to be very sensitive to that.

I am also struck by Dr. Simmons' comment that maybe internists and primary care physicians who are going to be referring to this, and following with all the comorbidities and other things that these patients have, may not be disinterested in an appropriate group to organize such a registry.

DR. PERLER: It seems to me the FDA can enter into negotiations and discussions as to how that registry is carried out.

What I would like to see is every patient who has this device implanted, at least from here on out for the foreseeable future, be entered into a registry so we have that data base, so we know a year from now how many women have had this device.

DR. HARTZ: There is an identification card. The company will have to have that information. I think the offer from Lifeline was a scientific offer from the vascular surgical/interventional radiology community, to collect science, to collect data.

That has nothing to do with safety and efficacy, and the other condition that you placed does have to do with safety and efficacy.

I don't think we should say anything about Lifeline. I think it is just a good offer and we should go

with the other condition that you placed, for the women and for the longer follow up on the present cohort.

DR. PERLER: I think the motion was made and seconded with the original stipulation, so I guess we have to --

DR. STUHLMULLER: Actually, the motion that was made and seconded is approvable with conditions. What is still being done is the conditions of approval are being identified.

Then they will have to be listed and then a motion made and seconded that they be accepted, and then they get voted on as part of the main motion.

I think from a regulatory perspective, what you need to stay focused on is the data that you want the company to collect, independent of any other organization that exists that may also independently collect data.

DR. CURTIS: What you had suggested was, at a minimum, annual imaging studies for five years of the original cohort, and that there be additional women studied with this device. The number of 100 was brought up. Those are the conditions for approval that the company can do and should do.

The other two things that we had were a patient education brochure and mandated physician training for the implantation of this device. Those are four conditions that

I hear.

Then, the fifth one, about the Lifeline, rather than as a condition for approval, maybe we could just say that we strongly endorse the concept of the registry and feel that it should be supported, but that it is not a condition for approval of this particular device. Is that fair?

DR. STUHLMULLER: Yes, I don't think there should be any linking from a regulatory perspective, from your recommendation to the Lifeline Foundation.

DR. CURTIS: So, leaving that one out, that leaves us with four conditions we have identified.

DR. ROBERTS: Could I just make a couple of possible things? Maybe I am wrong, Bruce, but I think what you meant is, you wanted follow up imaging, at least on a yearly basis, but also I think clinical follow up.

It doesn't do any good to have a CT of somebody that dropped dead of a ruptured aneurysm where you don't have rupture on CT.

The other one is that, in terms of the number of additional women, since I don't think we know what the right number would be, can we make a recommendation that maybe some statisticians put their heads together in terms of what kinds of numbers might be an appropriate group to look at, so that we don't just say 100, when maybe 50 would do?

DR. CURTIS: I think your point is well taken, that 50 could be enough. We don't know what it is, so there would be a recommendation that a number of decided upon, after consultation with statisticians, and that additional women be enrolled and followed with this device.

So, that leaves us with four recommendations that have been slightly modified now, but I think they are fairly clear.

DR. CRITTENDEN: Do we need to specify the things we talked about when we answered question number eight?

DR. CURTIS: I think they are all in the minutes.

DR. STUHLMULLER: If you feel they should be a condition, if it is part of your recommendation of approvable with conditions, then you should identify them now and vote on it.

DR. CRITTENDEN: That is what I was asking, because we are specifically addressing the post-market study cohort and how we want them analyzed.

DR. CURTIS: We mentioned clinical follow up and imaging follow up. Was there something else you wanted to put in there?

DR. CRITTENDEN: Surgical conversion was listed here, adverse event rates associated with device and/or procedure, and number of adjunctive endovascular interventions.

DR. PERLER: The clinical follow up includes, but is not inclusive of those items in question number eight. I think all of that should be considered specifically part of clinical follow up.

DR. CURTIS: We can't come up with a data form and say every question that we want to have answered. I think that imaging follow up and clinical follow up on the original cohort is what we are asking for.

DR. PENTECOST: If we are going to try to figure out how many women we are going to need to enroll to reach statistical significance, how do we know that enough of these patients are going to be alive five years from now -- they haven't died from other conditions -- to know that at the end of the five year study we have a meaningful sample of people.

DR. SETHI: I think we have got some data in the literature available about arterial survival. I am sure they can come up with a sample size.

DR. BAILEY: What is the total number of women that have been implanted so far? It is under 100, isn't it?

DR. PERLER: Thirty-six, I think.

DR. BAILEY: Several hundred men, and the rate in women is higher. I think it is important to try to understand what stratifies the risk in that group. It is very important to know how to apply this new device in

women.

I wouldn't be surprised if 100 turned out to be a reasonable number. It is a lot of effort.

DR. SETHI: We can leave that up to the FDA, to decide the sample size.

DR. SAPIRSTEIN: If you want a post-market surveillance study, you can leave it up to us at the FDA to generate one, because we have that capacity, and we can also enlist any other agency that we want to run it, whether it is the American College of Cardiology or the combined cardiovascular surgeons.

If you wish to have a post-market surveillance or trial studied out, you can just recommend it.

DR. CURTIS: I think it is implied in the condition we have there, so I guess that is what we are asking for, then, is post-market surveillance including imaging and clinical follow up on the patients.

DR. STUHLMULLER: Again, as a point of order, right now what you are doing is discussing conditions of approval, and that is a separate issue, potentially, from post-market, because post-market, again, implies that there is already a device approved. I think we should stay focused right now on the issue of conditions for approval and the PMA at hand.

DR. CURTIS: Any other comments about the

conditions for approval?

DR. STUHLMULLER: Can you for the record, again, identify them so that everybody is clear what they are?

DR. CURTIS: The motion was made to approve with conditions, the conditions being that there be follow up out to five years on the original cohort with, at a minimum, annual imaging studies, if not every six months, depending on what the final decision is, with clinical follow up of that original cohort. That is number one.

Number two, that an additional cohort of women be studied and reported on. One hundred women may be an appropriate number, but that is open for adjustment, so that we can find out what the long-term safety and efficacy is more clearly in women. That is number two.

Number three, that a patient education brochure be developed to explain clearly to the patients what to expect, and other issues, such as what kind of symptoms would they have, if they had impending rupture, that sort of thing.

Number four, that physician training be mandatory, in order to be able to use this device.

DR. SAPIRSTEIN: You were going to add the recommendation that further registry could be used?

DR. CURTIS: It is not a condition for approval.

DR. SAPIRSTEIN: Okay, it will come later. Okay.

DR. CURTIS: Now we need a motion for acceptance

of those four conditions.

[Motion made and seconded.]

DR. CURTIS: All right, we will go around the table, then, and one by one, let me know if you accept the motion.

DR. PERLER: I do.

DR. CRITTENDEN: I do.

DR. BAILEY: I do.

DR. GILLIAM: Yes.

DR. HARTZ: Approve with conditions.

DR. SIMMONS: Aye.

DR. ROBERTS: Yes.

DR. DE WEESE: Yes.

DR. PENTECOST: Yes.

DR. SETHI: Yes.

DR. CURTIS: All right, so the motion is approved with conditions.

At this point, we are going to take a 30-minute break to allow MedTronic to set up. We will reconvene at 2:45.

[Brief recess.]

AGENDA ITEM: Premarket Approval Application P990020. Medtronic AneuRx, Inc. AneuRx Bifurcated Endovascular Prosthesis System. Company Presentation.

DR. CURTIS: We are going to begin by hearing about the premarket approval application number P990020. Medtronic AneuRx, Inc's AneuRx Bifurcated endovascular prosthesis system. We will start with the company presentation.

MR. MESSENGER: Good afternoon, Madam Chair, and members of the panel. My name is Noel Messenger. I am the vice president of regulatory affairs, clinical affairs and quality assurance at Medtronics, AneuRx.

I am an employee of the company and a shareholder in the firm.

I would like to thank you for the opportunity to be here this afternoon to present the Medtronic AneuRx stent graft system.

I will be discussing the product design, clinical study objectives, patient enrollment status.

I will be assisted by Dr. Christopher Zarins, chief of vascular surgery at Stanford University Hospital, to describe the clinical protocol in more detail, and then begin the presentation of the study results.

Finally, to present the safety end points and the procedural end points, I am going to ask Dr. Rodney White, chief of vascular surgery at UCLA-Harbor Medical Center to present the primary end points, and the risk/benefit analysis.

We have some additional speakers who will be available to answer questions, but will not be making primary presentations.

Those are Dr. Allen Motsamoto, a radiologist from the University of Virginia, who is the chief of our core lab, Dr. Robert McPherson(?), a principal investigator. He is a cardiologist who can address questions regarding performing the procedure from a non-surgical point of view, and Dr. Dan Block(?), our consultant biostatistician.

AneuRx was founded in 1993 to develop a product for a new treatment for repair of AAA. This repair involved insertion of an endovascular prosthesis.

AneuRx, in 1993, confirmed that there were four critical design requirements for developing the optimal endovascular prosthesis.

Those four requirements were to design a product with a blood flow surface that replicated surgical grafts. In this way, we felt that we could avoid the long-term follow up that would be necessary for new graft materials, and that we would not have to demonstrate that placing architectural support, such as stents or other metallic surfaces, inside the blood flow surface, that we would not have to demonstrate that this would impact blood flow.

So, the goal of developing the AneuRx stent graft was to replicate the surgical graft, at least in terms of

the blood flow surface.

Conversely, the insertion mechanism for the device would have to be on the outside of the prosthesis.

AneuRx also felt that the device should be fully supported to give it strength, since it was suspected that during the depressurization of an aneurysm there would be remodeling and the external skeleton of the device was required to avoid kinking, or if kinking occurred, to avoid causing a thrombosis of the limb during the remodeling process.

Finally, and most important, AneuRx felt it was critical to design a product that was adaptable not only in terms of performance of the device but in terms of implantation of the device.

A physician could modify the configuration of the device during the implantation process, or go back after the implantation of the device, to change the configuration such as adding new components to fix or repair any findings that were found, such as endoleaks, after the initial implantation.

This design resulted in the AneuRx stent graft system pictured here. It has a polyester surgical graft material on the inside. It is a woven polyester material very similar to commercial surgical grafts that have been used for decades.

It has an exoskeleton made up of nitenol stents that run along the entire surface of the device. Nitenol -- nickel titanium or nitenol -- is a shape memory metal.

Shape memory metals work in such a way that at temperatures such as room temperature, the nitenol stent can be crushed into a catheter.

However, at body temperature, they will try to expand back to the original configuration to which they are manufactured.

The force that causes them to expand is called radial force, and it is this radial force that embeds the stent matrix into the vessel wall, and this is, in fact, the attachment mechanism.

The device is modular, as you can see. It comes in components. The main bifurcated segments ranges in size from diameters from 20 to 28. It has a matching iliac leg that varies in diameter from 12 to 16 millimeters.

They both come in different lengths and there are proximal and distal cuffs that can be added to lengthen the configuration or these components can actually be mix-matched to increase the diameter of the ends of the configurations in the patient.

Because the device is fully stented from top to bottom, they are actually made up on one-centimeter-long stents that are sewn end to end on a graft.

Originally the proximal stent was a longer piece, and early in the clinical trial process, we developed them all to be one-centimeter-long stents. So, it has column strength and conformability.

