5888 '99 JUL -1 A9:5

FOOD AND DRUG ADMINISTRATION

NATIONAL INSTITUTES OF HEALTH

Meeting of:

CIRCULATORY SYSTEM

DEVICES PANEL

June 23, 1999

Gaithersburg Hilton
Gaithersburg
Maryland

Reported By:

CASET Associates
10201 Lee Highway, Suite 160
Fairfax, Virginia 22030
(703) 352-009

TABLE OF CONTENTS

	Page
Call to Order - Dr. Curtis	1
Conflict of Interest Statement - Dr. Stuhlmuller	1
Open Public Hearing	5
- Anthony D. Whittemore, MD	5
- John A. Mannick, MD	8
PREMARKET APPROVAL APPLICATION P990017	
Company Presentation	12
FDA Presentation	58
Panel Discussion	66
Open Public Hearing Patricia Cole	190
Panel Deliberations and Vote	191
Premarket Approval Application P990020	
Company Presentation	204
FDA Presentation	245
Panel Discussion	252
Panel Deliberation and Vote	300

PARTICIPANTS

ANNE B. CURTIS, MD, Chairperson. University of Florida

JOHN E. STUHLMULLER, MD, Executive Secretary. Food and Drug Administration

VOTING MEMBERS:

MICHAEL D. CRITTENDEN, MD, Harvard University

FRANCIS R. GILLIAM, III, MD, Virginia Cardiovascular Specialists

RENEE S. HARTZ, MD, Tulane Medical Center

GULSHAN K. SETHI, MD, University of Arizona

TONY W. SIMMONS, MD, Bowman-Gray School of Medicine

CONSULTANTS APPOINTED TO TEMPORARY VOTING STATUS:

KENT R. BAILEY, PhD, Mayo Clinic

JAMES A. DEWEESE, MD, University of Rochester

MICHAEL J. PENTECOST, MD, Georgetown University Medical Center

BRUCE A. PERLER, MD, Johns Hopkins University

ANNE C. ROBERTS, MC, University of California at San Diego

INDUSTRY REPRESENTATIVE
GARY JARVIS, St. Jude Medical

CONSUMER REPRESENTATIVE:
Robert A. Dacey, Longmont, Colorado

FOOD AND DRUG ADMINISTRATION:
THOMAS J. CALLAHAN, PhD
BETTE L. LEMPERLE, RN, BSN, MPH
MEGAN MOYNAHAN, MS

CATHERINE P. WENTZ, MS
PAUL L. CHANDEYSSON, MD
JOHN DAWSON, MS, JD
GARY KAMER, MS

P R O C E E D I N G S (8:03 a.m.)

AGENDA ITEM: Call to Order.

DR. CURTIS: I am going to call this meeting of the circulatory system devices panel to order.

The first order of business will be the reading of the conflict of interest statement by Dr. Stuhlmuller.

AGENDA ITEM: Conflict of Interest Statement.

DR. STUHLMULLER: The following announcement addresses conflict of interest issues associated with this meeting, and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict exists, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect them or their employer's financial interests.

However, the agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved, is in the best interests of the government.

Therefore, waivers have been granted for Drs. Hartz and Perler for their interest in firms that could

potentially be affected by the panel's recommendations.

Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration other matters regarding Drs. Curtis, Crittenden, Pentecost, Roberts and DeWeese.

Each of these panelists reported interests in firms at issues, but in matters that are not related to today's agenda, or that involve no financial interest.

The agency has determined, therefore, that they may participate fully in all discussions.

In the event that discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firms whose products they may wish to comment upon.

Appointment to temporary voting status. Pursuant to the authority granted under the medical devices advisory committee charter dated October 27, 1990, as amended April

20, 1995, I appoint the following people as voting members of the circulatory system devices panel for this meeting on June 23, 1999.

Drs. Bailey, Deweese, Pentecost, Perler and Roberts. For the record, these people are special government employees, and are consultants to this panel under the medical devices advisory committee.

They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

It is signed David W. Feigel, Jr., MD, director, Center for Devices and Radiological Health, dated 6-21-99.

DR. CURTIS: What I would like to do next is have all the members introduce themselves. I am Anne Curtis. I am from the University of Florida and I am an electrophysiologist there. We can start over here.

MR. JARVIS: Gary Jarvis, industry representative.

MR. DACEY: Robert Dacey, consumer representative.

DR. SETHI: Gulshan Sethi from the University of Arizona, Tucson, cardiac surgery.

DR. PENTECOST: Michael Pentecost, intervention radiologist at Georgetown University.

DR. DE WEESE: Jim DeWeese, cardiac and vascular surgeon emeritus, University of Rochester.

DR. ROBERTS: Anne Roberts, University of

California, San Diego, interventional radiologist.

DR. STUHLMULLER: John Stuhlmuller, medical officer and executive secretary for the panel, with FDA.

DR. SIMMONS: Tony Simmons, Wake Forest University. I am a cardiac electrophysiologist.

DR. HARTZ: Renee Hartz, cardiac surgeon, Tulane University.

DR. GILLIAM: Roosevelt Gilliam with Virginia Cardiovascular Specialists. I am a cardiac electrophysiologist.

DR. BAILEY: Kent Bailey, biostatistician, Mayo Clinic.

DR. CRITTENDEN: Michael Crittenden, cardiac surgeon, West Roxbury VA, Harvard University.

DR. PERLER: Bruce Perler, vascular surgeon, Johns Hopkins.

DR. SAPIRSTEIN: Wolf Sapirstein. I am an associate director of this division of cardiovascular and circulatory devices, and standing in for Dr. Callahan, who is ill.

DR. CURTIS: There is no old business that we need to go over today.

In terms of new business, we have two members of the panel who have completed their terms as voting members. We would like to recognize them today, with a certificate

and a plaque.

We have one for Dr. Gulshan Sethi. (Certificate and plaque awarded.) We also have a certificate and a plaque for Dr. Rosie Gilliam. (Certificate and plaque awarded.)

We will move on now to the open public hearing. There are two speakers who have requested time today. Public speakers are allowed only a 10-minute limit for any comments they would like to make.

AGENDA ITEM: Open Public Hearing.

DR. CURTIS: Our first public speaker is Dr. Anthony Whittemore from the Society for Vascular Surgery. Dr. Whittemore?

STATEMENT OF ANTHONY D. WHITTEMORE, MD, Immediate Past President, North American Chapter, International Society for Vascular Surgery.

DR. WHITTEMORE: Madam Chairperson, members of the panel, my name is Andy Whittemore. My remarks will be brief. I have no slides.

I am the chief medical officer at the Brigham and Women's Hospital in Boston. I am also the chair of vascular surgery at the same institution. I am professor of surgery at Harvard Medical School.

I am here on behalf of the joint societies,

representing the Society for Vascular Surgery and, as its immediate past president, the North American Chapter of the ISCVS as well.

Before I go much further, you should know that I have implanted several of these devices in my own patients at our institution, neither of which are under consideration today.

I have no vested interest in either of these devices, or them as well.

The societies have carefully monitored the development of these devices over the years, and the use of endovascular grafts for the treatment of abdominal aortic and aorto-ileac aneurysms.

In the hands of properly trained and qualified individuals, the use of these grafts appears to be safe, at least in the short term, and efficacious.

However, the long-term efficacy is unknown and careful monitoring of patients who receive this therapy will be essential.

If you decide to recommend approval of the devices under consideration today, we would urge you to include, as part of your recommendation, a requirement that two specific conditions be met.

First, the use of any device should be limited to physicians who have received specialized training in the use

of that specific device.

The surgical techniques and skills that are required to safely and appropriately implant these devices vary from one device to another, such that training in one is not readily transferrable to the use of another. This training ought to be provided at industry expense.

Our second condition states that all procedures performed with endovascular grafts should be entered in some kind of national data registry.

In order to properly monitor and evaluate long-term efficacy of these devices, it is essential that all procedures be consistently and uniformly reported to a single location, such as the registry recently established by our Lifeline Foundation.

A national registry will serve as a rich source of information that will better enable us to answer critical questions regarding the long-term safety and efficacy of this very promising and emerging new technology.

Hopefully, you will agree with us and include these conditions in your recommendations to the agency. We believe they are in the best interests of the patients, as well as manufacturers and physicians, and that their adoption will assure that the devices will be used only by fully-trained and qualified physicians, and that information regarding long-term efficacy will become readily available.

The societies appreciate the opportunity to appear before the panel. Thank you.

DR. CURTIS: A second speaker is Dr. John Mannick from the Lifeline Foundation.

PRESENTATION OF JOHN MANNICK, MD, President, Lifeline Foundation.

DR. MANNICK: Madam Chairman, ladies and gentlemen, my name is John Mannick. I am a professor of surgery at Harvard Medical School and the president of the Lifeline Foundation.

I have no relationship with any of the manufacturers of any of the devices under consideration today.

The Lifeline Foundation, to describe it, is a not-for-profit charitable organizations, established in 1987 under the sponsorship of the two vascular societies, that you have just heard about from Dr. Whittemore -- in other words, the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery. They are the two sponsoring organizations for the foundation.

As a 501(c)(3) organization under the IRS regulations, the foundation is supported by contributions from individual members of the two vascular societies,

corporate sponsors, private foundations whose priorities include medical research, and by individual donors from the lay public.

The foundation, as Dr. Whittemore has already told you, contracted to set up a registry for endovascular grafts used to repair aortic aneurysms.

