidence, that the probable benefits to health, under the conditions of intended use, outweigh any probable risk.

Effectiveness is defined as reasonable assurance that, in a significant proportion of the population, the use of the device, for its intended uses and conditions of use, when labeled, will provide clinically significant results.

Your recommendation options for the vote are as follows:

1. Approval, if there are no conditions attached.
2. Approval with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, further analysis of existing data. Prior to voting, all the conditions should be discussed by the panel.
3. Not approval. The panel may recommend that the PMA is not approval if the data do not provide a reasonable assurance that the device is safe, or if a reasonable assurance has not been given that the device is effective, under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Following the voting, the chair will ask each panel member to make a brief statement outlining their

reasons for their vote.

DR. CURTIS: Dr. Roberts or Dr. Perler, do you want to make a motion?

DR. PERLER: I would move for approval with the conditions that we discussed and with the labeling issues that were enumerated, and I don't think I can repeat all of them.

DR. CURTIS: Why don't you give it a try.

DR. STUHMULLER: Actually, from a procedural point of view, you can do this in a stage. You can make a main motion and have that seconded, and then you can do a subsidiary motion, which is a motion to amend, and then you can add all your conditions.

Then make a motion and then second that and then vote on a composite motion.

DR. CURTIS: I think we have to have some recap of what the conditions are, so why don't you have your best shot at it.

DR. STUHMULLER: The motion is approvable with conditions, and we need a second on that.

DR. PERLER: So moved.

DR. ROBERTS: Second.

DR. STUHMULLER: What you need to do now is discuss the conditions, identify them, list them, have a list, and then introduce them as another motion, as another

amendment.

DR. PERLER: That the patients enrolled in this trial be followed for five years with annual imaging studies to be read at the core laboratory.

All patients who have this device implanted should have that implantation reported to the Lifeline registry.

That a cohort of -- did we decide -- of 100 women continue to be studied and reported to the FDA.

There were a number of labeling issues. Is that part of the condition?

DR. CURTIS: I don't think you have to worry about that. We made some recommendations for some minor changes in the labeling and that has been picked up.

DR. PERLER: That there be a patient education brochure outlining the risks, benefits and unknown issues in this technology.

DR. CURTIS: That is physician education?

DR. PERLER: That physician education is part of this, and we still haven't heard what actually constitutes physician education.

DR. CRITTENDEN: Another point of clarification. When you were talking about that, Dr. Roberts, I didn't know whether you wanted that to come from the actual training session that they have, a didactic and a practical one, and that they come away with the protocol or some sort of

syllabus, or do you want it to come with the device, the physician brochure?

DR. ROBERTS: I was thinking of the brochure as coming with the device, although certainly, hopefully, people when they go to the training course will at least have everything that would be in that brochure.

I was thinking that it probably wouldn't be a bad idea to have it available with the device, in case someone has forgotten what they are supposed to be doing, or else someone else has gotten their hands on it that hasn't been trained.

Certainly, I think we need to have some kind of a recommendation, or it needs to be stated that there has to be physician training for this device.

DR. CURTIS: I think that is actually pretty well laid out. Rosie?

DR. GILLIAM: I have one comment, and maybe we want to consider this. I hesitate recommending as a condition of approval the specific naming of another agency as the requirements for setting up the registry.

Maybe this would be great, and I think that the Lifeline registry might be willing to do this. I think if we make this as a condition of approval, that they establish something, I mean, the sponsor has no ability to require some outside agency -- I mean, as of today, the agency seems

to be willing and capable of doing such a registry, but tomorrow they may decide they won't want to do it.

The sponsor would have no ability to impact on that agency and compel them to do something in that manner.

I think we can recommend that the societies support such a registry, but I would hesitate to make that a condition of approval, if that is okay to change the motion in that manner.

DR. CURTIS: I would kind of agree. Maybe what we can do is make it not as part of the approval, but as a separate thing that has nothing to do with this.

It should be, in general, that these devices need to be followed in a registry fashion, and then leave it like that.

DR. GILLIAM: Even to the point of saying, we applaud this particular company for doing such a registry, Lifeline, I think their intentions are very honorable.

I think to say to the company that they have to have this company may be putting an unfair burden on the company. Is that out of order?

DR. STUHLMULLER: The issue is what do you want the company to collect.

DR. PENTECOST: Just to follow up a little bit with that, I think that if there is a question about the openness of this registry to other people, I think we have