The column strength means that you can push the device end to end and it will not buckle or kink, because it has resistance and column strength.

It is also very conformable and can be implanted in very tortuous anatomy as shown here, and will still completely comply with sharp turns in the iliac vessels, and/or the sharp turns that can occur in remodeling, both in the proximal portion of the device and the distal legs.

The bifurcated segment of the device is applied in a 21-fringe delivery catheter. The iliac legs and cuffs are supplied in a 16-fringe delivery catheter.

They are both deployed using this handle here, with a crank mechanism that allows for a very precise and accurate deployment of the device.

This is one of the keys to the high technical success that has been achieved with the implantation of this device.

Additional features are, there is a nose cone at the top, and the stainless steel runners here, which I will explain. The nose cone has a notch in the side which is pictured there, and a hole there.

Under fluoroscopy, that is very visible and can be used to orient the device with the open pathway then facing the contralateral leg.

The stainless steel runners that run alongside the catheter sheath, the catheter cover, track the device and allow for very slow and precise deployment, and also allow for the device to be oriented -- in other words, move either up or down or pulled back down, or moved to make the fine-tuning orientation of the open pathway, and these radio opaque markers here help the physician orient the open leg toward the contralateral vessel.

The device is deployed through bilateral arterial cut downs. The bifurcated segment is always deployed first.

The device, again as I said, is deployed at the level of the renal arteries, and final adjustments are made to the positioning. It is pulled down to just below the renal arteries.

The catheter cover is then withdrawn. The self-expanding nitenol then opens. The stainless steel runners and the nose cone is then removed.

The contralateral leg is then cannulated and the iliac leg is then inserted into what we call the landing zone, marked by radio opaque markers here. The catheter is then removed again and the implantation is complete.

There is no need to balloon open this device, as

the self-expanding nitenol at body temperature is all that is required to open up the limbs of the device.

Balloons can be used if inadequate acquisition against the vessel wall is suspected, but they are not required.

The clinical trial that was performed to evaluate the safety and efficacy of the device was a prospective, multicenter clinical trial comparing implantation with AneuRx stent graft with open surgical repair of AAA.

All patients in both arms met the same entrance criteria.

All patients enrolled were evaluated prior to hospital discharge -- that included a CT examination prior to hospital discharge -- at a one, six and 12 months. A color duplex ultrasound was substituted for a CT at one month.

Each investigational site enrolled five surgical patients prior to enrolling any of the endovascular patients, and this ensured complete enrollment in that arm of the study.

The goals of this study were to evaluate the acute and long-term safety and efficacy of the AneuRx stent graft, by comparing one-year follow-up data from the first 15 patients enrolled in this trial, 90 of which were planned to be from the endovascular arm and 60 from the surgical arm.

This enrollment began in April of 1997 and was completed in September of 1997. At that time, the physician group asked us if we could obtain permission from FDA that they be allowed to continue to implant the AneuRx stent graft, based on their very successful early results, if they could continue to implant that device during a follow-up period.

That permission was granted and eventually we ended up with 416 patients on an intent-to-treat basis in the stent graft group compared to 66 patients in the surgical control group.

We invited 13 clinical trial centers to be involved in this clinical evaluation. We invited centers that represented large teaching hospitals, small community hospitals, private practices.

We invited vascular surgeons, interventional radiologists and cardiologists to be PIs in this study. We scattered the locations of our clinical centers throughout the United States.

Most important, we invited physicians who had a wide variety of prior endovascular experience, and in particular, endovascular repair of AA experience.

So, some of these physicians had never used any device like this before, some had used other manufacturers' or homemade devices before.

Because of the disparity of the types of centers we enrolled and invited into the trial, we looked at our ability to pool the data.

In looking at pooling the data, the first thing you want to be sure is that all centers met the same entry criteria, they were trained in the same way, and the treatment techniques were the same way.

The training that we developed and that were used after product approval, is based on the training that we developed during this clinical process.

When we looked at differences in outcome, which will be discussed in more detail later, we did not see variety in outcome among the different sites.

However, when we looked at the centers that enrolled a larger number of patients versus the centers that enrolled smaller numbers of patients, we did see three differences in outcome.

Procedure time and blood loss were actually higher in the centers that enrolled more patients. This is primarily because those centers were the large teaching hospitals that were taking extra time to teach other physicians, and this is reflected in that outcome.

The outcomes are not clinically different. The procedure time is about 15 to 20 minutes more, the blood loss is about 100 ccs more. I don't think those are

clinically relevant findings.

What is more interesting is the major morbidity, which was found to be reduced in centers that enrolled more patients.

This is an impact of the learning curve, and I think this is very important. In centers that are now out 20 to 30 patients, the level of major morbidity and perioperative mortality is greatly reduced.

At the time of the PMA filing, we presented data to FDA on 199 patients who we had obtained one-year follow-up data on, compared to 53 patients that had survived out to the one-year time point from the surgical arm.

There were actually four additional patients in the surgical arm that had died in this period of time. We could actually account for 57 of the patients at that point in time.

This, of course, well exceeds the commitment made to FDA regarding the initial commitment of follow up of these patients of 150. Therefore, our conclusion is that this data is adequate to assess safety and efficacy.

Now I would like to ask DR. Christopher Zarins to come up and begin the data presentation that will, of course, demonstrate safety and efficacy for you. Thank you.

DR. ZARINS: Good afternoon. My name is Christopher Zarins. I am chief of vascular surgery at

Stanford University Medical Center, and professor of surgery at Stanford University.

I have 25 years experience in treating patients with aortic aneurysms. I am a clinical investigator in this trial, and I own stock in Medtronic.

What I would like to discuss today is the clinical study design. As Mr. Messenger told you, this is a prospective clinical trial, comparing surgical patients with endovascular repair.

It is interesting to note that this is a concurrent surgical group, although all the surgical patients at each site were entered prior to the endovascular patients.

This was done specifically, in order to try to obtain a comparable group of control patients to the endovascular group.

Once endovascular devices are available, patients tend to want them. So, the surgical controls were entered with the exact same criteria as the endovascular patients, before the endovascular procedure was available at each study site.

The inclusion criteria, each patient met the criteria for surgical repair for aortic aneurysm. I would just like to review those surgical criteria.

The aneurysm was greater than five centimeters in

diameter. There were patients who has smaller than five centimeter diameter, and five centimeter is not necessarily an absolute.

For example, women tend to have smaller aortas. The same size aneurysm is probably more significant in a woman than it might be in a man.

If the aneurysm is four to five centimeters in diameter, but had documented increase of a half a centimeter in the past six months, that patient was a candidate.

Also, for the small patient, if the aneurysm was twice the diameter of the neck of the infrarenal aorta, that patient was a candidate, and a small number of patients who had saccular focal aneurysms, they were also candidates.

I should note that 80 percent in both arms of the study had aneurysms greater than five centimeters.

Further inclusion criteria included morphologic features of the aneurysm, such as an infrarenal neck one centimeter in length, neck diameter of 18 to 26 millimeters, common iliac arteries 16 millimeters in diameter, and patent iliac and femoral arteries allowing access of the device.

We excluded patients with ruptured or leaking aneurysms, suprarenal, thoraco-abdominal, ilio-femoral and inflammatory aneurysms.

We excluded patients with vascular injury, patients with morbid obesity such that x-ray visualization

would not be possible to deploy the device.

We excluded pregnant or nursing patients, patients with connective tissue disease, and patients with hypercoaguability.

We further excluded patients with acute renal failure, active systemic infection, age less than 18 years, patients who had less than one-year life expectancy or other conditions that would preclude them participating in the trial.

The primary end points that we used to evaluate the efficacy and safety were technical success, and we defined this as vessel access being achieved, and the ability to deliver the catheter and the treatment to the site, and fully deploying the device.

We evaluated mortality and major morbidity, and we evaluated the major morbidity as severe treatment-related adverse events.

Of course, we wanted to know about rupture of the aneurysm, and we defined aneurysm enlargement as greater than .5 centimeters compared to baseline size, between one follow-up visit to the next.

We also defined endoleak defined as evidence of radiographic contrast external to the device, conversion to open repair, indicated by any surgical repair of the aneurysm for any reason, and we evaluated stent graft

patency.

Other primary end points included stent graft migration, device integrity, and any additional procedure that was needed to maintain patency or function of the device, including extender cuffs or treatments to restore patency of the limbs.

We looked at a number of secondary end points, which were periprocedural end points, and I won't read this list. You will see them again as we present the data.

Now, let's look at some of the clinical study results. We were very interested in the demographics. We made every effort to include female patients in the study.

We found that in both arms of the study we had a preponderance of male patients, and this reflects the preponderance, or the prevalence, of aneurysms in men compared to women.

There were 11 percent women in the stent graft, comprised of 46 patients, and the distribution between males and females was the same in the surgical control and stent graft groups.

Patients who received the stent graft were older, by about four years, than the surgical control group, and this was statistically significant.

The surgical risk category, these were high risk patients. A full 90 percent of all the patients treated

were either in ASA category III or IV, and a full 25 percent of the patients in both the surgical control group and the stent graft group were in ASA grade IV risk category.

There was no statistical difference between any of the groups in any of the risk categories.

We looked at a number of other patient characteristics listed here on this slide. Of significance were that there were three patient characteristics that were statistically different between the two groups.

Symptomatic cardiac arrhythmia and previous surgery in the affected area was higher in the stent graft group, and the presence of significant COPD was higher in the surgical group.

We carefully looked at aneurysm dimensions and, as you recall, we really wanted to balance the surgical control and endovascular groups, and carefully paid attention to making sure that the same criteria were met.

Indeed, the neck diameter was the same between the groups, the neck length was the same, the aneurysm diameter was the same, and again, 80 percent in both groups was greater than five centimeters in diameter.

There was a difference in aneurysm length in the surgical control group, a little bit longer in length, but the size of the iliac arteries was the same in both groups.

Mortality, comparing the surgical control, 66

patients, to the stent graft, 416 patients, there was no difference in perioperative mortality or late mortality between the two groups.

You notice that there are seven deaths in the stent graft group. I will review those in a minute, and I will also comment on the deaths that occur late.

These are the seven patients that died within the 30-day time frame in the endovascular groups. Three patients had colon ischemia. Two of those actually seem to have died of colon ischemia.

This patient died of a subsequent stroke, although that patient had a colon ischemia which was surgically resected.

One patient had GI hemorrhage. This patient was anticoagulated, and there was no evidence of colon ischemia in this case.

Thus, the incidence of colon ischemia is two percent in the stent graft group. I should note that the incidence of colon ischemia in the control surgical group was one percent. One patient had a colectomy following open surgery, for bowel ischemia.

This patient survived. So, the incidence of bowel ischemia, probably related to the inferior mesenteric artery, was the same in both groups.

Two patients died of myocardial infarction, one at

one day and one at three weeks, and one of aspiration pneumonia.

I would like to comment on this 45-year-old man who was a patient of mine who died of a myocardial infarction.

I had a long discussion with this patient, because he was young, and he was very insistent that the didn't want open surgical repair, because he was unwilling to accept the risk of potential sexual dysfunction, which is accompanied with open surgical repair.

He entered the clinical trial. He underwent preoperative cardiac evaluation, non-invasive testing. The cardiologist said he has no significant coronary disease.