The foundation is contracted with the New England Research Institutes, for professional services in connection with the development and monitoring of the data in this registry, and for following up the patients who undergo abdominal aortic aneurysm repair with an endovascular graft.

This initiative represents, we think, an important collaboration between device manufacturers, clinical investigators and other scientists, and will be facilitated by representatives of National Heart, Lung and Blood Institute and the FDA.

The registry proposal includes some important scientific and collaborative precedents. Scientifically, this registry will extend the follow-up of patients currently under short-term investigational trials of these devices, and we will also provide follow-up for patients treated with the same devices, or other devices, after FDA approval.

In other words, we propose to capture all of those who are currently under IDEs and those patients after IDEs,

insofar as we are able to do so, and we think we can get most of them, after FDA approval of any devices.

We will have centrally maintained standard protocols for patient follow up, adverse event adjudication and device explant evaluation.

We already have committees in place for adverse events and explain analysis. The adverse events committee is chaired by Dr. DeWeese on this panel.

We will also estimate the survival of patients with different risk profiles, and we will assess the performance of the devices. The end points, of course, the primary end points will be death of the patient from any cause, rupture of the aneurysm and device failure.

We also hope to identify further appropriate studies from analyzing the registry analysis.

Collaboratively, the registry reflects the combined input of clinical investigators, all 10 manufacturers of the devices under consideration today, those who have devices in trial and those proposed to do so, all of whom have decided to sponsor this registry with us.

I think we have everyone on board who has anything to do with making or proposing to make such devices.

We hope that this surveillance will advance scientific knowledge with respect to the benefit to patients of this type of vascular device which we believe probably

has the potential for considerably broader application in the future.

Now only have the manufacturers provided a standard minimum data set from their respective investigational trials and developed, for the first time, a standard explant protocol to be adopted by the industry, they are also committed to fiscal support of this initiative through the Lifeline Foundation, in a hands-off fashion.

So, we believe this registry, in summary, will be an important way to learn what happens in the long run to these devices once they are approved by the FDA, and we will also be able to follow, in the long-term, those patients already under surveillance under IDEs. Thank you very much.

DR. CURTIS: Are there any unscheduled speakers who want to come forward at this time? There will be a second short public hearing later on, near the end of the discussion on the first PMA.

If not, before we get started with the first PMA, I would like to remind the panel about the guidelines for reviewing two PMAs for similar devices with similar indications, because that is what we are going to be doing today.

Each PMA must stand on its own. So, the clinical evaluation of the safety and effectiveness of each device must be made using the clinical data contained with each PMA

based on its intended use.

The evaluation of safety and effectiveness for each device cannot be made based on comparison of clinical data relating one device to the other.

So, these are two separate PMAs. We have to consider them separately, and we should not be discussing data from one at the other hearing later today.

Let's now move on to premarket approval application P990017, Guidant Endovascular Technologies, the EBT Abdominal Aortic Tube Bifurcated Endovascular Grafting System, the company's presentation first.

AGENDA ITEM: Premarket Approval Application P990017. Guidant Endovascular Technologies, EBT Abdominal Aortic Tube Bifurcated Endovascular Grafting System. Company Presentation.

DR. NOVICH: Good morning, Madam Chairperson, members of the panel. I am a member of the board of directors of the Guidant Corporation, sponsor of the PMA that you are considering this morning, and a former deputy commissioner of the Food and Drug Administration.

I am pleased to initiate this presentation, which will describe our minimally invasive endovascular approach for treating grades I and II infrarenal abdominal aortic aneurysms.

The aging of our population and the disproportionate incidence of aortic aneurysms among the elderly, many of whom are burdened with other conditions, making them less than ideal candidates for open surgery, make the development of a minimally invasive procedure particularly important and timely.

As one might expect among patients who can avoid open surgery for this condition, the device provides a number of immediate benefits.

As also expected, the presence of an endovascular prosthesis raises unique issues of efficacy.

On balance, we believe that the benefits of the approach clearly outweigh its risks. The presentations to follow will summarize our data, elaborating on risks as well as benefits, appropriate labeling and informed decision making.

The device studied in the primary clinical trials is the endovascular grafting system, or EGS. It consists of tube and bifurcated endografts and related delivery catheters.

Now, during the EGS trials, a number of investigators often asked if we could design delivery catheters that are easier to use.

In response, Guidant developed a modified catheter to deploy essentially the same endograft, and this has been

named the ANCURE system.

The presentations will begin with the EGS systems, and will finish by showing that the ANCURE delivery catheters are at least as effective as the EGS catheters, and that the immediate benefits established in the EGS clinical study are maintained.

We have three speakers. Dr. Lori Adels of Guidant EVT will describe the device in more detail, tell you how it was designed and tested prior to use, and tell you the objectives of our clinical studies.

Dr. Wesley Moore of UCLA will address safety. He will cover two topics. First is the question of whether the device will reduce adverse events, and the data reveal that it will.

Second, he will describe the benefits derived from limiting physical trauma through the use of a minimally invasive device. EGS endografts were successfully implanted in over 90 percent of patients.

Dr. David Deaton of East Carolina University will address effectiveness of the device. He will describe what happens to the aneurysm sac after implant, and he will describe perigraft flow into the sac and explain its source, rate and consequences.

He will describe postoperative interventions, rates of success over time, and labeling guidelines for

properly following patients after surgery.

Ninety-four percent of patients who had a successful operative implantation and who were followed for at least one year, had a stable endograft and a reduced or same-sized aneurysm.

Dr. Deaton will close by comparing the ANCURE system with the EGS system, regarding their ability to properly place endografts.

With the ANCURE system, endografts were successfully implanted in 95 percent of patients.

Dr. Moore will then return to summarize the risks and benefits of the device, and the rationale for its approval.

This minimally invasive approach offers patients a reasonably safe and effective alternative to the open procedure.

It reduces adverse events over all and provides significant immediate benefits.

The device's performance characteristics are presented clearly in its labeling, so that informed choices can be made, and an extensive training program is planned for all physicians using the device.

Finally, performance will continue to be evaluated in a post-approval study, as is frequently done among emerging and innovative technologies.

Thank you for your attention and I look forward to your deliberations and I would like to now call on Dr. Lori Adels.

DR. ADELS: Thank you, Dr. Novich, Madam Chairman, members of the panel. My name is Lori Adels and I am the vice president of regulatory affairs for Guidant EVT.

Endovascular repair of abdominal aortic aneurysms involve the implantation of a sutureless prosthesis across the aneurysm using a delivery catheter inserted through the femoral artery.

It offers patients and physicians a minimally-invasive alternative to the standard surgical procedure.

My goal today is to describe our design philosophy and to briefly describe the preclinical validation testing that was conducted. I will also describe the clinical study design.

I would like to begin by showing you a brief video that demonstrates the deployment sequence of the bifurcated endograft.

As you can see, the delivery catheter is inserted through the femoral artery into the aorta and the jacket is retracted.

The bifurcated endograft is placed properly in the aorta and the superior attachment system is deployed.

A balloon is used to seat the hooks of the

attachment system into the vessel wall.

Then a tension is taken to the contralateral attachment system, a torque catheter is used to control the deployment of the contralateral attachment system.

Similarly, to the proximal attachment system, a balloon is used to seat the hooks in the iliac wall.

Next, the ipsilateral attachment system is deployed and, again, a balloon is inflated to ensure that the hooks are seated firmly in the vessel wall.

Once the procedure is complete, blood flows through the graft excluding the aneurysm.

In designing the EGS implant, our primary goal was to reproduce the excellent long-term results of woven grafts sewn to the aorta with non-resorbable sutures.

For this reason, a one-piece polyester graft, essentially identical to conventional aortic protheses, was chosen as the base graft.

The primary innovation was directed at endovascular delivery, thus avoiding the trauma and the physiological stress of open aortic surgery, and its associated morbidity.

We used hooks to provide secure fixation through all layers of the vessel wall at each end of the aneurysm, again, to mimic sutures in the surgical procedure.

These areas of the aorta are least likely to be

diseased, and least prone to future aneurysmal degeneration.

We designed self expanding attachment systems that were radially compliant, to accommodate irregularly shaped aortic necks and exert minimum radial force on the artery, to avoid acceleration of the dilating pathophysiology that causes aneurysms.

The attachment systems were designed to be sewn only to the ends of the graft and not throughout its length, so that the implant would be compliant to accommodate the changing shape of the aorta after implantation.

The intent was to duplicate current therapy with a minimally invasive approach, without introduce new graft materials, structures or biomechanical characteristics.

Finally, the entire implant was designed to have sufficient durability for a minimum 15-year implant life.

Both the tube and the bifurcated EGS endograft show the same design, and this slide represents the bifurcated endograft.

The sinusoidal shape of the attachment system, combined with the hooks, forms a circumferential seal similar to the line of sutures, and the fuzzy tufts sewn around the attachment system promote sealing to the vessel wall.

Radio opaque markers along the length of the graft allow for accurate visualization during the endovascular

procedure, and also allow post-operative evaluation of the implant position and integrity.

The limbs of the device are crimped to allow compliance with tortuous anatomy.

Endovascular aneurysm therapy introduces a number of new variables unique to this approach. As with all physiological systems, adaptation to a new environment is inevitable when an acute change is introduced.

This is manifested in the vascular system when, after aneurysm exclusion by the endograft, there are changes in the diameter, length and tortuosity of the aorta.

These images are 3-D reconstructions of spiral CT scans, which demonstrate the aortic remodeling that takes place after endovascular AAA repair.

The advantages of adherence to the proven standard of graft compliance and secure transmural fixation are appreciated when comparing these images.

