

leak, I think if it was major in one sense, and the other grading system moderate or minor, we take every endoleak very seriously at this stage.

It is not a high incidence, but those patients continue to be investigated. So, there isn't a differential between a lot and a little and us disregarding the study, if that would be the inference.

Again, I think that the indications to intervene or to think more about that patient are, first of all, is there a leak. Then secondly, is that associated with something that we see in that patient's evaluation that might lead to an intervention or be a risk.

We are all using our cumulative experience to do that, but what we have come up with so far, in terms of examining those leaks and doing subsequent studies, has been very reliable in order to predict and know what to treat and then successfully treat them.

I think, again, the imaging data is absolutely valuable in terms of making these, but the clinical decisions are based upon those studies in the centers, and so far it has been perfectly adequate to do that.

DR. CURTIS: Any other comments or questions?

DR. HARTZ: Just a couple questions for the company. This employment handle, which can be reused 20 times, does one of these handles come with every graft?

I can just see, there are a bunch of screws and somebody is supposed to be putting it together, and losing a piece.

MR. MESSENGER: It doesn't need to be disassembled or anything like that, but we always have back-ups available, always, for any endovascular procedure.

DR. HARTZ: The other thing is, in the patient information booklet, parts of it wouldn't pass the muster of an IRB.

The term, prolonged fluoroscopy, that statement does not need to be in there. That is not a layman's term. Then, cardiac complications, could you say heart attack or death? Thrombotic, embolic complications is not a lay term, dissection of a vessel is not a lay term.

I think especially on the adverse event section, that should be written in very specifically lay terms.

MR. MESSENGER: Thank you.

DR. PERLER: Assuming this is approved and Dr. Zarins and Dr. White are putting these in, in their practice, how do you plan to follow your patients in terms of frequency of imaging and what techniques you are going to carry out and for how long, as it may relate in terms of labeling and what we put out to the public?

DR. ZARINS: I think patients need to be followed closely, whether or not they have an endoleak, and I think

they need to be imaged.

I think that duplex ultrasound, at least at our institution, is a very reliable study, and I think most places it is very reliable for size. Size, I think, is a very important feature in this whole area.

I think that we are following a pattern of a duplex ultrasound at six months and then a CT scan at one year, with the proviso that not all patients would need a contrast CT if there is any question of renal impairment, in which case a duplex ultrasound may be perfectly satisfactory, or an MR imaging.

I think, at least on an annual basis, an imaging procedure which documents, primarily, number one, aneurysm size and, secondarily, presence or absence of endoleak, for me, is the most important.

DR. PERLER: Once a year for how long?

DR. ZARINS: Forever.

DR. WHITE: In our case, we plan to do annual CTs that may be substituted for duplex or color flow, if that technology, in our center, can reach the level that it is in Chris'. Currently, CT is the most sensitive test.

There are patients that we identify with a specific problem that we will bring them in, discuss it with them or do it more frequently, particularly if there were a leak or some suspicion and change in the device that we were

interested in.

We will do that. All of our patients currently, in all of the consents for any study, we send our IRB, say, five-year follow up. We let them know that the process is for that kind of evaluation through the registry, not necessarily from here, because we do plan to participate in that, and all the manufacturers have been willing to accept that, in that registry format, in discussions.

So, we are consenting them for what we think will be the case in the greatest extent, even now, when they sign up for any kind of an IRB study.

DR. ZARINS: I think a five-year follow up, perhaps in a regulatory sense, is perhaps the right time frame, until we get a lot of the answers that we don't know.

My comment on following the patient forever refers to my own personal practice, and that is my practice for all of my vascular patients.

DR. HARTZ: Do any of the investigative centers have SINI(?) CT scanners and has that been tried for this? To me, it is a much more exquisite visualization technique than spiral CT is. Have any of you tried it? I bet there are a few of those scanners out there.

It is such a small contrast load, it is an IV contrast load, and the imaging is so short that it might be appropriate for these patients.

DR. ZARINS: I think the imaging is getting so much better in many different modalities. That is why, to mandate a particular imaging modality is perhaps not what we want to do at this point in time.