On the second post-operative day, he was discharged, had an uncomplicated stent graft repair, was discharged home.

Outside hospital, three weeks later, he developed chest pain, went in the hospital, was found to have 95 percent left main disease, and efforts on the cath table to treat that left main disease were unsuccessful, and he died.

Late mortality, again, the relationship between coronary disease and aneurysm disease, particularly in young patients, was apparent.

One of the two cardiac deaths in the surgical control group, was a young man, age 52, who died in eight

months of coronary ischemia and myocardial infarction.

One patient in the surgical group died of an arch aneurysm rupture, and both groups had deaths due to cancer.

There was one patient listed here as an undetermined death in the stent graft group. This patient did not die of a ruptured aneurysm.

This patient was on chronic hemodialysis, and chose to discontinue his dialysis. He had imaging studies a month before his death that showed that his aneurysm was intact with no endoleak.

Just to compare those mortality data to the mortality statistics for open surgical repair, reviewing a large number of study with open repair, we see that the 30-day mortality rate is approximately four percent.

So, the mortality rate in our two arms of our study are well within the published mortality rate for open surgical repair.

Looking at patient survival, this is a 12-month Kaplan-Meier survival curve. Patients who were out past 12 months and who happened to die, were included in the 12-month time frame.

There was no difference between the stent graft and surgical group in patient survival at 12 months.

Here we see listed the cumulative adverse events over the entire course of the study, not simply just the

periprocedural or one-month time frame.

I will call your attention to the fact that there were more gastrointestinal complications in the surgical control group, and there were more pulmonary complications -- these were statistically significant -- in the surgical control than the stent graft group.

I would just also like to point out that the incidence of cardiac events was the same -- 11 and 12 percent -- in both groups.

As you can see, there are a couple of things that are of significance here. One, you see a notation here for renal events, 17 patients, 4 percent.

Fifteen of these patients have elevated creatinine of greater than 50 percent of their baseline level, which was transient following their procedure.

These returned to normal and no patient required hemodialysis. One patient had a nephrotic syndrome and one patient had obstruction of one renal artery with the device, with normal creatinine, normal renal function. This was an asymptomatic event, but it is included here under renal events.

Severe treatment-related adverse events, this again is a cumulative listing of all treatment adverse events.

We see that there are 15 percent incidence in the

surgical control group and 10 percent in the stent graft group.

The number of events could have been more and, in fact, frequently more than one event in each patient. Therefore, you see 20 events and some patients had three or four or five very significant events, such as colon infarction, stroke, myocardial infarction, need for tracheostomy, in some instances.

This was not a prospective randomized trial, as you know. In order to adjust for the baseline differences in risk factors, which I had previously noted, such as age and the incidence of symptomatic arrhythmias and the like, we used the Cox proportional hazard model and we found that surgical patients were at greater risk of experiencing severe treatment-related adverse event by a factor of two, and this was statistically significant.

If we look at the perioperative time frame alone, we see that there is a two-fold increase in the number of severe treatment-related adverse events in the surgical group compared to the stent graft group, and this is highly significant.

Furthermore, if the surgical patients have a complication and an adverse event, it significantly prolongs their hospital stay, whereas when a patient with a stent graft has an adverse event, such as the need to adjust the

graft or a groin problem, it does not really significantly affect hospital length of stay.

So, these are really significant complications that happen in the surgical group.

Other procedural end points, we see that in each category there was a benefit for the stent graft patient. There was a reduction in the duration of anesthesia, reduction in procedure time, two-thirds reduction in blood loss, one-half reduction in the number of patients requiring transfusion, significant shortening of the time to extubation, much earlier ambulation and earlier resumption of normal diet.

The intensive care unit time was decreased from 3.5 days to 0.9 days, and the hospital length of stay was reduced from 9.3 days to 3.4 days, and all of these results are highly significant.

Thus, to summarize the results, we found that in comparing AneuRx stent graft repair to open surgical repair, we find that there is no difference in mortality between the two groups, there is reduced major morbidity in patients receiving the stent graft, there is reduced blood loss and blood transfusion, there is reduced ICU stay, there is earlier return to function and reduced hospital length of stay in patients receiving the stent graft, and there is no difference in patient survival at one year. Thank you.

I would like to now introduce Dr. Rodney White, who will tell us about the primary end points and the risk/benefit analysis.

DR. WHITE: Thank you, Chris. My name is Rodney White. I am chief of vascular surgery at UCLA-Harbor Medical Center in Torrance, California, and a professor of surgery at the UCLA School of Medicine.

I was chairman of the advisory committee for the AneuRx study and I was compensated to do this. I have, as part of my portfolio, some Medtronic stock.

My duty today is to describe with you the primary end points and to make a risk benefit analysis of the data that you have just seen presented.

On this slide are the primary end points that we will go through in the next series of slides. These were factors that we felt were particularly important in order to address this technology and to make the risk/benefit assessment.

Those are technical success, morbidity and mortality, aneurysm rupture, enlargement of the aneurysm, conversion to surgical repair, stent graft patency, stent graft migration, any additional procedures that were required, assessment of device integrity, and a discussion of endoleaks.

The technical success in treating patients in this

study -- and this was accumulated on an intention to treat basis -- that being any patients where there was an attempt to treat the catheter is counted in this analysis.

There were 66 patients in the surgical control and, obviously, the device was surgically implanted in all of those.

In the endoluminal graft categories -- you will see two different numbers, one of 415 and one of 416, the difference being that one patient had, on the table, angina and myocardial infarction before the procedure was begun.

So, in the intention to treat analysis, in that there was no attempted placement, that patient is not included.

Of that 415 patients, 405 successfully had the device implanted, for a 97.6 percent success rate. There was no statistical significance.

Of those 10 patients, seven had no device implanted, and that was due to vessel access difficulties. There were limitations in being able to actually position the device.

There were three patients who had surgical repair. The device had been place, it was maldeployed and there were three conversions immediately to treat that.

Morbidity and mortality has been emphasized earlier. I listed here as the primary end point that we

would all like to focus on here, as Dr. Zarins mentioned, comparison of the surgical control group to the endoluminal group.

There was no perioperative difference at the follow-up interval of the study in the surgical group compared to the stent graft group, again, no significance noted.

If we look at major morbidity in the perioperative period, there were 10 events in the surgical control group, 30 in the stent graft group.

If you compare the percentages, there was twice the number in the surgery control group, and this was statistically significant in favor of the endoluminal graft patients.

There were two aneurysm ruptures in this study. One was less than 24 hours following the procedure and one at 14 months.

The two patients out of the 405 was a .5 percent incidence, and I would like to tell you about both of these in detail.

The first patient was a patient that we treated at Harbor UCLA. It was an 81-year-old female with a previous cardiac history.

She proceeded well through the procedure, had no problems, was able to take a late diet. Eighteen hours

following the procedure in the ICU, with one of the nurses at her side, she experienced back and chest pain, had an arrest and a very rapid resuscitation.

Upon clinical assessment of this patient, we were unable to tell whether she had an acute cardiac event or a ruptured aneurysm.

For that reason, she had a CT scan that I will show you in a moment, that demonstrated a retroperitoneal hematoma, minimal contrast in the aneurysm.

Based on these findings alone now, we probably would have chosen to transfuse her and observe her, but this was early in the study and we talked to her and her family, and we elected to take her to the operating room.

She had an open conversion performed. There was a rupture in the anterior surface of the aneurysm. The device was in position as we displaced it.

There was then free bleeding from that perforation. We were unable to tell if that perforation was an eminent rupture that had just gone 18 hours after the procedure, or if this might have been a catheter injury at the time we made the deployment that didn't present until 18 hours after the procedure.

There were no defects in that endoluminal prosthesis. The patient had a successful repair, was discharged from the hospital, and expired four months later

of a cardiac arrest at home.

The CT scan on this patient demonstrates the seven-centimeter aneurysm in this patient. The one relevant finding is a quite short neck, although we were able to securely fix the device.

These are the MIPS and surface rendered 3-D reconstruction of the device in the aneurysm, here on the MIPS view, and then the axial views, I would point out to you on these larger images, that there is very minimal contrast outside.

Again, if this were probably today, we would have transfused her and not converted her, but this was our clinical decision at the time.

The second patient with a rupture occurred in a gentleman at 14 months after implantation of the device.

At the time of discharge from the hospital, his CT scan was read by the hospital and the core lab to have an endoleak.

At six months, that endoleak persisted. At 12 months, a color flow duplex ultrasound did not demonstrate a leak.

Just prior to coming to the hospital for his procedure, he fell at home. He had abdominal pain and a retroperitoneal hematoma.

On the CT, this showed perigraft flow and aneurysm

expansion. The patient underwent surgical repair. There was a rupture in the body of the aneurysm, no defects seen in the device and, although he was successfully converted, he expired three months later of pneumonia.

This is a picture of a flat plate on this particular patient at six months. The reason we show you this is -- I should say all of this data was generated, and includes learning curve analysis, so that the technical success rate of 97.8 percent is also the learning curve reflected.

Now, this was a patient very early in the study who had a very angled neck. The neck came very much across like this and was short.

The tip off that we now see on this kind of an x-ray, where there is indentation of the device, would spur us to make an additional intervention.

Now, eight months later, when the patient comes to the hospital with the rupture, you can see the very short-angled neck here on the axial view, the device is here, there is obviously a leak, and retroperitoneal hematoma.

Again, this type of patient we would pick up very early on the imaging studies and put a proximal extension or take advantage of the segmented proximal device that Mr. Messenger showed you, in order to treat this kind of patient.

Another important end point that we have all focused on, because our imaging parameters and assessments have been based on aneurysm diameter, not only for our clinical decisions but for endoluminal graft follow up.

We have looked at, based on the core data, at pre-discharge to six months, six months to one year, and then globally over that interval, pre-discharge to one year, any evidence of aneurysm enlargement or decrease.

The definition that was used is the five millimeter increase, particularly because these are CT follow up, and imaging average would let us be specific within that range.

For any of the patients with aneurysm increase in size, we have correlated that with an endoleak at the time of the increase.

In the pre-discharge to six-month interval, there were six patients who showed an increase, and all six of those had a leak.

At the six month to one year interval, there were seven patients, or 4.7 percent, which showed an increase. Two of those seven had an endoleak, so that five patients had no evidence of an endoleak at that interval studied.

When we take the global interval from pre-discharge to one year, the amount of enlargement is 3.8 percent. This is less, actually, than the addition of the

other two, in that there were patients who would have increased, sealed a leak and then decreased or, for whatever reason, decreased in diameter, so that the overall incidence of enlargement was less than four percent. This represented six patients in a year, and four of those had an endoleak.

Now, if we look at the corresponding finding that we have all talked about related to these devices, a significant number of patients also decrease in size.

In the patients that had greater than five millimeter decrease in size, at the various intervals, it was nine percent pre-discharge to six months, and then an additional eight percent in that six-month to one-year interval. At the pre-discharge to one year time frame, about 21 percent had decreased in diameter greater than five millimeters.

Conversion to open surgical repair is obviously one of our end points that we would like to focus on specifically.

In this slide, we break them into two categories. The overall percentage of conversion at any time during the study was two percent.

Six of the patients that were converted had devices in place at the time of the conversion. We have talked about most of these already.