One day post implant, you can see the large aneurysm sac and the position of the endograft within the aorta.

By 12 months post implant, there has been considerable remodeling of the aneurysm, to which the graft conforms and retains a shape consistent with good flow.

Prior to clinical use, extensive finite element analysis and corrosion fatigue testing were conducted to

ensure the structural integrity of the attachment systems and hooks for at least 15 years.

Extensive in vitro testing was conducted on the graft material, ensuring its durability and comparability to currently marketed woven polyester surgical grafts.

Testing was conducted on all delivery system components, to ensure that the delivery system would withstand the expected in vivo loads, and the implant and delivery catheter passed biocompatability testing, as required by the international standards.

In the chronic animal implants of both the tube and bifurcated devices, there was no evidence of migration, twist or structural failure in any of the implants.

More than 50 bovine deployments, acutely, were conducted to ensure the functionality of the delivery system.

Having validated our design with bench and animal testing, we proceeded to FDA-approved clinical trials.

There were three main objectives in these studies. The first two involved a comparison of the outcomes of the patients treated with the EGS systems to patients treated with the open procedure, which constituted the control group.

The study evaluated a number of device and procedurally-related adverse events, and the immediate

benefits resulting from the minimally invasive procedure.

Third, we wanted to evaluate the devices effectiveness in preventing aneurysmal enlargement and rupture.

For this last analysis, there is no explicit control, because the nature of the minimally invasive procedure is unique. You can think of the open procedure is an implicit control, assuming that it is almost always effective.

To accomplish these objectives, we designed a trial that would provide valid scientific evidence.

To ensure the validity of our results, we initiated a concurrently controlled, prospective, multicenter clinical trial with patient enrollment procedures that were specifically designed to ensure the comparability of the EGS patients and the control.

We recruited a large number of centers to ensure participation by multiple physicians.

We, of course, investigated both tube and bifurcated devices, and enrolled sufficient subjects in each group to achieve good statistical power.

We designed patient follow up programs that were appropriate for the treatment groups.

Finally, we foresaw that EGS endografts may not be successfully implanted in a few patients. Because all

subjects needed aneurysm repair or would not have been considered for inclusion in the trial, we planned that subjects in whom implantation was not successful would immediately undergo conversion to standard AAA repair.

These patients are included in the conservative, intent-to-treat analysis that will be presented by Dr. Moore, to accurately evaluate the overall benefits of the device.

We attempted a randomized trial on an early design device, but randomization was not practical. We found that enrollment was limited, and many of the patients randomized to the control arm declined participation.

We therefore defined a concurrent control group, that had the same inclusion/exclusion criteria as the EGS subjects, except for specific vascular dimensions critical to successful endovascular repair.

Specifically, while control subjects were required to have sufficient healthy tissue above the aneurysm to perform the standard repair using an infrarenal clamp, they did not have to have the full one-and-a-half centimeters of proximal net necessary for necessary endovascular placement.

Similarly, while control patients were excluded if they had significant femoral or iliac occlusive disease, they were not required to have vessels large enough to accommodate the delivery catheter.

In this way, all patients eligible to be treated with the device could be treated, and controls knew that they were ineligible for treatment with this endovascular device.

This concurrent control approach was developed in agreement with FDA, and the protocol was approved under the IDE prior to subject enrollment.

The tube and bifurcated studies were designed to provide good statistical power when evaluating the differences in adverse events.

The protocol required that a minimum of 83 subjects in each of the three treatment groups be followed for at least one year.

The PMA includes data on 118 tube, 88 control and 162 bifurcated patients.

We enrolled these 22 centers. All were chosen for their expertise in standard surgical AAA repair, thus ensuring a good result for the standard AAA repair in the control group.

As this was the first clinical study of a AAA device to be initiated in the United States, none of these centers were experienced in endovascular AAA repair.

Three of our investigators are here today, Dr. Wesley Moore from UCLA, Dr. David Deaton from East Carolina University, and Dr. Barry Katzen from the Miami

Vascular Institute.

Drs. Moore and Deaton will present the clinical data as part of this presentation, and all three physicians will be available during the Q&A session.

The standard follow up schema required that the patient be evaluated at discharge and regular intervals thereafter.

Contrast enhanced CT scans and abdominal ultrasounds were required to evaluate the performance of the implant, including the presence of perigraft flow and the changes in aneurysm size.

If subjects were found to have perigraft flow at discharge, they had an additional visit at three months, and if the flow persisted, they continued to be evaluated every six months.

Abdominal x-rays were used to evaluate implant position and integrity, and bilateral ADIs and physical exams were used to assess graft patency and adverse events.

Control subjects did not require the same rigorous schedule of CT scans, ultrasounds and x-rays, because there are no metallic components that can be identified on x-ray in a surgical graft, and as part of the open surgery, the aneurysm sac has been surgically reduced and the branch vessels ligated, eliminating the possibility of perigraft flow.

Before Dr. Moore presents the clinical findings, I want to describe the baseline characteristics of the two bifurcated and control groups which resulted from our enrollment program.

Overall, we believe that the EGS and control populations provide for a valid comparison of outcomes, particularly when statistical techniques are used to account for any differences that do exist.

There is a remarkable similarity between the treatment groups. The EGS and controls were the same with regard to race, height, weight and body mass index.

They differ with respect to gender and age. The age difference between the tube and control groups was statistically significant. However, it is just over two years and probably not clinically significant.

The majority of patients in all groups are men, but the proportion was higher in the EGS groups. This was statistically significant for the bifurcated group when compared to the controls.

This is not unexpected, since women tend to have smaller vasculature than men and, therefore, fewer women met the anatomical inclusion criteria for endovascular repair. This similarity is also evidence when comparing medical histories.

When comparing such a long list of preexisting

conditions, it is not unexpected to see some difference between treatment groups based on chance alone and, in fact, some differences between the test and control groups did exist.

There was less hypertension and smoking in the treatment groups and more arrhythmias.

These differences were taken into account when analyzing the study results, and the benefits of the device were shown, even after adjusting for these differences.

There were, of course, differences in vascular measurement based on the study design and the inclusion/exclusion criteria.

During the design of the clinical trial, we met closely with our physician advisory board, who assured us that these differences in vascular dimensions would not affect surgical outcomes.

While the mean aneurysm size for the treatment group was statistically significantly smaller than the control size, aneurysm size distribution curves indicated that the populations were, in fact, similar.

I would now like to introduce Dr. Wesley Moore of UCLA, who will begin the presentation of the clinical data.

DR. MOORE: Thank you, Dr. Adels. Madam Chairman, distinguished panel members, good morning. My name is Wesley Moore. I am a professor of surgery at UCLA Medical

Center.

I am board certified in vascular surgery. I have more than 30 years experience in vascular surgery, and I am pleased to be here with you this morning. I hope that my presentation will be helpful to you in your deliberations.

DR. CURTIS: Could you please state what your financial interest is in the product?

DR. MOORE: Yes. I was an investigator in the clinical trials of both the EGS and ANCURE systems. Guidant EVT has paid my expenses to be here, but I have no financial interest in Guidant EVT or in the outcome of this meeting.

During the next few minutes, I will discuss two safety-related findings, first, that the EGS system reduces certain adverse events when compared with the conventional aneurysm repair.

Second, the EGS system provides immediate patient benefits, as a result of reduced physical trauma that would be an ordinary consequence to the conventional aneurysm repair.

Because the EGS system is minimally invasive, we expected to see these results in comparison to the open control group.

Finally, all data were analyzed on an attempt-to-treat basis. Therefore, all analysis of EGS patients include patients that were not successfully implanted with

the device.

This slide summarizes the experience in the two groups. One hundred fifty-three patients were treated with the tube graft, 268 patients were treated with the bifurcated graft.

Successful implantation of the tube graft amounted to 92.2 percent and 90.3 percent in the bifurcated group.

I would like to just make a comment concerning conversion. Again, all these candidates were surgical candidates at the time we brought them to the operating room, and our contractual agreement between patient and physician is, when they left the operating room, they were going to have their aneurysm repaired.

If we were not successful in repairing them by endovascular means, indeed, we were committed to go ahead with conventional repair. Therefore, this accounts for the conversions.

The majority of the conversions were related to difficulties in access of the artery. When we speak of the next few slides, we will be talking about three groups, those that were implanted, those that were converted, and then the entire group in an intent-to-treat protocol.

Let's take a look for a moment at the death data. We are going to look, first of all, at the 30-day mortality rate.

The 30-day mortality rate in the tube group was zero. The 30-day mortality in the bifurcated group was 2.6 percent, and the 30-day mortality rate in the control group was a remarkably low 2.7 percent, essentially identical between the two, and being remarkably low, and certainly lower than one has seen in previously-reported multi-institutional studies, suggesting that we chose very well as far as the centers that were participating in the study.

We will now look at all the deaths that occurred during the conduct of the study. This includes both the 30-day mortality as well as any late deaths.

We can see that the most common cause of death in all the groups treated were cardiovascular, usually cardiac. Respiratory deaths accounted for another category, and then finally, other causes including cancer.

The three late mortality rates, 9.2 percent in the tube, 7.8 percent in the bifurcated, and 6.3 percent in the control, while seemingly different, are in fact, not statistically significantly different.

What appears to be a higher rate in the tube group can well be accounted for by the high incidence of late cancer death in that particular group of patients.

I would like to point out that none of these patients died from a ruptured abdominal aortic aneurysm and, in fact, no ruptured aneurysms occurred in this series.