Imaging is improving all the time, it is getting less invasive. We may or may not need to use a contrast which is toxic to the kidneys.

The point is that we do need to do some imaging, and that is good or accurate in determining aneurysm size and endoleak.

DR. CURTIS: I think we can have the company representatives step back from the table now, and we will move on to the questions from the panel. You will all notice that they are quite similar to what we looked at already, so hopefully we can come to a consensus reasonably quickly.

AGENDA ITEM: Panel Deliberation and Vote.

DR. CURTIS: The first question is, do the data presented permit assessment of the safety and effectiveness of this device? Comment?

DR. PERLER: Yes.

DR. CURTIS: We have a yes, and I think there will be a consensus about that, which will allow us to go on and deal with the other questions here.

Number two, does the following indications for use statement adequately define an appropriate population for use based on the data presented? It has been read already. Comments on the indication.

The thing that strikes me about this -- we can't discuss the data from previously, but these questions are identical to what we dealt with before.

It is a little more specific and it is probably a little more accurate, I think, as to what we are looking for. It is clearer and I like it. That is what you need to have in order to be able to deploy the system.

It is basically saying it is for infrarenal aneurysms, which is what we are looking at here. Any other comments on that indication?

Okay, number three. Is the proposed contraindication section appropriate. Are there any other contraindications for the use of this device?

It says, do not use this device in patients unable to undergo necessary pre-operative imaging procedures or patients with unsuitable morphologies.

I like this as being more specific, too. In particular, the statement about patients unable to undergo necessary pre-operative imaging procedures gets into the issue about impending rupture and all that sort of stuff that we were talking about before.

If you can't imaging somebody, if you can't figure out what size to use, you can't do this. It is a simple, but accurate way of stating it, I think.

DR. GILLIAM: Should you say anything about the components of this, allergies?

DR. CURTIS: I think we could wind up borrowing, cut and paste. I think the allergy issue, certainly if somebody had an allergy to one of the components, you wouldn't want to use it here. Other comments?

Number four. Would it meaningful and useful to include the following information in the labeling? Some of these, again, are things that we have dealt with already.

The incidence of endoleaks associated with the system, we had earlier said yes, that information is important, needs to be included, so the details should be in there. If anybody wants to break in here, go right ahead.

We had previously said that we didn't think it necessary to include the statement about young, healthy patients. We had wanted to strike it earlier. I think it should be struck here.

The acute symptoms that may be expected if rupture occurs, we don't need that in a physician's manual, but the patients need to know what that is, and we had stated that earlier.

A warning regarding the use in patients with

impending ruptures. I forget exactly how we had concluded that earlier.

DR. GILLIAM: A warning about complications.

DR. PERLER: We didn't like the term impending rupture.

DR. CURTIS: Yes, we didn't like impending rupture. There is the issue that you have to be able to image somebody to figure out what size to use. That kind of covers that.

The possibility of dislodging the device in the case of trauma or falls. We haven't talked about that one before.

DR. GILLIAM: I don't think we have data for that. I think that the confounding data about the one patient who had the fall the day before might suggest, I think, as Dr. Hartz suggested, that maybe the fall was the result of the rupture, not the cause of a dislodgement.

I mean, I don't feel compelled to say that we have to warn people that a fall could dislodge the device, when we have really no evidence that that is true.

DR. CURTIS: I agree with what you were saying. That was pretty dramatic about the boat and getting thrown. Tripping over a chair at home, I am sure that that should require extensive imaging, and we don't have any information on that.

DR. GILLIAM: I am just imagine every other patient, every time they get jostled a little bit, calling you up and asking if you should get some kind of imaging.

DR. CURTIS: A CAT scan. We don't have any information on that. It doesn't seem important to include that.

DR. PERLER: It seems to me that the patient with the large aneurysm was probably at significantly more risk for abdominal trauma than someone who has this device, or some other like it.

DR. CURTIS: Okay, the non-specific relationship between endoleaks, aneurysm growth and rupture. We did discuss that earlier. Does anybody want to recap that one? I can't recall. A statement in there was fine?