Three of them were the patients who were failures

to have technical delivery initially, for device malposition, the two aneurysm ruptures.

There was also one patient who had an endoleak at six months, was informed about the condition, was felt to be safe to continue in the study, but he opted for surgical conversion. Again, there were six patients with devices that had conversion.

Throughout this interval, there were also two patients who, at the time of the initial intervention, when they were not able to have the device deployed, had a conversion.

These two patients were consented prior to that procedure for the conversion. So, there was obviously a suspicion of the investigator that there would be a conversion and the patient was consented for that, and that occurred.

The total of these eight patients are two percent of the overall patient group.

To look at that surgical conversion in another way, to look at it related to immediate conversions at the time of device deployment, this was about one percent of the total study in post-procedure, one percent in that immediate group, and three device malpositions, and two patients who elected to go directly, whenever access was impossible.

There were also, then, in the post-procedure --

this is throughout the entire length of the remainder of the study -- the two ruptures and the one patient that elected on his own for an endoleak to be converted.

Stent graft patency is one of the primary end points that we can correlate directly with the surgical control group.

It is one of the things that we assess patients for when they come back on their follow up visits, when we look at them in routine examinations to talk to them about their ABIs and their history for any change in ambulatory status.

When we compare the surgery control group with the stent graft group, there were comparable primary patencies, being 98 percent.

In the surgery group, there was one limb thrombosis. That patient had restored patency with thrombectomy.

In the endoluminal graft group, there were eight patients, being two percent again, of the total of 405 compared to one out of 66 in the surgery.

Four of the patients had restoration of flow to the contralateral occluded limb in the endoluminal graft category by a femoral/femoral bypass.

Four of the patients had restoration of flow with either a stent or a balloon angioplasty or a thrombectomy.

So, of the two percent limb thromboses, one percent of those were treated by endovascular means and one percent by an additional surgical bypass to the contralateral limb.

The issue of migration has been very important for all of us when we consider not only being able to successfully deploy endoluminal devices, but do they stay in place.

The core lab definition in this study was very sensitive, in that it was any movement by CT or flat plate. This was in deference to the ISO recommended standard of a one centimeter migration or movement from a fixed anatomic landmark.

We felt very comfortable with this, in that any evidence of migration would be inspected and the implications looked at.

We looked at this again at the various follow-up intervals, one month, six months and a year. The incidence was very low in all cases, where at any interval being no more than three or four patients and the percentage being less than two percent.

An interesting finding related to this is at the six month interval, two of the four patients that had evidence of migration developed an endoleak.

Both of those were treated successfully with the addition of a cuff, and we will consider that on the next

slide when we add these two patients in, and our total accumulative evaluation of additional procedures performed.

The additional procedures performed here are, again, throughout the entire length of the studies, and fall into two categories.

We have already mentioned two categories, the limb thromboses, there were eight patients treated, for two percent of the total study group. Again, four of those were with the surgical bypass, four of those with an endovascular method.

The other additional procedures that were performed, 19 patients, or 4.7 percent of the 405 patients being followed had a placement of an additional cuff for an endoleak.

Of those 19 patients that were treated, 16 had successful exclusion at the time of that primary re-intervention.

One patient did not have a successful exclusion and had a conversion, and two others are being followed at the present time for what are characterized as minor endoleaks. Both are actually distal leaks, and I will explain our classification system in a moment.

Of the patients who had additional procedures required throughout the time of the study, all but three of those had resolution immediately by an additional catheter

or minor surgical procedure.

Device integrity, again, is an issue with any combination of material and stent. At all follow-up intervals, there was no evidence of stent fractures at any interval for a zero percent incidence. There was also no reported incidence of a fabric defect.

Device configuration was looked at, as many of you are aware. As the aneurysms shrink over time, there are morphologic changes that change the configuration of a device, although it may have actually been put in initially with something that looks like a confirmational difference from what you might expect.

This was quantitated by the core lab as kinks or twists. There was a reported incidence from two to four percent at the various follow-up intervals of this particular finding.

I would point out to you that there are no occlusions, migrations or additional procedures related to this finding. We did not attribute any clinical significance to that.

Part of it is an advantage of this particular device, in that it is stent supported on the outside of the graft so that, as it makes conformational changes, it does not tend to narrow or kink the lumen.

As I open the discussions regarding endoleaks, I

would first like to show you the device and how we classify the endoleaks, as this is an important factor related to how we interpret these leaks, and also to some recommendations that I would like to tell you we have come up with regarding treatment, as these will be part of the subsequent discussion related to the type of endoleak, the interval, and then how they were resolved in each of those cases.

In this prototype diagram, with the AneuRx device in the aneurysm, proximal leaks -- designated A -- are out of the aortic lumen around the device. Distal leaks flow from the iliacs back along the device in the aneurysm.

A junctional leak is anywhere there is a connection in the device. The classic place would be here, the contralateral limb as it is in the body of the device.

Flow across the porosity of the device is being transgraft -- this is a phenomenon that occurs early and goes away. Then, branch flow, any flow back through a lumbar accessory, renal or inferior mesenteric artery, then enters the aneurysm sac.

There is also always an indeterminant group that we can't tell where they come from.

Now, related to these endoleaks, then, there were some things that we recognized early in the study. One is, because of the porosity of the polyester fabric which seals over several days, and also because patients got CTs pre-

discharge -- and later on in the study this was within 24 to 48 hours of the procedure -- there was enhancement of the aneurysm by flow across the device in a significant number of patients.

This phenomenon was examined by the investigator sites. When the phase III study was begun, actually, no early CTs were performed unless clinically indicated, because the relevance of this porosity diffusion was felt to have no predictive clinical outcome.

In the overall study, there was three percent of the patients in this study had an endoleak associated with aneurysm enlargement. We had talked about that earlier, and I will emphasize our focus on that in a second.

Based upon, then, this classification system, our ability to look at the early flow across the grafts, and to also try to come up with recommendations for anything that was recognized, the recommendations for treatment were based on severity and location, with any endoleak associated with aneurysm enlargement being considered for treatment.

Also, unresolved proximal, distal or junctional leaks were felt to need further investigation and treatment, if possible.

The modular design of this catheter-based method obviously enhanced the ability to do that.

When we look at the endoleak data -- and this is

core lab data that correlates very well with the clinical investigator-site data -- although there is a lot of information here, the relevant points can be summarized quite easily.

Early in the predischarge patient evaluations, the branch flow being 18 percent or, in the indeterminant category 13 percent, most of the endoleaks are in this area.

If you look at proximal, distal or junctional, they tend to decrease throughout the length of the study and, at the one-year interval, are a minor percentage of endoleaks, and we will discuss this again in a moment.

Now, if you look carefully at our classification system for endoleaks, being proximal, junctional, branch flow and indeterminant, the core lab data, because of their system, doesn't always match this.

There was not a category for the transgraft flow. It appears to be in this indeterminant group here, and this early incidence quickly decreased and, by the time of a one-year interval, the amount of aneurysm enhancement on a CT scan was 17 percent, with the majority of those patients being in the branch flow and indeterminant group.

As I mentioned to you earlier, secondary interventions for proximal, distal or junctional, in all cases, were reconsidered for treatment and were successful in 16 of 19 patients throughout the study as an immediate

seal.

So, as we look at the risk/benefit analysis for this device, we would like to take into consideration what we feel are the relevant parameters -- that being perioperative mortality, aneurysm rupture, aneurysm expansion, surgical conversion and thrombosis.

If we look at those in a brief summary initially, there were no differences in mortality compared to the surgery control group.

There was a 50 percent reduction in major morbidity. The technical success rate at the time of the procedure on an intention to treat basis and, again, including the learning curve for most of the phase II centers, was 98 percent, and the surgical conversion rate throughout the entire length of the study was two percent.

Dr. Zarins has presented this to you, but I would like to summarize it just briefly again. These are the secondary periprocedural end points, with blood loss, time to ambulation, time to a normal diet, ICU stay and hospital length of stay, in all of those cases being two-thirds less than the corresponding surgery control patients, with a major benefit in the secondary periprocedural end points favoring the endoluminal graft.

What we have done, in an attempt to try to look at -- and this is based on the vascular surgery and

interventional radiology mentality that a primary success, we would like to know how frequently that happens.

Then if there is an event that we can restore patency to a device, we call that secondary success. So, my next two slides are primary success and secondary success based on that rationale.

Using the primary end points that we have just mentioned as our major end points -- perioperative mortality, rupture, expansion, conversion and including any secondary procedures, the thrombectomies or the patients treated for endoleaks, as we have classified, according to that recommended scheme for treatment -- if we look at the percent success, primary success at the time of discharge, it is essentially 97 percent.

That decreases a little bit through the one month and six-month intervals as adverse events occurred, that took away from this primary success determination.

At 12 months, we have, on this basis then, nearly a 90 percent primary success rate.

Now, as I mentioned to you, we would also like to be able to credit the technology for any restoration of patency or treatment of something that can be done by particularly a catheter-based method.

What we have then done on the next slide is to remove those secondary procedures where we were able to do

that successfully.

If we then analyze this data with our primary end points and add in any place we were able to seal an endoleak with a cuff or restore patency to a thrombose limb, we end up with a secondary success rate, at the time of discharge, of 98 percent.

This decreases to 92 percent at the 12-month interval, in the study patients that we have looked at.

Based on the data that we then heard from Dr. Zarins and myself, we feel that this forms the basis for approval of this device.

Compared to a surgery control group, there was comparable mortality, there was a 50 percent reduction in major morbidity.

Even including the learning curve for phase II centers with the device, there is a 98 percent primary technical success rate on an intention to treat basis.

If we look at the last two compilations I showed you, using our primary end points and loss of those as failures, we have a 90 percent primary success rate at one year.

We have a 92 percent secondary success rate at one year, and these are also enhanced by the fact that there are dramatically reduced ICU and hospital stay, and very dramatic, quicker patient recovery that has been

demonstrated by the patient group.

Thank you very much for the chance to present this data.

DR. CURTIS: The FDA presentation now.

AGENDA ITEM: FDA Presentation.

MS. WENTZ: Good afternoon. My name is Catherine Wentz, and i am the lead FDA reviewer for this PMA - the Medtronic AneuRx Stent Graft System for abdominal aortic aneurysms.

The FDA review team for this PMA consisted of nine individuals covering clinical, statistical, animal and in vitro testing.

The AneuRx Stent Graft System is a bifurcated modular system designed for endovascular repair of AAA, with or without iliac involvement.

It is comprised of an aorto-iliac bifurcated component, a contralateral iliac straight component that fits into the aorto-iliac component, a delivery system, and extender cuffs for adjusting the lengths and/or diameters of the device once implanted.

Preclinical testing of the AneuRx Stent Graft System included biocompatability, sterilization, packaging, shelf-life, MRI-compatibility, and animal and in vitro bench studies, to demonstrate reasonable safety prior to use in a

human clinical trial.

In February 1996, reasonable device safety was demonstrated through the preclinical testing, and the sponsor was permitted to initiate its proposed Phase I feasibility study of 40 patients.

In April 1997, the sponsor was then approved for a Phase II clinical trial. Some minor modifications made to the system, such as material changes, design specification changes, were all validated through bench testing, and did not affect the clinical study. All preclinical issues have been addressed.

The clinical data was obtained from a prospective, non-randomized, controlled clinical study.