In looking at the significant complications that can occur with any of these devices or in the control group, we constructed what is called an IDE composite safety measure, in consult and consultation with the FDA.

Therefore, if a patient exhibited one of the following, such as death, a major cardiac complication, a major respiratory complication, renal bleeding, bowel vascular wounded or ischemic, this was counted as having experienced an adverse event and would be counted against the safety of that particular procedure.

This histogram shows the incidence of these events as a percentage of patients in the group. You can see that the control group has the highest incidence of these adverse events, followed by the bifurcated and the tube grafts. Both of these did significantly better than the control.

It is important to point out that, in the intent-to-treat protocol, the conversions in the endografts are included in the adverse event categories.

Since we know that conversions do somewhat worse than those patients who were treated primarily with either procedure, this is going to have an adverse effect on the adverse event incidence.

In spite of that, this is still considerably less -- essentially half -- of the control group.

If we look at selected adverse events, we see some

differences. For example, with respect to the cardiac complications, the tube and the bifurcated experimental groups have statistically fewer events than the control. This is also true for respiratory events.

This is, not surprisingly, true for the incidence of severe bleeding, which is markedly reduced in the experimental when compared to the control groups.

There is a statistically significant improvement in the bowel complications between the experimental, particularly the bifurcated group versus the control.

I should state parenthetically that no patient in any group experienced colon necrosis requiring colectomy. The bowel complications that we are talking about are things such as prolonged ileus requiring intubation.

There is a statistically significant increase in renal insufficiency in the bifurcated group. We assume that that is related to the use of iodinated contrast material during the operative procedure.

However, in going back and looking at the analysis in detail, if you correct for preexisting renal insufficiency in this patient population, that difference disappears.

The final area is the issue of arterial trauma, in the form of injury to the femoral or the external iliac artery, most often requiring a simple suture.

We report no instance of arterial trauma in the control group, because that is generally considered to be a part and parcel of the operative procedure and is not recorded as such.

For example, if one is doing a conventional aneurysm repair and you have difficulty with the proximal suture line and have to put in some plungets, that is simply part of the procedure and is not recorded as arterial trauma.

Likewise, if you are doing an endarterectomy in the area of bifurcation and you have an end point problem that requires correction, that is simply a part of the procedure, and not recorded as a traumatic event.

This is a Kaplan Meier representation of the IDE composite safety measure. It indicates that the major drop occurs within the first 30 days.

This is the time when we would expect this to be related to either the procedure or the device. We see that these lines now become relatively parallel, indicating that there is no further deterioration as a function of time.

With respect to the immediate benefits, we find that the patients undergoing vascular repair with the bifurcated graft have a statistically significantly shorter interval than patients undergoing conventional repair in the control group.

While there is a tendency for a shorter time with the tube, this difference did not achieve statistical significance.

There is also an anesthetic benefit. Several investigators in the series chose to do these implants using regional anesthesia.

That is an option that is available in the experimental group, but it is certainly not available in the control group. The control group obviously requires a general anesthetic to be able to complete the operation.

Operative blood loss indicates a dramatic reduction in the experimental groups compared to the control group, being an average of 800 mls interoperatively in the control, dropping down to 300 or 200 in the experimental implants.

Likewise, there is a marked reduction in intensive care unit stay in the experimental groups compared with the control.

Again, this includes the intent-to-treat patients. Therefore, those patients that were converted obviously went to an intensive care unit, whereas rather few of the patients who underwent implants required intensive care monitoring.

Finally, this also translates into a shorter hospital stay. Again, we can see the marked reduction in

the bifurcated tube group.

Once again, this also, in the intent-to-treat analysis, includes the conversions. These are the median number of days of the stay, two days for the tube, three days or the bifurcated, six days for the control.

So, as you can see where there has been a significant conservation of precious resources that enure to the benefit of the experimental group when compared with the control.

We have also shown that the experimental group has a marked reduction in adverse consequences, as measured by the IDE composite safety measure.

I now would like to turn the podium over to my colleague, Dr. Deaton, who will discuss effectiveness, as well as present the data on the ANCURE system.

DR. DEATON: Thank you, Dr. Moore, and good morning, Madam Chairman and members of the panel. I am David Deaton. I am a board certified vascular surgeon with 14 years experience in the diagnosis and treatment of patients with vascular disease.

I was the primary investigator at East Carolina University during these clinical trials. Guidant Corporation paid my expenses to this meeting, and I have provided consultative services to the company, for which I have been paid.

I own a small number of shares of the Guidant Corporation, which I purchased on the open market.

In the following slides, I will describe the findings attributable to implant performance in patients actually implanted with the EGS device.

The ultimate measures of implant effectiveness are the absence of aneurysm rupture or aneurysm enlargement, requiring conversion to open surgery.

This reflects the ability of the prosthesis to alter the natural history of the aneurysm by preventing further aneurysm growth and rupture.

Late conversion is invariably related to diagnosis of an enlarging aneurysm. Conversion, as a result of aneurysm enlargement, can present as either a symptomatic patient requiring emergency treatment, or as an asymptomatic finding on routine follow up, amendable to elective intervention.

This distinction is important in considering the safety of the device.

Measures of implant performance are important for determining the potential for graft failure. As with the principal measures of implant effectiveness, the incident of emergent or catastrophic presentation is also important.

While some of these measures are unique to endovascular grafting, others have clear correlates in open

surgical grafting.

Perigraft flow, often referred to as endoleak, is liquid blood in the aneurysm sac. While this can represent the continued direct communication to the aorta, it can also represent low pressure collateral flow with an entirely different hemodynamic profile.

Perigraft flow was recorded if any study provided that finding, to provide a "worst case representation" of this variable.

The data will show that perigraft flow is not synonymous with aneurysm growth. Graft patency or limb flow is very important, but unlikely to present in a life-threatening manner.

As will be discussed, this performance variable is readily amenable to simple techniques that very easily avoid occurrence or recurrence.

Graft migration is probably analogous to pseudoaneurysm formation and open procedures. Re-establishment of aortic pressure in an aneurysm can occur without evidence of perigraft flow, and is probably more likely to do so in this circumstance. Migrations have the potential to present in a catastrophic manner.

Graft limitation or rupture and aortic perforation are also serious complication that can present with exsanguinating hemorrhage and may be equivalent to aneurysm

rupture.

Attachment system integrity is critical to long-term graft effectiveness. In these studies, a core radiologic interpretation facility -- the Cleveland Clinic Core Lab -- evaluated these and other measures of device performance to ensure consistent, standardized interpretations of diagnostic tests.

The fate of patients with respect to the hard end points of rupture and aneurysm growth, is probably the single most important variable in assessing graft effectiveness.

Since the inception of these studies in 1995, there are no reports of aneurysm rupture.

A total of three patients, less than one percent, were converted to an open surgical procedure during follow up, with a diagnosis of continued aneurysm growth.

The determination that conversion was necessary was made by the treating physician in each of these cases, based on their own observations.

Patients requiring conversion were asymptomatic and the diagnoses were made during routine follow up. Conversions were elected surgical procedures, and there was no mortality.

Complications in hospital recovery were consistent with elective primary aortic surgery.

Perigraft flow is our next topic, and is significant only as it relates to aneurysm growth. Perigraft flow will be discussed next in that context.

Endoleak, or perigraft flow, is a measure of whether or not any liquid blood remains in the aneurysm sac after endovascular exclusion.

Its imaging similarity to an untreated aneurysm led to an early assumption that this finding was equivalent to ineffective aneurysm exclusion.

Because it is a finding uniquely associated with the endovascular technique of aneurysm repair, it has little corollary in prior surgical experience.

It has become clear with time that endoleak is present for a variety of fundamentally different reasons, which may have distinctly different prognostic implications for graft effectiveness.

Dr. Jeff White described the most widely accepted classification of endoleak in 1998 in the Journal of Endovascular Surgery.

Type I, or attachment endoleaks, are a result of an incompetent seal at one of the graft attachment sites. This represents a direct communication of the aneurysm sac to aortic pressure.

This type of endoleak is generally felt to be graft related.

Type II, or branch endoleak, represent aneurysm tributary flow. Here, one tributary reverses flow, or back bleeds, to provide inflow to another tributary with a lesser back pressure across the aneurysm sac. These tributaries are thus functioning as a collateral circuit.

The hemodynamics of a collateral circuit are variable, but generally have a markedly reduced pulse wave form and mean pressure.

Branch endoleaks do not represent a direct communication to the aortic pressure. They are technique related, since tributaries are not addressed as they are in open surgery.

Type III and IV endoleaks did not occur in these studies, but are listed here for completeness. Type III endoleaks represent incompetence in the body of the graft as a result of a perforation from stent fabric chafing or modular dysjunction.

Like type I, this represents a direct communication of the aneurysm sac to the aorta and is considered graft related.

The type IV category is used to described the phenomenon where contrast can be seen to generally emanate from the graft, and is felt to be a result of porosity or suture perforation. This, too, is graft related.

This slide characterizes the incidence of

attachment or Type I endoleak, and branch-related or type II endoleak. For the purposes of analysis, any endoleak whose origin was indeterminant, was categorized as attachment related, to ensure the most conservative interpretation.

Perigraft flow was reported by the core lab, if either CT or ultrasound evidence of perigraft flow was detected to maximize the finding of perigraft flow.

Type III and IV perigraft flow did not occur, as they largely related to biomechanical characteristics not found in this endovascular or conventional graft.

The bar chart illustrates that, for both tube and bifurcated grafts, branch perigraft flow represents the large majority of endoleaks.