DR. GILLIAM: It was information in the physician handout.

DR. CURTIS: Then the warning regarding anticoagulants we said to strike, because there is no issue of long-term use of anticoagulants with this device.

Are there any other issues that ought to be included there?

DR. GILLIAM: What about for women? Is that the place to put it in?

DR. CURTIS: You might as well bring it up. I am not sure which question that went in exactly, but we have

the same situation here, where there weren't a whole lot of women.

DR. GILLIAM: We put it as a warning, not a contraindication, but as a warning.

DR. CURTIS: A warning that there had been only a small number of women studied and that sort of information should be included there; that is correct

DR. SIMMONS: You know, compared to the last device, probably something in the warning section that intervention for proximal leaks, that if the proximal leak is identified and is judged to be a certain severity, that intervention is required rather than observation or something? Shouldn't that be in the warning?

Isn't that what they are recommending, that if you have a significant proximal leak, that the patient should have intervention immediately? Is that what I got out of that? Should that be in the warning?

DR. CURTIS: Probably some statement about that should be in there, because otherwise you could have people who identify the leak and just let them go. If it is recommended to put in a cuff and expand it, that should be stated somewhere in the labeling; I agree.

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

We went through this before, too. Basically we are coming up with six months to one year of some sort of imaging technique, I think is where we concluded. I think that should be recommended here, too.

DR. CRITTENDEN: Just to throw it out for discussion, should we put in something about an algorithm for endoleak monitoring?

DR. CURTIS: Such as?

DR. CRITTENDEN: That for those that are not proximal or distal, that they ought to be followed more frequently than the six months to one year that we are probably going to specify for routine follow up.

DR. CURTIS: Sure.

DR. HARTZ: For the ones that aren't proximal? I thought the proximal ones are the ones that we were the most worried about.

DR. CRITTENDEN: Those are the ones you are going to intervene on. I am talking about the ones that you want to follow but not necessarily intervene.

DR. CURTIS: Other suggestions for labeling?

DR. DE WEESE: I would like to make the suggestion, however, that you do say, at least once a year, and at least each six months. I think this is to help the clinician give them latitude on how often they order it, and also may answer the concerns of the HMOs as to how often

these are done.

DR. CURTIS: That is a good point, too.

Okay, 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.

I think this raised the issue of, we don't know what happens long term with these devices. There needs to be clinical follow up and further imaging of the patients who are included in the study, so that we know what the long-term incidence of endoleaks, aneurysm enlargement, rupture of the aneurysm and interventions for stents and things like that, to open the inside of the lumen, are going to be in the future. I think we have pretty much spelled that out.

Number eight, the long-term safety and effectiveness of endovascular grafts has not been established. Then we have the long-term issues to be addressed through a post-market study.

These are the same kinds of risk factors that were talked about before. We thought that they were all reasonable to talk about.

I don't know if this discussion would be any different from the one we held earlier.

DR. HARTZ: I would just like to point out,

although this is not a regulatory issue, again, this Lifeline Registry points out to me some of the factors that must be followed up, both by FDA and in any registry.

There is no height, weight, race or gender on this form. The gender issue could completely conceivably fall out with body mass index. Those, in any follow up, have to be included.

DR. CURTIS: Any other comments?

It mentions here about post-market study and we got into a long discussion before about approval with condition versus post-marketing study.

I think the general consensus here is that there needs to be longer-term follow up of the patients that have been included in the trial, with clinical follow up and with imaging follow up.

That will give us the basic information that we need, and that the Lifeline registry is an excellent idea, and we support it and we would like to see the information collected there because we believe that would also be very worthwhile.

At this point, we need to have our final public hearing of the day, which would mean that if anybody from the company would like to make any last-minute comments?

MR. MESSENGER: I also would like to thank the panel for your timely review of the product. Thank you.

DR. CURTIS: FDA?

MS. WENTZ: Nothing further.

DR. CURTIS: Do any members of the public want to make a comment?

I don't see anybody coming forward, which would mean that we are at the point of making a motion for approval or disapproval.