Prior to entering stent graft patients into the Phase II study, each site was required to enroll five surgical control patients meeting the entrance criteria.

Only after all surgical patients were completed was the site permitted to then enroll patients into the test arm.

For the purpose of the PMA, data presented here represents enrolled Phase II patients through December 7, 1998, with follow up through March 31, 1999.

This data includes 416 test arm patients, and 66 control patients. All statistical issues related to the study have been resolved, with the exception of evidence of

a statistically significant difference noted in the severe adverse event rate between centers.

This point, however, was discussed earlier in the sponsor's presentation.

Safety end points were evaluated by a direct comparison between the surgical and test groups for major morbidity and mortality.

Many efficacy end points, however, were unable to be compared to the surgical cohort because they weren't applicable to the surgical group.

For example, delivery and deployment success, migration and conversion to surgical repair are all end points for device effectiveness and success, but are not applicable to the surgical cohort.

Clinical utility end points, or secondary end points, were compared between the surgical and test groups, and included days of hospitalization, blood loss and quality of life.

Ongoing issues affecting device evaluation for safety and effectiveness include:

The two ruptures that have occurred so far over the course of the study;

2. The high leak rate and determining he clinical significance of these leaks; in other words, their relationship to aneurysm growth and rupture.

To demonstrate this point, I have summarized some data presented to the FDA under the IDE, at the end of December 1998.

This table was designed purely to evaluate a relationship -- if any -- between leaks and aneurysm growth.

I would like to point out, the 116 patients up here are all patients that were followed to one year as of December 1998, and the majority of them, if not all, had both leak and aneurysm growth data.

This table here points out that, out of the 116 patients, 45 had no leak and no growth, 56 did present with a leak some time over the leak, whether it be a late leak or an early leak.

Of those 56 with a leak, 16 had a growth in their aneurysm. Fifteen had no leak, but those 15 did present with a growth.

To continue on with the issues, 3. The apparent difficulty in interpreting the films to determine the origin and significance of a leak -- as is evident from the discrepancy between core lab and hospital findings.

4. Appropriate follow up for patients implanted with the device, with or without a leak.

The primary limitation of this study was the use of a non-randomized, non-concurrent control group.

The next slides will be the questions to the

panel, and I will just review these. They are very familiar, I think.

1. Do the data presented permit assessment of the safety and effectiveness of the device?

2. Does the following indications for use statement adequately define an appropriate population for use based on the data presented?

Indications for Usage. The AneuRx Stent Graft System is indicated for us in patients having infrarenal abdominal aortic or aorto-iliac aneurysms with adequate iliac/femoral access, infrarenal non-aneurysmal neck length of at least one centimeter, and morphology suitable for endovascular repair.

3. Is the proposed contraindication section appropriate? Are there any other contraindications for the use for this device?

Do not use this device in: Patients unable to undergo necessary pre-operative imaging procedures.

Do not use this device in patients with unsuitable aneurysm morphologies and/or excessive angulation or tortuosity of abdominal aorta and/or iliac vessels.

Would it be meaningful and useful to include the following information in the labeling. Do you have suggestions regarding wording and/or placement.

(1) The incidence of endoleaks, and types,

associated with the system;

(2) Due to the absence of long-term data, the device should not be used in healthy, young -- less than 50 years of age -- patients;

(3) The acute symptoms that may be expected if rupture occurs;

(4) A warning regarding the use in patients with impending ruptures;

(5) The possibility of dislodging the device in the case of trauma/falls;

(6) The non-specific relationship between endoleaks, aneurysm growth, and rupture;

(7) A warning regarding the use in patients for whom antiplatelet, anticoagulation therapy, or thrombolytic drugs are contraindicated.

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

6. Have you any other suggestions for the labeling?

7. 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?

8. The safety and effectiveness of endovascular

grafts beyond one year, has not been established. FDA has identified the following long-term issues to be addressed through a post-market study on the original cohort. These issues are:

Identifying the risk factors associated with rupture;

Identifying the risk factors associated with surgical conversion;

Identifying clinically relevant device integrity issues;

Identifying adverse event rates associated with the device and/or procedure.

Are there any additional issues you feel need to be addressed in a long-term study?

What type of data needs to be collected, and for how long, in order to address these issues?

To conclude: FDA is concerned with the two ruptures -- one occurring within 24 hours of implantation, and the second occurring 14 months after implantation -- and the lack of understanding as to why these ruptures occurred.

Characterization of different types and locations of leaks and their clinical significance is unknown. The absence of aneurysm growth at follow-up intervals after implantation of the device doesn't necessarily eliminate rupture potential, since pressure in the aneurysm may cause

rupture.

Also, leaks due to device failure, migration, et cetera, can occur between follow-up intervals and without symptoms, putting the patient at risk for rupture. Thank you.

AGENDA ITEM: Panel Discussion.

DR. CURTIS: The lead reviewers among the panel were Drs. DeWeese and Pentecost. Dr. DeWeese, do you want to start, or Dr. Pentecost, it doesn't matter.

DR. PENTECOST: I am happy to. Thanks very much for the opportunity to review this. I had a couple of concerns about this.

One was the sequential nature of the recruitment of patients into this study, in that five patients had surgery at each institution before the endovascular trial began.

I wondered if those patients were apprised of the fact that a supposedly better treatment was going to be initiated soon, whether or not the data in the surgery patient was prospectively patient, and whether or not they were advised about the fact that if they waited, these elective patients, they would be eligible for different treatment later.

DR. CURTIS: Do you want an answer to that?

DR. PENTECOST: Yes. Should we do these later, these kind of specific things?

DR. CURTIS: No, this is the appropriate time. Otherwise, you are just going to have to ask the question again. If the company will step forward?

MR. MESSENGER: In response to your question, all patients in the study, regardless of the arm they were enrolled in, were informed of the nature of the study that they were participating in.

The surgical patients were aware of the fact that there was another arm of the study that would be enrolled at a later date.

DR. PENTECOST: I noticed also that in two of the sites, there was a year gap between the time that the surgery arm concluded and the interventional arm began.

MR. MESSENGER: The only reason for that is, there were four pilot centers of the 13 that enrolled their surgical patients first and then performed the pilot study, and that pilot study was not included in the phase II results that you see here.

All the other centers, then, were enrolled, and enrolled their patients sequentially from surgery directly into the phase II stent graft arm.

DR. PENTECOST: So, the data that we are presented, then, started -- there was a one-year gap in

which this procedure was done on patients?

MR. MESSENGER: No, the only gap was in the four pilot centers that enrolled their surgical patients first, participated in the pilot study, and then rolled into the phase II study without re-enrolling five other surgical patients.

All the other centers, all the other nine centers, then started when phase II was started, enrolled their five surgical patients and went right into the phase II endovascular enrollment.

DR. PENTECOST: One of the sites, too, was still recruiting surgical patients after they started the endovascular arm.

MR. MESSENGER: No, I don't believe that is correct.

DR. PENTECOST: Site number 7?

MR. MESSENGER: I will check on that, but I don't believe that is correct.

DR. PENTECOST: I also noted that the mortality in women with the stent graft was two-and-a-half times that of men?

MR. MESSENGER: That is true.

DR. PENTECOST: Do you think that will hold up with a larger analysis or a larger number of patients?

MR. MESSENGER: Dr. Zarins, do you want to comment

on that?

DR. ZARINS: In many studies of cardiovascular devices, women are at higher risk for treatment. The exact explanation for that, I don't know.

The one patient who had an early rupture was a female. Whether there are additional factors that we are unaware of, perhaps the smaller arteries that they have, or perhaps they have a more advanced state of disease, it is not clear what the explanation is for why women may have more adverse events than men.

DR. PENTECOST: Another question I have is the way you break out the size of the aneurysms that you follow.

In other words, a patient who has a five millimeter growth in an aneurysm is regarded as no growth, no change, because you couldn't discriminate at the millimeter level.

In the entry criteria, you admit patients that have a four to five centimeter aneurysm that grows half a centimeter within a year, not .4 centimeters, not .6 centimeters.

So, you do make a one millimeter distinction when you are recruiting patients into the study.

MR. MESSENGER: The five centimeter guidance for an aneurysm enlargement was a recommendation made by professional societies that we adopted.

Part of it has to do with the inherent inaccuracy of reading the CTs. Some of it just has to do with the variability of imaging techniques, et cetera.

We also, of course, look at, and do measure, and do record any changes seen in aneurysm diameter change, regardless of whether it is five centimeters or more.

DR. PENTECOST: Do you have the raw data that shows that some patients had a two millimeter growth or a three millimeter growth?

MR. MESSENGER: We collect all data on all patients. What we reported here was just simply broken down and stratified by whether or not it grew by more than five centimeters.

DR. PENTECOST: Finally, the core lab discrepancy here, I think, was significant. For example, it was significant in every stage that you looked at it.

At six months, in your hospital data, two of 54 patients who were considered to have a major endoleak, whereas the core lab described 14 patients, seven times as many, who had a major endoleak. To what do you attribute that?

MR. MESSENGER: Are you referring to the core lab identification of major endoleaks?

DR. PENTECOST: Major endoleaks, seven times more frequently than your hospital data.

MR. MESSENGER: Evaluation of endoleaks is partially subjective. In addition, the evaluation of endoleaks depends on the information available to the person doing the identifying.

The core lab was asked to evaluate CT labs. That is all they were sent. The hospital had access to other imaging modalities to make a decision on how to rate an endoleak.

In addition, they did use slightly different scoring systems for evaluating how serious an endoleak was.

The hospitals used two categories, major and minor. We wanted additional detail for the core lab. So, we asked them to use a four-tier scoring system. So, it is difficult to draw a direct comparison between the reporting criteria.

DR. CURTIS: Excuse me. We are going to have to take a five-minute break now to close the divider behind us.

[Brief recess.]

DR. CURTIS: Would you like to continue with your questioning?

DR. PENTECOST: I am through.

DR. CURTIS: Okay, Dr. DeWeese.

DR. DE WEESE: I thought the application was interesting and well presented. FDA's suggestions were good. There are just a few things I would like to mention.

I notice that there were I guess 10 or 11 people who had to be converted at the time of the first operation.

I assume that this was because of problems with anatomy and so on, but I wonder, also, was it early in the experience and whether things that you later were able to handle you weren't able to handle as well. Is that true or not? When did these 11 early conversions have to be done?

DR. WHITE: I am trying to remember the slides. The one I remember is the technical success slide, where there were 415 patients, 405 were treated.

Of those, only three were converted at the same time, and those were patients who had the device maldeployed and were converted for that reason.

The other seven of those 10, the device was not able to be delivered because it wouldn't go through the access vessels.

So, those were not immediate conversions. In fact, of those seven, only two of them that wanted to have conversion right away had that done, and they were consented for that, because there was suspicion.

The rest were not treated nor had a conversion. They are not part of that data set on conversions.

DR. DE WEESE: My question is, are some of those earlier ones, ones that you later may have been able to get into?

DR. WHITE: Yes, I think so. The learning curve that has been associated with identifying access vessels, particularly heavily-calcified stenotic vessels, as we go on, we all not only extend the criteria as to how to do that, but those would be patients that probably with a bypass graft to the iliac would have access. The answer to your question is yes.