Only 5.7 and 4.6 percent of patients with tube and bifurcated prosthesis respectively, were categorized as having attachment or indeterminant perigraft flow at 12 months. Nearly half of these are actually indeterminant.

Branch endoleak is present in roughly one third of both groups initially, declining to approximately 20 to 25 percent at one year.

The fundamental nature of branch endoleak would suggest its resolution over time. Tributary vessels, deprived of aortic inflow, adapt to a new flow rate. Those with lower flow should shrink in response to diminished flow.

If they have a higher flow rate, this would suggest a marked pressure gradient from one tributary to the next, and a diminished main pressure.

The detection, classification and characterization of perigraft flow, and its implications for the prognosis of effective aneurysm exclusion, are unclear. For that reason, the relationship of these findings to aneurysm size was examined.

This table describes the relationship of perigraft flow with aneurysm diameter. A chance of five millimeters in greatest transverse dimensions was chosen by the FDA as a standard for detection.

In the II group, five of six patients with an increased aneurysm diameter had perigraft flow.

Only three patients in the bifurcated group had an increase in diameter, and all had perigraft flow.

While the finding of perigraft flow was usually positive in a patient with aneurysm enlargement, the vast majority -- nearly 90 percent of patients with perigraft flow -- showed no evidence of aneurysm enlargement.

One patient demonstrated aneurysm enlargement without perigraft flow. This finding has been reported in other series, and underlines the reliability of perigraft flow as a positive or negative predictor of aneurysm exclusion.

While the presence of perigraft flow is not a strong predictor of aneurysm growth, it demands careful attention to aneurysm diameter.

As a finding unique to endovascular aneurysm therapy, much remains to be learned about perigraft flow. Accurate classification will allow a better understanding of prognostic implications with this and other devices.

What is clear from these data is that the finding of perigraft flow has little predictive value, and no patient had any adverse outcome from the observation of this finding, in the absence of aneurysm growth.

All patients require an observation of their aneurysm diameter and follow up, regardless of the presence or absence of perigraft flow.

The issue of careful observation of patients with perigraft flow is addressed in the labeling of the device.

In contrast to perigraft flow, aneurysm enlargement is an unequivocal indication of inadequate aneurysm exclusion.

Only six tube and three bifurcated patients had increased aneurysm diameter at 12 months. A progressively larger percentage of patients had decreased aneurysm diameter during follow-up, indicating that, over time, more aneurysms shrink.

Another important quality of graft follow up is

the ability to detect inadequate aneurysm exclusion prospectively, and to address such failures in an effective fashion and at minimal risk.

Again, no patient in these studies had rupture of their aneurysm or any symptoms from the aneurysm requiring emergent intervention.

All size increases were detected prospectively in asymptomatic patients. All size increases were detected by the treating physician without assistance from the core lab.

Specifically, no mortality was incurred in patients in whom an enlarging aneurysm was detected.

The primary physiologic function of an aortic prosthesis is as a conduit for blood flow. In traditional aneurysm surgery, the surgeon can ensure that the implant has a smooth, unrestricted course for optimal function.

A variety of adjunctive maneuvers are used in open aneurysm surgery and other vascular reconstructive procedures to assure this result.

In contrast, the endovascular graft is placed within the native anatomy. Guidant specifically designed the GGF graft to be as identical as possible to conventional grafts, to lessen its exposure to unintended consequences of departures from the biomechanical qualities of conventional grafts.

This design retains qualities that allow it to

withstand the dynamic and the pulsatile nature of the aortic environment, to adapt to arterial remodeling, and to conform to tortuous anatomy.

These same qualities also lend susceptibility to reduced limb flow in the iliac limbs. Tortuosity, native stenotic disease and vessel graft-size mismatch can all impair flow in a fabric prosthetic constrained to the iliac artery.

Fortunately, available diagnostic techniques, such as IVIS, pressure measurements and arteriography identify reduced limb flow.

Routine therapeutic procedures quickly and definitively relieved any real or perceived threat to iliac limb patency in the vast majority of patients. Most were treated with either balloon angioplasty or iliac stent placement.

These techniques allow the physician to optimize the configuration of the graft limbs, and relieve any obstruction to flow within the iliac arteries, in much the same way as when used primarily.

This table describes the types and frequency of interventions undertaken to address the diagnosis of reduced limb flow.

The impact of native iliac pathology on limb flow was better appreciated by investigators as the study

progressed.

Interventions were taken at the time of graft implantation, progressively lessening the incidence of post-procedural intervention.

Patients presenting with limb flow problems never exhibited limb threatening ischemia or tissue loss. Open surgical procedures were rare, and those required were minor and did not require aortic cross clamp.

Ninety-seven percent of the patients were treated successfully. When treatment was not successful, there was adequate collateral circulation present to prevent tissue loss or critical ischemia.

Radial support in the form of mechanical stents were applied only when necessary in a target location of the native iliac anatomy.

Compliance of the graft in the native aorta was maintained. All stents placed were successful in preventing further limb flow reductions.

There was never a requirement for further intervention or any late complication related to stent use.

In summary, the majority of patients did not require any intervention for iliac limb flow. Of the minority that did, 97 percent were treated successfully, none suffered debilitating ischemia or tissue loss.

The other measures of graft performance are listed

on this slide. Two cases of graft migration, representing one half of one percent of patients, were recorded.

One case was a tube graft mispositioned at the original procedure. Placing a second endograft within the first successfully treated this.

The second case was the result of placing the proximal attachment system in a flared aortic neck, which continued to expand in diameter and shorten over time.

This patient has had no perigraft flow or aneurysm enlargement and continues to be followed closely.

There were no cases of graft dilatation or rupture, graft extrusion or erosion or loss of attachment system integrity reported in these clinical studies.

The adherence of the endograft design to the features of conventional surgical grafts, coupled with the endovascular position of the graft, allowed it to enjoy a remarkable record of safety and efficacy with respect to these measures of graft performance.

In summary, all objectives of the EGS study were met. As Dr. Moore described, the EGS system substantially reduced major complications, even when controlling for preoperative characteristics.

Patients treated with the EGS device required fewer operative and post-operative resources. They lost less blood, had fewer and shorter ICU stays, and were

discharged home earlier than control subjects by a wide margin.

Adjunctive procedures were generally minor and definitive. There were no serious graft complications that could not be detected prospectively and treated in an elective manner.

The implant prevent aneurysmal enlargement in greater than 95 percent of patients.

Finally, there was no report of rupture or any mortality related to the aneurysm or the graft during follow up since the inception of these studies in 1995.

It is difficult to adequately describe the full impact that a minimally invasive approach to aneurysm repair has on the lifestyle of a typically elderly patient, both physically and mentally.

They and their families can anticipate treatment of a life threatening condition without the additional anxiety associated with a major open surgical procedure.

They recover at home without serious physical impediments or the necessity of relying on family or other resources for maintenance of their daily activities.

At this point, I would like to switch and describe the ANCURE delivery system. This is a new, more intuitive, delivery catheter that delivers essentially the same graft as was delivered with the EGS system.

The ANCURE system incorporates a new delivery catheter system and uses a very slightly modified endograft. This study was designed only to show equivalence to EGS with respect to delivery and short-term benefits.

Comparison end points will demonstrate that ANCURE performance is at least equivalent to EGS performance.

The ANCURE delivery catheter was developed based on investigator suggestions requesting a more intuitive delivery catheter design that would provide reliable and accurate endograft implantation.

The functions of the two handles on the EGS system were combined into a single handle for ANCURE.

The updated delivery catheter design is intended to be more intuitive to use, and more ergonomic, while maintaining the same basic principles of deployment as EGS, and essentially the same implant design.

As was done with the EGS system, design validations were done prior to embarking on the clinical trials.

The new features of the delivery system were tested for their ability to withstand expected in vivo loads.

A few new materials in the delivery system were used, and all were tested to ensure biocompatability.

Acute deployments in bovine were conducted to

determine technical performance.

Because the fundamental design of the endograft is unchanged, the study focused on delivery catheter performance.

Specifically, the primary study objective was to determine if implant success with ANCURE was at least equivalent to implant success with EGS.

The bifurcated EGS group was used as the control group because a preponderance of bifurcated enrollment was anticipated.

Short-term benefits of the ANCURE procedure were also assessed and compared to EGS.

The follow-up interval for evaluating implant success rate was 30 days. This is adequate, since the implant was the same, and long-term outcomes are unlikely to be impacted by the delivery system if short-term results are equivalent.

The ANCURE and EGS studies had equivalent inclusion and exclusion criteria and 30-day outcome measures.

Many of the same centers that participated in the EGS trial also participated in the ANCURE trial. Eleven of the 16 participating centers were experienced EGS investigators and five centers were new.

We compared demographics, medical history and

vascular characteristics for ANCURE and EGS subject populations and found them to be comparable.

This is expected, given the consistence of the inclusion/exclusion criteria.

The rate of successful implantation with the ANCURE system is at least equivalent to the EGS system, and may, in fact, be better.

These findings remain, whether analysis included all ANCURE subjects or only ANCURE bifurcated subjects. An updated data set, including 242 patients treated with the ANCURE delivery system, demonstrated 95 percent technical success in this larger population of subjects.

This represents a reduction in the rate of conversion of one-half compared to EGS. This analysis gives us a reliable estimate of the deployment success that will be experienced in commercial distribution.

The complication rates for ANCURE and EGS bifurcated subjects are similar, with the exception of respiratory. Respiratory complications might actually be lower in ANCURE subjects.