DR. STUHLMULLER: I have to read the options.

DR. CURTIS: Go ahead.

DR. STUHLMULLER: Panel recommendation or 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, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications -- PMAs -- 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 the applicable publicly available information.

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

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. Approvable with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or a further analysis of the data. Prior to voting, all of the conditions should be discussed by the panel.
3. Not approvable. The panel may recommend that the PMA is not approvable 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 present a brief statement outlining the reasons for their vote.

DR. CURTIS: Dr. Pentecost, would you like to make a motion?

DR. PENTECOST: Yes, I would make a motion that we

approve -- what was the middle category, I am sorry --

DR. CURTIS: Approve with conditions.

DR. PENTECOST: Approve with conditions.

DR. CURTIS: Do we have a second?

[Motion is seconded.]

DR. CURTIS: Now, would you like to state what you conditions would be?

DR. PENTECOST: I think that the conditions, similar to our discussion earlier, should be that there is a five-year follow up of the patients in this group that have already commenced study.

I think that the 13 percent mortality in women versus five percent in men is disturbing and that we should have a cohort also of 100 women that are studied, as we discussed similarly.

Patient education brochure. Lastly, physician training should be a part of it.

DR. CURTIS: Comments?

DR. SIMMONS: Second. That is the motion?

DR. CURTIS: Yes, assuming that we make the recommendations about the changes in the labeling that we had suggested, yes.

DR. BAILEY: Did you want to be specific about the frequency of imaging, or at least a minimum amount of clinical imaging data?

DR. PENTECOST: I don't think we spelled that out before, so I don't see any reason to do it now, but you are welcome to amend if it you wish.

DR. CURTIS: Any other comments?

So, then the conditions that have been put forward are five-year follow up on the original cohort of patients, with clinical follow up and imaging at six month or one year intervals, however it is finely determined by the FDA.

A cohort of women be followed, so that we get a better idea of what their long-term outcome is with this device.

That there be a patient brochure, and mandated physician training to go along with that. Those are the four conditions. Do we have a motion to accept those conditions?

DR. ROBERTS: So move.

DR. CURTIS: Second?

DR. SIMMONS: Second.

DR. CURTIS: So, we can go ahead and vote on the motion as a whole. Dr. Perler?

DR. PERLER: Approve.

DR. CRITTENDEN: I approve with conditions.

DR. BAILEY: Approve.

DR. GILLIAM: Approve with conditions.

DR. HARTZ: Approve with conditions.

DR. SIMMONS: Approve.

DR. ROBERTS: Approve with conditions.

DR. DE WEESE: Approve.

DR. PENTECOST: Approve.

DR. CURTIS: So, the motion passes.

DR. STUHLMULLER: You have to ask for a statement for how they voted.

DR. CURTIS: I have been asked that we have to actually state why we voted the way we did. Let's get this out of the way and we have a long day. Each panel member, just state briefly why you voted the way you did.

DR. PERLER: I believe the evidence supports my voting decision.

DR. CRITTENDEN: I think this device is safe and efficacious.

DR. BAILEY: I think that the data indicate short-term safety and efficacy, and with the conditions, it is able to be approved.

DR. GILLIAM: The data supports my vote.

DR. HARTZ: Yes, safety and efficacy is fine. We need more information long-term.

DR. SIMMONS: I agree.

DR. ROBERTS: I believe the data supports the short-term safety and effectiveness, and the conditions will allow us to get the rest of the information.

DR. DE WEESE: I believe the data supports continued use of this device, increased use, with more long-term follow up.

DR. PENTECOST: I think also the data supports the short-term effectiveness of this, with the caveat that we need more long-term follow up.

DR. CURTIS: And do we have a motion to adjourn?

DR. GILLIAM: So move.

DR. CURTIS: A second?

DR. HARTZ: Second.

DR. CURTIS: All in favor?

[Voices heard in approval.]

DR. CURTIS: Thank you. We stand adjourned.

Thank you all very much.

[Whereupon, at 5:28 p.m., the meeting was recessed, to reconvene the following day, June 24, 1999.]