DR. DE WEESE: I noticed that the adverse events of migration and obstruction and integrity of the graft were pretty stable at six and 12 months, and that looks good. I am not sure it will continue.

Rupture was a question I did have a little about. It seems very unusual that someone would rupture the night of their procedure, and the other one was kind of unexpected, too.

At the time of the procedure, you said they were anterior ruptures, which means -- was there bleeding from endoleaks that you could identify at that time in either of those?

DR. WHITE: The patient at 24 hours, that was a patient at our center, so we had first-hand experience with her.

As you saw in the CT, there was very minimal contrast if any that extrapolated.

When we explored that patient, we were actually

able to isolate the aneurysm completely due to the exposure, in deference to what it would look like if you were really treated a ruptured aneurysm.

The only time we encountered bleeding is when we actually uncovered that perforation. So, we were able to, with the aneurysm isolated, essentially with the endoluminal graft, perform that procedure.

Why it ruptured 18 hours afterwards, we don't know. Again, it could have been we produced that injury passing the device or with the guide wire or, again, it was an eminent rupture that we had no symptoms of that 18 hours later went.

DR. DE WEESE: You say there was bleeding from that point of rupture. Where was the bleeding from? The graft had been excluded.

DR. WHITE: When we isolated the aneurysm, as we uncovered it and then pulled the device down and disengaged it, there was a lot of bleeding, because it then communicated with the aortic lumen.

Before we disengaged the device, there was essentially no bleeding and everything was very much controlled.

In fact, going through that exercise, as I mentioned, we probably now, if we saw this again, would transfuse the patient and not convert them.

DR. DE WEESE: I notice that the endoleak problem apparently is still not solved, where you don't know what happens to all of them.

It was interesting that you saw an increase in diameter of four out of the five endoleaks that occurred in patients that were greater than five millimeters at six months, and later you only found two out of four.

Anyway, it looks to me like we still don't know whether endoleaks are routinely involved with increased diameter. Is that still your conclusion? Do you know the answer to this?

DR. WHITE: You are right, we still don't know the answer to that. Part of it relates a little bit to what Dr. Pentecost's comment was.

If you are looking at the same level and quantitative diameter and the sensitivity of the test is five millimeters, and that is the reason that was chosen, then there is, by any study that you look at, subjective evaluator variation.

In fact, looking back at the core lab data, related to patients where we made clinical decisions based on the imaging at the clinical center, that data correlation, in retrospect -- again, I don't have the core data -- there is very good correlation.

Although there is variability in the readings,

which we would expect, when it came to a relevant clinical decision, there is very good agreement between the clinical centers and the core lab.

I think that is something that you have to take into consideration.

DR. DE WEESE: In the early death in hospital, I guess, or within 30 days, there were four with colon ischemia. Any ideas on these? Did you find that they did have mesenteric lesions, or do you do arteriograms before to rule out mesenteric lesions?

DR. ZARINS: There are actually three patients with colon ischemia. One had GI hemorrhage and did not have colon ischemia.

In those three patients, I think that there is a relationship between occlusion of a previously patent inferior mesenteric artery and the risk of colon ischemia.

I think that risk exists, both in the endovascular group as well as in the open surgical groups. We saw in both groups that such an event was possible and, indeed, did happen, two percent in the endovascular group and one percent in the open surgical group.

DR. DE WEESE: There was one aspiration pneumonia, which I am sure was unexpected, because the aspiration problem was much lower in your stent graft group than it was in the control group.

DR. ZARINS: Yes, but it does happen from time to time and some of these patients are quite elderly with multiple comorbidities, and some have gastroesophogeal reflux, and those patients are particularly prone to aspiration.

DR. DE WEESE: I have no other questions.

DR. PENTECOST: Can I just follow up with Mr. Messenger with site 7, the surgery patient recruited after?

You were going to check on that?

MR. MESSENGER: I am sorry, there was one patient. Apparently it was originally consented and the procedure was delayed.

He was consented before the endovascular procedure started. You are correct, and I apologize for that statement. He was consented before, but the actual procedure, the date got delayed, so he was actually treated after the first enrollment of the endovascular arm at that one site.

DR. PENTECOST: But all the patients knew that there was an endovascular trial beginning.

MR. MESSENGER: All the patients were consented and, in their consent, they knew that the endovascular trial was beginning.

DR. CURTIS: Dr. Sethi, do you want to make any comments?

DR. SETHI: That slide you showed about the growth rate, can you put that slide back again? You had a slide on the growth rate of the aneurysm.

MR. MESSENGER: The diameter slide?

DR. SETHI: I don't know the number.

MR. MESSENGER: Fifty-six.

DR. SETHI: The one slide where you showed there were 116 patients. I tried to write this stuff down, but there was a significant number of patients that had --

MR. MESSENGER: That was an FDA slide.

DR. SETHI: Could you show that slide, please?

MR. MESSENGER: I liked that slide. I would like to get a copy of that.

[Slide is shown.]

DR. SETHI: It appears that of the 116 patients, 41 patients had increase in aneurysm size. Is that the way I read it? Maybe you can tell us, how do you read that slide?

MS. WENTZ: The way I did this, this is based on some data that they gave me back in December. I have to qualify this by saying that the leak was defined as any leak over the whole course, between discharge and one year.

It could have been a late leak, it could have been an early leak, it could have resolved itself, but it was a leak that was found any time during that time period.

Now, what was your question again?

DR. SETHI: What do you mean by growth? How big did it become?

MS. WENTZ: The growth was any growth. I can't remember whether the data was given to me at .5 centimeters -- no, it was any growth at all. Again, it could have grown from zero to six and shrunk again. So, it was any growth at all.

This table was designed to demonstrate whether or not there was a relationship with this device between leaks and aneurysm growth, purely for that purpose.

DR. BAILEY: It seems that in this slide there is no category of no leak and same size. I don't see that category displayed.

MS. WENTZ: You are right; it is not there -- it should be under -- there it is, no leak, no growth, the very first.

DR. SETHI: It would have been nice to bring a slide about the significant growth versus minor growth. You don't have that, do you? Five millimeters versus one millimeters. That is what I am looking for.

MS. WENTZ: The analysis that I have up here included five millimeter, one millimeter. The analysis that they did was just five. A comparison of those two, I don't think we have done, because this was my own little chart.

DR. SETHI: That is all, thank you.

DR. CURTIS: Dr. Roberts?

DR. ROBERTS: I guess my question was a little bit of a concern about some of the data. You originally showed that you had completeness of data on 94 percent of the stent graft patients at six months, which was 372. Now, I don't know exactly how you defined that.

You had the AAA diameter change in 150 patients at six months, at six months to one year. So, we are kind of missing a bunch of patients there.

Then you had the endoleak data at the end of a year at 172. So, at least I assume that the endoleak patients are based on CT.

I would assume that if you have 172 patients with endoleak data, you would have 172 patients with diameter data, but we seem to be missing about 20 patients there.

At 172 patients in one year, since you say that you should have 212 patients with completeness of data, we are missing what, about 40 patients there.

At the six-month data, where you say on your completeness of data you should have 372 patients, for endoleaks you have 291, which we are missing not quite 100 but about 80 or so, and on the diameter change at six months, there are 261 patients.

I would think that the diameter and the endoleaks

would be the same. I don't know, maybe you are not getting CT endoleak data on all of them.

I would think that those ought to compare so that at least you don't have all the data, but at least for the data we do have, we ought to be able to compare the diameter with the endoleaks, and that would certainly give us a little bit more information about this.

MR. MESSENGER: Let me address a couple of questions there. First of all, the data on endoleaks and diameter were solely core lab data.

The core lab data, there was approximately an 80 to 90 percent of the hospital data that was obtained was reviewed by the core lab.

So, there was a slight gap in the evaluation by the hospital, because then the films needed to be sent to the core lab.

At any time that you cut the data point off, you are going to lose the tail end of the data before it can be evaluated by the core lab. That is one element of why the data are slightly less.

However, the second issue is, you are mentioning several different criteria for core lab evaluation.

For instance, any evaluation of a diameter change, you have to have a matching CT from where you are starting from to where you are ending at, to make any evaluation of a

diameter change.

If you are talking about an endoleak, all you need is one of those values, so at baseline you just need one value, at six months you just need one value, to establish whether an endoleak was present or not, as read by core lab.

To correlate that to a diameter change, you would have to have a diameter change that you had a valid CT at both one and six months.

Because of that, the diameter changes are based on N values, where there was a valid CT at both ends of the spectrum, for producing that range.

For instance, at one month, CT images aren't required. Color duplex is performed at one month, so there would be no image for a core lab to read at one month, unless for instance, there was a leak or unless the hospital performed a CT and sent that to the core lab.

DR. ROBERTS: I guess I just remain a little bit confused. For example, on pre-discharge -- maybe I am misreading this table, but predischarge on endoleak, you have an N of 354. I am assuming that means 354 CTs?

MR. MESSENGER: Correct.

DR. ROBERTS: Then for predischarge, since presumably these patients had a CT before their -- from predischarge to six months, then, you are saying you only had 261 CTs that were done within that time period?

MR. MESSENGER: At six months? No, I am sorry. That means that for patients who had both an image at baseline and an image at six months that could be compared in such a way to determine diameter change, that was the amount of data that the core lab could assess a diameter change in.

DR. ROBERTS: If you look at, for example, six month data, you have 291 patients that had endoleaks, I would assume that since you are talking about a diameter change on the AAAs from pre-discharge to six months, since presumably there was one done pre-discharge and then, in 291 patients there was one done at six months, you should have at least 291 patients whether or not there was a diameter change. So, we are missing like 30.

The only reason I bring it up, obviously one of the big things that the panel is struggling with, and I guess everybody is struggling with, is the relationship between diameter and endoleaks.

To have 291 patients with data and not be able to sort of correlate those more closely, it is disappointing, because it would be nice for the panel to have that information.

MR. MESSENGER: I think your point is relevant and it also highlights the discussing regarding the core lab.

The core lab data is ultimately very variable, but

the issue is that the clinical decisions and the centers get their CTs and make an evaluation that day and that is always available.

Then the films go to the core lab and come back at some later interval, and are not available during the study to the investigators to make a decision, or know even what the interpretation was, unless there is an endoleak or a discrepancy, and then you get a notice of that.

So, the discrepancy in that data is important, although the investigator data sets are complete.

It is not part of the package, so I would be offering something that you don't have, but I think investigators individually have looked at all of these data in their own centers.

When we meet as an investigator group, we use that to make clinical decisions and recommendations without the core lab data.

Where there are discrepancies or holes, that is one of the problems with the core lab unless, as you had suggested earlier, everybody gets the same data set uniformly, and that is very difficult to do with 100 percent of that data set.

DR. WHITE: The other thing that comes into play is the patient's condition. Some patients may have compromised renal function, cannot have a CT scan with

contrast.

Some of them might have MR imaging. Some of them may have duplex ultrasound imaging, and that sometimes is impacted by the clinical status of the patient.

Those types of studies, of course, would not be read by the core lab, so that complicates some of the features with the core lab.

DR. ROBERTS: Just out of curiosity, maybe you can help me out, what is the core lab data? Is it the endoleak data or is it the diameter change data?

MR. MESSENGER: All the data you have is core lab data.