Overall, these data demonstrate that ANCURE systems are at least as safe as EGS systems. Subjects did not experience a high rate of complications during the 30-day post-operative period.

The immediate benefits of the EGS system were

maintained with ANCURE. The ability to use regional anesthesia was comparable. The need for ICU stay was actually lower. Operative blood loss was similar, and hospital stay was reduced by one day.

While there was an increase in operative time, it occurred in a setting of better technical success and decreased hospital stay.

This chart shows a comparison of physician assessments of perigraft flow for ANCURE and EGS bifurcated grafts.

This is different from the data presented earlier for EGS bifurcated subjects, which was the result of poor lab assessment.

This is as expected, given that there have been only minor modifications to the implant, that perigraft flow rates are comparable.

The core lab generally reports a higher rate of perigraft flow, as expected, given the conservative and sensitive criteria used.

The intention of this comparison was to show that rates of perigraft flow for ANCURE and EGS groups are at least equivalent. Comparisons of physician assessments are a valid way to determine this.

FDA has requested core lab assessment of ANCURE data, and this has been submitted.

Core lab assessments of ANCURE perigraft flow are similar to those reported for EGS.

ANCURE and EGS groups were similar in the use of adjunctive procedures to prevent or treat evidence of reduced limb flow.

The types of procedures were also similar, with endovascular techniques predominant.

The vast majority of these procedures were performed in conjunction with the implantation, and not post-operatively.

Interventions were successful in 97 percent of ANCURE patients treated. As with EGS, there have been no reports of limb loss or limb-threatening ischemia due to reduced limb flow, in ANCURE subjects.

In summary, the ANCURE system performance is at least equivalent to the EGS system, and technical success was achieved in 95 percent.

The investigators believe that the new system is more intuitive and ergonomic and, therefore, easier to learn how to use.

Thank you, and I would now like to turn the presentation back to Dr. Moore, who will provide summary and conclusions.

DR. MOORE: Based upon the investigational experiences documented in the PMA application, and

summarized in our presentation today, I believe that several conclusions are warranted.

With regard to patient benefits, it must be kept in mind that we are dealing with an older patient population, having significant underlying comorbidity.

For example, the average age of patients in this study was approximately 72, the majority of patients had coronary artery disease and hypertension.

Almost 90 percent were smokers, and there was a high incidence of chronic obstructive pulmonary disease.

In spite of this, we were able to achieve significantly shorter hospital stays with endovascular repair as compared with the control group.

This benefit also extends to post-hospital discharge, where patients, having undergone repair by endovascular means, have a quicker return to their pretreatment state, as they have only two small femoral incisions to recover from, as opposed to a large abdominal incision with its incumbent trauma to the associated viscera.

Endovascular repair is also conserving of important resources. There were significantly fewer ICU stay days, and a marked reduction in operative blood loss. These reductions translate into savings for patients and hospitals.

A reduction in blood loss means that fewer patients will require transfusion, and avoid the attendant risks associated with blood replacement.

It is also important to note that the option of using regional anesthesia exists with endovascular repair, in contrast to conventional open repair, which mandates general anesthesia.

The data provide assurance of safety of the Guidant EVT device. First of all, we documented that there are significantly fewer complications when compared with the control group, within the first 30 days.

In the combined EGS groups, major complications were reduced by more than 40 percent.

The mortality rate for this procedure is low at less than three percent. This is comparable to our control group, which is also low, and emphasizes the expertise of the surgeons who have been selected to participate in this study.

This is far less than other multi-center or community-based reports of mortality rates for conventional aneurysm repair.

With respect to device efficacy, one major advantage of the Guidant EVT graft is that it is compliant.

We now know that there is significant remodeling of the aneurysm following endovascular repair. This

remodeling includes both shrinking of the diameter as well as the length of the aneurysm.

The compliance of the Guidant EVT graft permits accommodation to aneurysm sac remodeling, without angulation or kinking.

We have achieved a high rate of successful deployment, which now is 95 percent in the recent ANCURE series.

Since all patients in this series continued to be considered to have appropriate indications for repair of their abdominal aortic aneurysm, the patients and their surgeons entered the operating room with the intent of complete aneurysm repair.

While it would have been possible to terminate the procedure in the few patients in whom endovascular repair was not possible, thus avoiding the need for conversion, we were committed to achieve aneurysm repair at the initial settings and, therefore, converted to open repair when that became necessary.

The ultimate test of the effectiveness of the procedure for repair of abdominal aortic aneurysm is its ability to prevent rupture. There were no aneurysm ruptures in this series.

Additionally, very few patients showed enlargement of their aneurysm sac at 12 months. Those few patients with

sac enlargement must be followed at close intervals, and this is so stated in the proposed labeling of the device.

Aneurysm sac enlargement is often associated with perigraft flow, but not vice versa.

There is clearly a declining rate of perigraft flow over time, and the majority of patients with perigraft flow had no aneurysmal enlargement.

Graft migration is a rare occurrence and was only seen in two cases. Additionally, there has been no evidence of graft extrusion, graft dilatation or attachment system failure.

In conclusion, Madam Chairperson, and members of the panel, we believe that all study end points have been met.

We believe that we have proven the benefits of endovascular repair significantly outweigh the risks, and the data show that the Guidant EVT device is both safe and effective.

Speaking from the perspective of a vascular surgeon, who has watched the evolution of managing patients with abdominal aortic aneurysm over the years, I can well remember the status of surgical repair of abdominal aortic aneurysm in the 1960s.

At that time, we were experiencing mortality rates in excess of 10 percent, prolonged hospital stays, major

blood loss with the need for multiple transfusion, organ damage and prolonged recovery time for the survivors.

In the ensuing interval, there has been a marked improvement in surgical technique, graft material, suture material, fluid and electrolyte and anesthetic management.

These improvements have all made management of patients with abdominal aortic aneurysm a safer and more universally applicable technique.

Yet, all of these advances pale in comparison to what I consider to be the most dramatic breakthrough in the management of patients with abdominal aortic aneurysm, that of endovascular repair.

I am now able to tell my patients that they can be admitted to the hospital on the morning of operation. The evening following operation, they may be able to have a light meal, while having only minimal discomfort from two small groin incisions. In the majority of cases, they are going to be going home the following morning.

From my perspective, this is an incredible contrast to the best that we have to offer with open repair.

Recovery from endovascular repair is quick, and patients are able to return to their regular activities, whether that be their jobs or the enjoyment of their retirement years.

I appreciate having had the opportunity to

participate in this trial, and in particular, to participate in the presentation of the data to this distinguished panel. Thank you very much for your attention.

DR. CURTIS: We are going to take a 15-minute break at this time. We are going to open up the wall behind here and create some more seats in here for the people who are standing up back there. We will reconvene in 15 minutes.

[Brief recess.]

DR. CURTIS: We will continue with the FDA presentation.

AGENDA ITEM: FDA Presentation.

MS. MOYNAHAN: Good morning. My name is Megan Moynahan. I am a biomedical engineer and the lead reviewer on the PMA submission that is before the panel for consideration this morning.

The device is the Guidant EGS and ANCURE endovascular grafting systems for the treatment of abdominal aortic aneurysms.

A number of people contributed to the review of this submission. These reviewers evaluated all aspects of the submission, including the clinical data, and the preclinical testing, which covered biocompatability, sterilization, and engineering bench tests of the graft, the

delivery catheter and other system components.

The Guidant device is a complete endovascular grafting system consisting of the implantable graft, the delivery catheter and other system components.

The PMA under evaluation covers two generations of the device. The first generation of the device is referred to as the EGS system, the second generation is referred to as the ANCURE system.

The ANCURE system is a modification to the delivery catheter, which deploys the same graft.

You are being asked to evaluate the clinical data that supports both of these systems. The EGS studies were designed primarily to characterize the long-term performance of the tube and bifurcated grafts, by comparing patient outcomes to a surgical control group.

The ANCURE study was designed to characterize the performance of the delivery catheter, by comparing conversion rates to the EGS studies.

The PMA has been under expedited review since it was submitted on March 15 of this year. Preclinical testing in support of the EGS system was reviewed, and much of it approved, under the modular PMA process.

However, between March 30 and April 4, three amendments were received for the ANCURE system and its accessories.

The review of these amendments was still ongoing when the panel pack was shipped to you on June 3.

We included a table in the panel pack, on page 4-5, that outlines the status of the outstanding deficiencies that were noted up to that point. This morning I have handed out an updated version of that table, if you could refer to that now, please.

The table shows that all the requested items have been provided by the sponsor. In many cases, the responses adequately address the consult reviewer's concerns, as noted. In other cases, the information is still under review by the FDA.

Because some of these FDA requests require the sponsor to provide additional data that was not included in your panel pack, the information is not available for you to review or consider today.

I mention these points only to apprise you of the status of our requests, and also to remind you that final approval of this submission by FDA would be contingent on satisfactory responses to all the remaining issues.

I would like to draw your attention to three of the items from the table. Item number 6. We asked the sponsor to provide core lab readings on the ANCURE subjects, which was not a requirement of the original protocol, because we had concerns about the discrepancy in the rate of

perigraft flow observed by the investigators, compared to the rate observed by the core lab.

As noted in the sponsor's summary, the core lab identified perigraft flow in 48 percent of the EGS cases, compared to 24 percent identified by the investigators.

Since the ANCURE study did not include the requirement for the core lab assessment, the sponsor appropriately compared the investigator reading from the ANCURE study to the investigator readings from the EGS study.

However, to complete our understanding of the similarities or differences between the ANCURE delivery system and the EGS delivery system, and possibly for labeling purposes, the FDA requested that the ANCURE images be evaluated by the core lab. This information is currently under review by FDA.

Item number 2. We asked the sponsor to provide any additional data on new patients treated in the ANCURE study, because we were concerned that there may not have been sufficient data to support the ANCURE tube delivery system.

While we agree that the long-term performance of the tube graft is best characterized by the data from the 153 patients who received the tube graft in the EGS study, we were concerned that the ANCURE tube delivery system was

only used in nine cases.

The sponsor provided acute findings on additional ANCURE subjects, but was unable to include it in their section of the panel pack summary. Therefore, FDA included a brief review of it in our clinical summary.

We noted that the ANCURE tube delivery system has now been used in 31 cases total, with 29 successes. For the record, the data that FDA summarized had not yet undergone the sponsor's complete monitoring process.

In the panel's discussion of question one, you may want to consider this information.

We asked the sponsor to do an analysis on the patients that required stenting of the graft, because we were concerned about the high rate of adjunctive stenting that was performed. We also asked the sponsor to provide this information in the labeling.

Stents were used as an adjunctive treatment for reduced flow through one or more of the bifurcated limbs of the graft.

Twenty-one percent of the patients with the bifurcated graft received stents.

FDA asked the sponsor to provide an analysis of the stented patients compared to the unstented patients in terms of thrombosis rate at 12 months.

The results showed that 10 subjects who received

stents experienced prosthetic thrombosis prior to stent placement. No subjects treated with a stent experienced prosthetic thrombosis after stent placement.

FDA also asked the sponsor to provide an analysis of the risk factors leading to stenting. The resulting logistic regression analysis identified several factors that influenced stent placement, including physician or center preference, the subjects at centers 105, 112, 119 and 121 being more likely to receive a stent.

Physician experience. Experienced physicians were more likely to implant stents.

Gender. Females were more likely to receive a stent.

History of coronary artery disease, the subjects having coronary artery disease were less likely to receive a stent.

In summary, FDA has no outstanding issues related to the preclinical testing of the EGS system. On the ANCURE amendments, the FDA is working with the sponsor to finalize one remaining preclinical issue related to sterilization validation.

As noted in the previous slides, FDA is currently reviewing the sponsor's responses to our requests for additional data analyses and core lab readings.

At this point, I would like to turn the forum back

to the panel chairman, for discussion and for consideration of the eight questions posed to you. Let me briefly read through those questions.

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

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

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

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

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

Do not use this device in patients with a sensitivity or allergy to the device materials -- PET polyester, silicone-treated polyester sutures, platinum, cobalt, chromium and nickel.

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

The incidence and types of endoleaks associated

with the system;

Due to the lack of long-term data, the device should not be used in healthy, young patients;

The acute symptoms that may be expected if rupture occurs;

A warning regarding the use in patients with impending ruptures;

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

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. Question 8 has a long preamble, which I am not going to read.

Do you have any comments regarding a post-market study for endovascular devices in the treatment of abdominal

aortic aneurysms?

Thank you for your help with this important program.

DR. CURTIS: If that completes the FDA presentation, we will move on to the panel discussion. Our two lead reviewers for this PMA are Drs. Roberts and Perler. We will go ahead and start with Dr. Roberts.

AGENDA ITEM: Panel Discussion.

DR. ROBERTS: Thank you. To begin with, I would like to express my thanks and appreciation to the FDA team and work in putting together this panel pack.

I am sure I speak for the rest of the panel members as well, in commending you on putting together what is a very thorough but concise and well-organized approach to the data for this device.

I can only imagine the number of orange folders that this data was distilled down from. I certainly appreciate this effort, as do my shoulder and back, since I don't have to carry all of those things.

Basically, what we are looking at is the Guidant device, and the two parts of this, one of them as being the endograft, which is basically the same between the two systems, the EGS and the ANCURE, the difference being the delivery system.

My feeling is that there has been a very practical approach to the change in the delivery system, by allowing the sponsor to combine the two devices into one approval.

I think that is probably a reasonable approach to the changes that were needed in the device.

The study, of course, is a non-randomized, concurrent control study between the endograft and the standard surgical treatment. I think it is important that everyone realize that the control patients -- I am not sure they are thoroughly founded in the data -- they apparently were not qualifying for the endograft arm, mainly because either the iliac femoral artery was too small or the femoral neck was too close to the renal arteries.

Although, certainly we like to think about randomized control trials being the best way to evaluate new devices, I can understand that there was a problem in doing a randomized controlled study.

I do think this was, again, a fairly reasonable approach with what really is, from what I can see in the material, a fairly good concurrent control done approximately the same time as the device study was being done.

One of the things that I would have liked to have seen a little bit better was a better delineation of the primary clinical end points in the study, sort of laying

those out perhaps a little bit better.

From looking at this, it seems as if the main things that were being evaluated in terms of complications, length of hospital stay and effectiveness, were well delineated and do appear to be showing a favorable response with the endograft.

Certainly, the concern of perigraft leakage, it is clear that we don't, I think, yet understand what the significance of this is.

I think certainly, although there have been no ruptures and no large number of patients with enlargement of the aneurysms, by and large much of the material that is being presented is for 12 months.

It may be that over time, as we get out to several years, perhaps that will change. I think that certainly this is one thing that we are going to have to look at carefully.

I am going to bring up a few comments regarding some of the information that I would have perhaps like to have seen or perhaps the FDA might want to at least think about, either in this study or in future studies.

One was, how many patients were screened compared to those enrolled. Certainly it would be helpful for physicians who may be putting in this device to have some kind of idea how many patients may be candidates for this

procedure, and perhaps what the primary indications are going to be that would disqualify them from being candidates.

In the directions for use, there is a reference to the endosac occlusion device. Although I found separate sections in the panel pack regarding the iliac balloon catheter and the contralateral torque catheter, there is nothing in this panel pack regarding the endosac.

I don't know whether this means it is already approved or being approved separately, or what the status is of that closure device.

Certainly some of these patients are going to require that device. I just want to make sure that the status of that is also in the works.

I will make a comment that the size of the aneurysms being treated in this study are relatively small, with a mean diameter of 5.2 centimeters.

It would be helpful, I think, to have a size range of what size aneurysms could be, or were, treated with this device.

One of the things that I found lacking a little bit in the instructions for use is what type of a protocol the manufacturers would suggest in terms of how patients should be evaluated, prior to planning the endograft procedure.

What are the recommendations regarding spiral CT, MRI, angiography, ultrasound, intravascular ultrasound, that could be used or should be used in terms of determining which patients would be suitable for this procedure.

In terms of the device itself, I can see that the patients are getting follow-up KUBs, and apparently there are no hook breakages reported.

I think this is marvelous. I, quite frankly, have never seen a metallic device implanted in someone that doesn't break at some point with some kind of failure. I certainly think this is something that ought to continue to be watched for in the post-marketing evaluation.

One of the things I was very concerned about is the marked discrepancy between the core lab and the investigators, regarding the perigraft flow.

This discrepancy, I think, is going to be a particular problem -- and obviously the FDA also recognizes this -- it is going to be a particular problem, particularly if perigraft leakage is a predictor of aneurysmal enlargement and potential rupture over time.

I think it is going to be very important that either we figure out a mechanism to better educate whoever the physicians are who are assessing the studies, looking for perigraft leakage, or that perhaps we need to continue to have a core lab involved, in order to make sure that we

have got accurate delineation of what the rate of perigraft leakage is.

It wasn't totally clear to me from the panel pack as to what bearing the twisting of the graft has on function.

Were the patients with twisting, did they go on to have another procedure to fix the twisting that was found.

There was apparently an increase in twisting with the ANCURE device which was felt, at least in one part of the submission, to perhaps be due to the visualization of the graft, presumably meaning that without the ANCURE device, where you have more of the radio opaque markers, perhaps you had more twisting than you realized.

On the other hand, since they were radio opaque markers, it was not clear to me why the operators are having more trouble making sure the graft is not twisted, and again, what bearing the twisting has on the problem of decreased flow in the graft.

DR. CURTIS: Would you like somebody from the company maybe to address that, when you are asking questions? Can anybody answer that?

DR. ADELS: Many of the twists that you saw reported in the PMA did not require any intervention. No cases of twist in the tube graft required intervention.

Those cases of twist in the bifurcated graft that

did require intervention were included in the figures for induced lymph flow, so they are kind of counted twice in the PMA.

DR. CURTIS: Let me follow up, you had a question before, too, that I think is worth answering or asking about, the aneurysm size, about what could be used. Is there a size beyond which you don't want to use this device? Is there a recommended range?

I know you have to get a 23-fringe device into the leg to use this thing, but is there such a thing as too big and it won't seat properly?

DR. ADELS: We don't think there is such a thing as too big as long as there is adequate proximal neck and adequate distal neck for the tube device, or adequate neck in the iliac arteries for the bifurcated device.

We did treat a wide range of aneurysm sizes and I think we have a back-up slide that shows you what the aneurysm sizes were. This is the aneurysm size distribution.

So, we treated aneurysms, the majority were between four and six, but there were some larger aneurysms in the study that were successfully treated.

DR. CURTIS: The key about the neck, is it the length of the neck or the diameter of the neck?

DR. ADELS: Both. The length of the proximal neck

needs to be at least 1.5 centimeters in length and the diameter needs to be appropriate for size of graft.

The graft comes in 20, 22, 24, 26 millimeter diameters. We do not treat necks greater than 26 millimeters in diameter.