DR. ROBERTS: If the core lab has 291 endoleaks, and only 261 diameter changes, and it is all core lab --

MR. MESSENGER: Dr. Matsamoto is here from our core lab. Perhaps he can address the question.

DR. MATSAMOTO: I will try to help sort that out. i am Alan Matsamoto. I am board certified in internal medicine and vascular interventional radiology. I am a professor of radiology at the University of Virginia and core lab director for this project.

DR. CURTIS: What is your financial relationship?

DR. MATSAMOTO: I have no financial relationship with Medtronic, other than being the core lab site.

DR. CURTIS: And your expenses were paid here?

DR. MATSAMOTO: Expenses were paid to come here. As we set up the endoleak criteria, there are multiple boxes where we can check off where we think the leak is occurring, whether we think it is proximal, distal, lateral, other.

If we check off more than one box, it may count how they are assessing it as more than one endoleak per patient.

So, when we looked at our actual numbers, we actually had more endoleaks than patients. I think it is because the data gets entered as two endoleaks, because we think we see two sites of leakage.

So, that may be why there are more endoleaks than diameter numbers.

DR. ROBERTS: So, when you have an N, the N is the number of endoleaks, not the number of patients.

DR. MATSAMOTO: I am just speculating on maybe how their data was interpreted, because I know we check off more than one box and that may account for that.

MR. MESSENGER: It is also possible here that some CTs that might have been readable for endoleak were not necessarily readable, for one reason or another, for diameter.

For instance, if there was some kind of severe angulation or something that prevented the diameter from being read, that might account for the 30 reading

difference.

Basically, we record every recording that is sent to us by the core lab, we record, and of course, that has been reported to FDA in our report.

DR. ROBERTS: The only reason I bring it up is because, at least in the table that I have in the FDA panel pack, it only shows 161 patients with diameter change, and here it is like at six months, and here it is 261.

I am sorry. Part of it, I am sure, is just having a lot of different numbers in front of me. On the other hand, it is just a little confusing about why we don't have a little bit better understanding of the percentages here.

DR. CURTIS: Dr. Simmons?

DR. SIMMONS: I don't really have any comments.

DR. CURTIS: Dr. Hartz?

DR. HARTZ: Two or three questions.

Mr. Messenger, the nitenol stent, have you had any patients who have had iliac stenosis deploying this graft, placing this graft, that needed to be ballooned? Anybody with isolated iliac stenosis?

What I am getting at is, is this nitenol really resistant to atherosclerotic stenosis or instanstenosis?

MR. MESSENGER: There were patients who required ballooning prior to the deployment of the device. Is that your question?

DR. HARTZ: Yes. So, you have been able to balloon an iliac, still place this and you have not seen instanstenosis at the site of the iliac lesion? Do you follow?

MR. MESSENGER: Yes, I do follow and yes, that is correct. We have ballooned open iliac vessels, placed the device without any difference in outcome.

DR. HARTZ: Dr. White, the first patient who had the rupture, the 81-year-old who had the rupture, that is fairly easy to understand; frail, elderly, perhaps an impending rupture.

The other patient, though, 12 months out who had a leak, what do we know about that leak? At what rate was his aneurysm growing?

Did he fall at home because he had already ruptured? That is a very disturbing patient to me, to have a 12-month rupture.

DR. WHITE: The data we have available is that, at the time of discharge, there was hospital and discharge endoleak status recorded.

At six months there was a CT scan with an endoleak. At one year, the patient had an ultrasound, did not have a CT scan, and there was no endoleak apparent on that study.

At the 14-month interval in the study you saw,

there was an endoleak. The angulation in that patient and the very short neck, with that patient being entered in the series, is one that now we would not recommend for treatment based on the angulation and the short neck.

It is also one where, if we had had the six-month image now in a patient that we were evaluating, we would actually add an extension or would, in the initial patient, have had a device that has the segmented -- that actually accommodates that curve.

There is a way to treat that, there is a way to recognize it, and it is part of how we teach new physicians to address that or, even in our own practice, evaluate whether somebody is a candidate.

We look specifically at length of neck, angulation, and we use that as a parameter. In this particular patient, that device and that angle with the CT scan would have recommended another intervention. I don't know whether that answers that.

DR. ZARINS: I might add, if I could, to that, that there were two other patients who had similar angulated, short necks, who later did develop proximal endoleaks and were treated with extender cuffs, successfully totally excluding the aneurysm.

I think this is an issue that is recognizable and I think we have learned from that experience about those

short necks and how to treat them.

DR. HARTZ: Those two patients were treated subsequent to that rupture?

DR. ZARINS: I believe they were treated before that rupture, but they presented as a new endoleak. In other words, they had not had an endoleak, had a new endoleak, were investigated, were found to have a short neck, and an extender cuff was placed to seal the endoleak and successfully excluded the aneurysm.

DR. HARTZ: I just have two more things for you, Dr. Zarins. I am still a little concerned about a 24-percent transfusion rate.

I have never understood why patients who have catheter-based procedures ever get transfused. So, what was our threshold, what hematocrit, for transfusing patients in this series?

DR. ZARINS: Those were individual judgements by the treating physician at each individual institution.

I think that the blood loss that occurs, occurs through the introducer sheets, and through valves, and I think that as we get more experience, as we get through the learning curve, I think that in each center we learn how to avoid that blood loss.

I think a lot of that has to do with the fact that this is the initial learning curve in nine out of the 13

centers.

These patients were the very first patients that were done by these centers using this device.

DR. WHITE: If I could add one comment to that, in almost all patients, this also includes autotransfusion. So, this is not all otologous blood transfusion.

Anything the patient received back as a transfusion is counted. The frequency of a patient, at least in our center, who gets blood from the blood bank is -- I can't remember the last time. It is very infrequent.

We routinely now use the autotransfuser to collect any blood and, if there is a significant amount, they get it back.

DR. HARTZ: Then the final thing, is there any instance from any dye or stent that you know of, of paraplegia or impotence.

Can it happen on a vascular basis, not just in this series, but in any? I am thinking of the patient information booklet here.

DR. ZARINS: I know that there is an incidence of paraplegia with open surgical repair. It is extremely rare, but it does happen on occasion. I think it happens so rarely, that we routinely don't think about it in open surgical repair.

I think probably that same very, very remote

possibility would exist, but we have not have that experience.

DR. HARTZ: Is it something that you think should go into the risks and benefits section of the patient information booklet?

DR. ZARINS: I don't think so, since we don't do it for open surgical repair.

DR. CURTIS: Dr. Gilliam?

DR. GILLIAM: I don't have any questions at this point.

DR. CURTIS: Dr. Bailey?

DR. BAILEY: Just a few minor questions. First of all, I again want to thank the FDA statistician, Mr. Dawson, for his summary and basically endorse the points that he raised, mostly centering around the comparative issues in this study, and of course, the non-randomized design.

The issue of whether it is concurrent or recruiting surgical patients first doesn't seem like a real big deal to me. I guess you can see pros and cons to each way of doing it.

Although the surgical mortality of zero is within the expected range, it is almost on the margin of what you might expect.

I wonder if it suggests anything about, that these are perhaps better than average patients coming into this

whole trial. I don't know if you have any thoughts on those results.

DR. ZARINS: I think the good results of the surgical group attests to the high quality of the centers that were chosen for this investigation.

At the same time, if you look at the complication rate in those surgical patients, it is really quite high.

If, for example, a patient had died rather than had a multiple series of complications, that would have been listed in the death rate, rather than having survived a prolonged intensive care unit stay with multiple complications.

So, it is a little bit misleading to think that the surgical patients, in fact, did not have problems because they had a zero mortality rate.

They, in fact, had significantly more complications than the endovascular group.

DR. BAILEY: That actually leads to the other sort of set of questions which are basically around a basic comparison of the morbidity rate, which you analyzed in various ways.

First of all, I guess the first thing is, I don't know if it was predetermined, but did you ever include, in the comparison of the severe adverse treatment-related events mortality as an additional look at the comparison?

DR. ZARINS: We calculated both mortality rates, morbidity rates, severe morbidity rates, and combined morbidity and mortality, and there was no difference in the combined morbidity and mortality rates.

DR. BAILEY: So, what you are saying is that there was a significant difference in the morbidity by itself, but not in the combined morbidity and mortality.

DR. ZARINS: Correct.

DR. BAILEY: The groups seemed fairly comparable. There are a few perhaps not significant differences, but in a small study, one still would be perhaps concerned about them.

I don't know if this was used in the analysis, but the AAA grading was slightly shifted in the stent group toward -- I gather a grade A is less severe?

DR. ZARINS: The only difference in the aneurysm morphology was in the length of the aortic aneurysm in the surgical group.

These patients included aortic aneurysms and aorto-iliac aneurysms. The key feature for the endovascular group was to have a suitable distal common iliac artery in order to anchor the distal portion of the stent.

So, they could not have an iliac aneurysm that extended to include the hypergastric artery.

DR. BAILEY: I am referring to a five-point scale

that you have, A,B,C,D,E.

DR. ZARINS: I am sorry, I guess I don't understand the question, then.

DR. WHITE: I think this is maybe what you are referring to, and it is used as either 1,2,3,4,5 or A,B,C,D,E as a schematic that refers to a certain type of aneurysm.

So, the I, or type A, is the patient who has a proximal and distal neck. Morphologically, the B goes down to the bifurcation, the C extends into the iliacs.

This slide, for the surgery control and stent graft patients, puts in the numbers for each of those classifications as to how one group correlates to the other with regard to that finding.

DR. BAILEY: I believe there were a couple of significant differences there, but in general there is a shift toward better -- I presume A, then, is the simpler lesion.

DR. WHITE: That is correct.

DR. BAILEY: And that is more predominant in the stent group. Was that analyzed as one of the covariates and its effect -- there are a couple of other variables, I guess.

DR. WHITE: Yes, it was taken into consideration in the multivariate analysis.

DR. BAILEY: Right. I guess one point that comes up with a small study is the whole technique for how you adjust for potential confounding variables.

I gather, with a step-wise logistic regression, you just enter variables that come out as winners in the lottery of which variables get into a model for predicting whichever end point.

Another way of approaching it is to say which variables are different between the two treatment groups, and then simply force those variables, or at least look at them one at a time to see what their effect is on the apparent differential in an adjusted outcome rate.

I was wondering if, a, there is any evidence that it is that variable or the variable in previous surgery in the affected area has any bearing on complication rates.

MR. MESSENGER: We did look at those and, in particular, the previous surgery was one which we picked which could have been clinically relevant, that we looked at.

I believe when we showed the slide of how we took into account the risk factors entering the study, that was one of the ones we selected, because of course, it was different; you are right.

DR. BAILEY: It was selected, but then it was eliminated in the step-wise logistic, or was it forced in?

MR. MESSENGER: I think you are exceeding my rather meager knowledge of statistics, so I will invite our statistician up, if you would like to answer the questions.

DR. BLOCK: I am Dan Block. I am a professor of biostatistics at Stanford University. My expenses are paid to attend this meeting, and I have no stock interest in the company.

To answer the question, I will just give one example. That has to do with our major end point of severe treatment-related morbidity, or major morbidity.

There were seven variables -- I don't remember all the names of them -- that were entered in a step-wise, both logistic regression and cost proportional hazards model. I believe the latter is more appropriate because there were differential times to follow up.

The group variable was forced in, as we wanted to know if there was a difference between the surgery group and the treatment group.

In the light of the other variables, the two variables that were predictive were age and previous surgery, both variables different at baseline.

With those two variables in the model, the group effect was significant at the .04 level. Without those variables in, it was not, in favor of the treatment group.

That is, the hazard of major morbidity was

increased in those subjects who were in the surgery arm.

DR. BAILEY: So, I guess my question is, then, or comment is that non-significant variables in a small study might nevertheless have an impact on your estimate of the treatment effect.

DR. BLOCK: Right.

DR. BAILEY: Since it is not a randomized study, they could conceivably be relevant.

DR. BLOCK: Absolutely, and of course, the model might be wrong, too. It is a poor man's way to adjust for that which we wish we wouldn't have to adjust for.

DR. BAILEY: Thanks. I am sorry, one other point. I just wanted to echo, again, Mr. Dawson's point about analyzing the potential heterogeneity across sites, realizing that, again, this is a very difficult thing to do when you have a small N for each site.

Perhaps it is nothing more than recognizing that the apparent confidence intervals that you achieve with just assuming a binomial model are probably -- you are exaggerating the precision with which you -- a patient going to a random center, hopefully they don't go to a random center, but at any rate, to a center, has confidence in what the results are going to be.

DR. BLOCK: Just for your knowledge, in the cases where we had percent data, we did use exact binomial

confidence intervals for the differences. That is, we did not base it on normal approximations.

DR. BAILEY: Right, but I guess my point is not about the normal versus binomial, but rather extrabinomial variation because of real variability across sites and the results.

DR. BLOCK: That is right.

DR. CURTIS: Dr. Crittenden?

DR. CRITTENDEN: I just want to ask the question that I seemed to have missed. Did the same investigator place all the devices at each site?

MR. MESSENGER: The principal investigator was responsible for the implantation at all sites.

DR. CRITTENDEN: Do you think there is a learning curve associated with this? Do you get better vis-a-vis the incidence of endoleaks? That is the point of the question. Do you think there are less endoleaks over time, or did it not seem to make a difference?

MR. MESSENGER: It did not make a major difference. There certainly were some factors that did make a difference and I think I commented on some of those.

We saw a decrease in morbidity, perioperative mortality, procedure times, things which are predictable, that you would encounter on the learning curve.

Although there may have been some decrease in

endoleaks, it was not a significant finding.

DR. CRITTENDEN: Were there any significant differences between the testing centers or investigators?

MR. MESSENGER: Not in terms of endoleak. I think I mentioned three criteria where we did find a statistical difference between centers, but endoleak was not one of them.

DR. CRITTENDEN: Then the last question is, do the surgical investigators believe that there is no association with endoleaks and diameter change of rupture, or is the answer to the question we don't know yet?

DR. WHITE: The scheme that I had shown you, and that we had developed, using the proximal distal junction, those we feel are pressurized leaks, and that those should be treated, the reason for that being that there is a potential for rupture risk.

With the collateral flow or the transgraft flow, we have not been able to establish a correlation with either of those two.

I think not only in this study, but in other studies, it has been the same. So, the answer there is unknown.

DR. ZARINS: I think there is definitely a relationship between the risk of rupture and aneurysm enlargement. I think that is true for patients who are

untreated, as well as patients who are treated with endografts.

I don't know whether there is a relationship between endoleaks and subsequent outcome. There are endoleaks, and what they mean and what the natural history of those endoleaks is, I think, is something that we don't know.

I think that the solid piece of data that at least I like to hang my own hat on is the aneurysm size, and changes in the size of the aneurysm.

I think that, at least to me, will dictate the treatment and the subsequent outcome.

DR. WHITE: If I could just add for one second, we did, during the study, come up with treatment recommendations based on the variables you asked about, location and size of the aneurysm. Those parameters have been used for those secondary interventions that we talked about.

DR. CURTIS: Dr. Perler?

DR. PERLER: Just a couple of points. There has been a lot of discussion of location of leaks. In the panel packet, there was an attempt to quantify the leak. They were defined as minimal, moderate or equivocal.

Maybe I missed it, but it wasn't clear to me. I didn't see how those definitions were arrived at. I guess

it is a qualitative description, but how did you go about stratifying those?

DR. MATSAMOTO: We wanted to try to create some objective criteria of subjective findings. The best we could come up with was a compromise where we stratified in the four classifications, as Mr. Messenger had alluded to.

We said equivocal is, there is something there, we can't tell. Whether it is the quality of the scan, the slice thickness or the absence of a non-contrast scan beforehand, whether we can tell between calcification or some high attenuation versus just a small amount of transgraft leak or a little proximal leak. We call that equivocal.

We call it a minimal leak if you only saw a contrast in the aneurysm sac on the delayed scan, but not in the early pictures of the CT scan.

We called it marked if it was just very obvious that there was contrast in the aneurysm sac during the dynamic phase of the scan.

We left the moderate classification as somewhere between marked and minimal. That is how we classified.

DR. PERLER: I guess the obvious follow-up question is, have you correlated your definition with aneurysm growth or the need to convert, or outcomes related to the risk of rupture?

Someone with a marked leak that wasn't treated and just followed, have they done as well as the patients with minimal or equivocal leaks?

DR. WHITE: We did do -- again, the core data comes after the fact. The clinical centers -- you have to correct me if this is incorrect -- it was a lot or a little. I mean, it was only two designations.

In the patients in which it was proximal, distal or junctional, and there was a lot, that was an intervention recommendation made on the clinical scan decision without the core lab feedback.

When you get, retrospectively, the core lab data, and you look at the correlation between marked and moderate and what we saw as a lot in the clinical centers, there is actually very good correlation.

That is where my comment came from earlier, that if you look at the discrepancy in the overall numbers, it looks like there is a big difference.

If you look at the clinical significance of that difference, there is apparently, at least from our standpoint, none, because where we saw that and made clinical interventions and then looked back and looked for a correlation, the correlation in that marked category was a lot of contrast, and in the ones where we recommended intervention, there was a 90 percent or better correlation

there.

I think that, although it is subjective, and again, in all these imaging studies that are published, there is variability.

The correlation between being able to recognize, at least by our current criteria -- and whether that is right or wrong, I don't know -- but the recommendation to depressurize a big leak, we could have called it on either set of data, and the interventions were successful, based on that.

DR. ZARINS: I think that the situation of having a clinically significant large endoleak appear on an imaging study and have it unrecognized by the treating physicians and having it only subsequently recognized later at a core lab is extremely unlikely.

DR. PERLER: Just the last question, I believe there was -- acknowledging Dr. Roberts' concerns about the varying denominators in some of the end point measurements, there is about a 21 percent aneurysm shrinkage, or decrease in size at, I guess, a year.

I guess my question is, have you been able to correlate a decrease in aneurysm size with other complications such as migration or kinking or I believe there was one migration that was also associated with a leak. Is aneurysm shrinkage worrisome for some of these

other complications?

DR. ZARINS: I don't think so. I think the fact that this is an externally supported device with longitudinal columnar support, I think, maintains the device in good position.

That incident of migration that you referred to was actually predominantly a lateral migration in a short, angulated neck, which then resulted in a proximal endoleak which was corrected with the extender cuff.

That, in fact, was the situation in that one patient who ruptured at 14 months as well. So, I think that there is potential for movement. I think it has to do with the angulation and perhaps the length of the neck and the security of the fixation.

I don't think we have substantial longitudinal movement, and we do see decreases in aneurysm volume and diameter, but not significant migration associated with that.

DR. WHITE: We actually have -- again, this is investigator, our site data, different from what you have in the packet.

What we do know about the morphology is that, as the aneurysms shrink, in this particular device, it accommodates the change by the legs spreading apart and actually shifting with that morphology. That is an

important parameter for long-term function.

The other part is, even if the iliacs do angulate, the external support keeps the device open. So, we have been able to look at morphology changes related to shrinkage, and that is a very important phenomenon, and see how the device conforms. There are patterns that are predictable.

DR. PERLER: Thank you. I have no further questions.

DR. CURTIS: Mr. Jarvis?

MR. JARVIS: No questions.

DR. CURTIS: Mr. Dacey?

DR. DACEY: I have not had the opportunity to look at -- I guess we call it the patient education materials. Acknowledging the general age of the patients in the study, are patients being advised, in the risk/benefits consequences categories about such issues as falls, bumps and so forth, at it might affect -- I can call it the implant -- in some negative way? Are they being told to be more cautious?

MR. MESSENGER: That is not currently in the patient education material. Perhaps you are alluding to the one patient that fell that had the rupture.

There is no known correlation, or we don't know for sure whether that fall had anything to do with the

rupture.

It is an N of one, and in this study it is difficult to make conclusions that that one event is significant enough to change labeling. It is certainly something that we watch for.

MR. DACEY: I would only raise the issue as one for consideration. I can recall, in all my years dealing with bypass patients, the early ones especially were advised not to drive a car for three months because, they certainly could drive, but they didn't want to bump their sternum against the steering wheel.

DR. ZARINS: Perhaps I could amplify that one case with another case. A patient of mine, who I actually saw in the clinic last week, he is six months following stent graft.

He was in a boat and was fishing. A water skier came by, and the boat went on one side and the water skier went on the other side. They caught him right in the abdomen with the ski rope and threw him about 50 feet.

He came in and his stent graft was in perfect condition and he had no endoleak and had suffered no adverse circumstances.

I don't know what the impact of external forces are on the situation in this regard.

DR. WHITE: We actually have recommended to the

patients, and do this routinely, that there are no limitations in their activity.

That has been from day one, when we have done these and patients go home and do whatever they want, at whatever interval they have recovered.

We have taken the other perspective and have not seen anything that would relate to a change, and don't recommend any restrictions.

DR. ROBERTS: I just wanted actually to compliment you on the patient brochure, which I have gone through. Actually, I think it is very good and looks to me like it is pretty well written.

One thing I would suggest, assuming that this is approved, that you would certainly want to indicate to the patient that long-term follow up is necessary, I suspect.

You do say short-term complications include movement of the stent graft away. Yet, what your data show is that at a year is when you are starting to get a larger number, or there is nothing at short term one month, and then at six months it is more, and one year it is still more. Perhaps you want to change that from a short-term complications.

DR. CURTIS: Any other panel member have any questions for the company reps?

DR. PENTECOST: One more. I accept the fact that

you say that there are two categories of endoleaks, the ones that are significant and the ones that aren't.

At six months, the hospital data showed 54 patients with endoleaks. Two of the 54 were regarded as major. That is four percent or so.

At six months, the core lab data showed 74 patients with an endoleak. They were in four different categories, but if you lumped the two most severe or significant ones, there were 58 out of 74, which is 70 percent or something.

That is a huge difference for what seems to be discrepant with what you all are saying.

MR. MESSENGER: Again, you are right, there were two different categories used. I can tell you that, in every case where the hospital reported a major leak, it was either noted as a marked or moderate leak by the core lab. So, there is good correlation in that way.

You are right, the core lab did read them differently and read additional leaks that the hospital did not necessarily call major, to be either moderate or marked.

Again, this is an evaluation. I think Dr. White commented on this, regarding how he would have evaluated a major leak, would have been different from the way the core lab did.

DR. WHITE: The other thing about a six month