DR. CURTIS: So, if a patient had that, they should not get the graft.

DR. ADELS: Right, and that is clearly stated, I think, in the labeling, as far as the sizing recommendations.

DR. ROBERTS: As perhaps another point in terms of the aneurysm itself, I couldn't find anywhere -- certainly some of it I may have missed; even though it was a smaller panel pack, it has still got a lot of information in it.

I didn't find any information on the description of the patients regarding tortuosity of the aorta or the iliac arteries, and whether or not there was any evaluation as to how tortuosity affects the placement and performance of the device.

When you look at your figures and you see that a fair number of these were pretty small, I suspect it wasn't a lot of tortuosity.

I think that certainly might have an impact on how the graft lays into the aorta. I was wondering if you had looked at anything in terms of tortuosity.

DR. ADELS: We don't have any measures that quantify tortuosity, but I would like Dr. Deaton to address the issues of tortuosity and the implant of the device.

DR. DEATON: In terms of tortuosity, it is difficult to quantify and there is some learning involved in terms of assessing the access route with respect to both the diameter and the tortuosity.

In terms of the graft, if it can be delivered into place, it can be seated in a very tortuous neck, since it is simply a fabric graft. There is nothing that doesn't allow it to conform to whatever tortuosity there is.

The primary impediment tortuosity presents is as a delivery or access issue.

DR. ROBERTS: Was there any kind -- again, I don't know how many of your patients, you would have to quantify it in terms of what the tortuosity was -- but was there any relationship to the decreased flow through the graft due to tortuosity, that you know of?

DR. DEATON: Tortuosity certainly plays a role in reduced limb flow, too. If there is an acute angle in an iliac where the graft has been placed, that can tend to kink off the graft.

When stents are used as an adjunct in those circumstances, it is usually distributing that curvature over a larger length of iliac, rather than having an acute

turn.

DR. ROBERTS: How about an acute turn in the abdominal aorta, in the proximal part of the graft. Do you know whether there is any decrease in flow because of that phenomenon?

DR. ADELS: We have had no decrease in flow in the trunk portion of the bifurcated graft or in the tube grafts.

DR. ROBERTS: A few more things. Given the perigraft leak problem, it wasn't clear to me how many of the patients -- there was certainly a decrement in the number of patients who had leaks over the period of time.

It wasn't clear to me how many of these patients had undergone some type of other therapy to decrease the leaks, for example, embolization. Were any of these patients embolized? Was that some of the reason the leaks were less prominent?

Is there any thought, if you do an angiogram before putting in these devices, and you see that there are patent branch vessels, is there any feeling whether or not these should be embolized before the graft is placed to try to decrease the leak problem?

DR. ADELS: Let me address the first part of your question initially, which is how many patients were treated.

There were several patients treated pre-operatively and interoperatively, and a few post

operatively, with coils and branch vessels. This was effective some of the time, but not all of the time, in eliminating branch flow.

In addition, there were a handful of patients, a very small number, actually eight subjects to tube and six bifurcated, that were actually treated with stents across the attachment system, for the reduction of perigraft flow.

Again, this was effective about half the time and it is really too small a number to draw any fundamental conclusions from.

Additionally, there were seven tube subjects who had a second endograft placed within the first. This was usually successful in resolving attachment system flow, but obviously is not going to affect branch leaks.

Those are the types of interventions that were used, although they were all used in quite small numbers. I would like to ask maybe Dr. Katzen to come up and address the possibilities for that.

DR. KATZEN: Good morning. My name is Barry Katzen. I am the medical director of the Miami Cardiac and Vascular Institute. I am an interventional radiologist, board certified in interventional radiology.

I do own shares in the Guidant Corporation, that are held in managed accounts, and I have been a principal investigator at our site.

To address the question of adjunctive embolization procedures for perigraft flow, I think among the investigators there was no clear experience as to whether any pre-implant benefit would occur from doing an embolization procedure.

The group of patients, as you have heard already, was so small that I don't think we can provide any real specific recommendation for whether pre-implant embolizations, or other interventions, should be performed.

Peribranch flow can be eliminated when abundant collaterals develop from a hypergastric artery, generally with simple intervention procedures on an outpatient basis.

DR. ADELS: I would also like to just clarify that the number of interventions for perigraft flow was small and most of the reduction in perigraft flow was spontaneous, and not from treatment.

DR. ROBERTS: Other things in terms of the indications for use, or the directions for use, is whether or not the patients should be heparinized during the procedure. If so, how much or how long, they ought to be heparinized.

DR. MOORE: We would use standard heparinization therapies, similar to what we would do at the time of an implant of a conventional aortic graft.

My own personal practice is to give 5,000 units of

heparin when we place the sheath. Assuming that the procedure is concluded in a reasonable length of time, then we don't usually add further heparin to that, but simply let it wear off.

DR. ROBERTS: You may want to consider putting that in the directions for use.

The other thing was that I suspect that all of the investigators have found that there are certain problems that are likely to be encountered, certain situations that people start having problems with in terms of placing these.

It might not be a bad idea to have some kind of a listing of those types of possible complications or problems. I won't say complications, but problems in terms of using the device, that perhaps people who have experience with this will be able to give some potential solutions.

Obviously, one of the major things, I think, is how these patients are going to be tracked over time, for what period of time.

I think that is something that certainly is going to need to be addressed in terms of the tracking.

The other thing, I think, that is very important is the plans for training physicians to use this device, what criteria are going to be used for training, what type of proctoring is going to be available, how long that will be done, how many cases.

Also, I think another important issue is how fast is this technology going to be disseminated. In other words, are we just going to turn this loose and just let everybody sort of run in there and start putting in these things, or are we going to try to, to some degree, limit it or diffuse it more slowly, so that there can be a tracking that goes on with that.

Those are some of my perhaps more general questions that don't specifically address the FDA questions. I thought perhaps I could stop at this point and let Dr. Perler, who is the other lead reviewer, address his thoughts on this and then perhaps we can come back to the panel questions.

DR. CURTIS: Dr. Perler?

DR. PERLER: I, too, want to thank the FDA staff for their work in putting together this data in a very reviewer-friendly fashion.

I have been involved with this panel for a number of years and practicing vascular surgery for a few more than that, and I have seen a lot of new technology, endovascular technology, sort of come down the pike with a great deal of enthusiasm and hoopla, lasers and arthrectomy devices and so forth.

Often, at times, I thought to myself, technology is in search of indications.

I must say, I think this endovascular technology is for real. I think it is going to clearly improve with time, as the technology evolves. I think it is going to be a real benefit to patient care, particularly at a time when we are going to see a tremendous growth in the elderly segment of our population, in whom aortic aneurysms predominate.

I also think this was a well-conducted trial and I congratulate the company. The data was clearly presented. Patient follow-up was almost totally complete.

One of my concerns is that one-year follow up is really not long term, as I think everybody recognizes. I think there is no question that some sort of registry and very strict patient follow up will be absolutely necessary in this regard.

I approach the review of this data sort of as a physician who is going to sit down with a patient and get an informed consent.

You know, what are the risks, what are the benefits, what are the advantages and disadvantages.

Most of my conclusions kind of mirrored, I think, what Dr. Moore presented. I think I can safely tell a patient that there is an excellent chance you will avoid an open surgical procedure, you will recover much more quickly, less time in the hospital, maybe avoid a general anesthesia,

maybe avoid an ICU stay.

On the other hand, if that patient were to require a bifurcated prosthesis, based upon the data in this protocol, that patient's chance of having an operative mortality is probably equivalent to a major conventional surgical procedure, the stent graft patient probably no less likely to experience the so-called IDE composite complications, no less likely to experience cardiac complications.

One year later, there is about a 50/50 chance the aneurysm will be the same size, although overwhelmingly the chances are that it will be excluded from the circulation. I think we really don't know the natural history of that state, and how it will play out with time.

As a payoff for getting out of the hospital more quickly and recovering more quickly, I think it is going to consign our patients to many years, perhaps a lifetime, of periodic imaging studies, to see how they are doing and how the device is doing.

I don't think those comments should be construed as prejudice on my part with respect to safety and efficacy, but I think that is how I kind of put this together in terms of big picture.

One of the problems I had with the study relates to gender. Acknowledging that women make up a relatively

small fraction of the population of patients who undergo conventional aneurysm repair, and recognizing that vessel size is certainly an issue in terms of applicability of the endovascular approach to aortic aneurysms, yet, as I read the data, only 28 of the EGS bifurcated grafts and eight of the ANCURE grafts were placed in women, only 36 women included in the trial, which obviously is a very small number of patients.

It is of particular concern in view of the fact that women were much more likely to require conversion to open surgery, 28 percent versus 6.5 percent.

They were significantly more likely to require intervention for reduced blood flow, probably related to vessel size issues, and were more likely than men to experience IDE complications.

I guess that leads to my first question which is, do you think we have enough data to make a comment with respect to the safety and efficacy as it relates to women with aortic aneurysms.

DR. ADELS: I would like to start by addressing your issue with the IDE composite index. We have looked at the frequency of occurrence of the IDE composite index in women controls as well. I think we have a back-up slide on that, if we can locate it.

At the end of the day, women continue to benefit

from this device. Women in the tube group -- as you can see, women controls also experience more complications than men.

It is important to point out that women in the EGS groups still benefitted from a complication standpoint, based on this device.

I should also point out that the ANCURE conversion rates were lower for women, roughly 12 percent of the women in the ANCURE study and, admittedly, it is a small number of patients.

In the updated data set that includes 206 patients, only 12 percent of the women were converted.

DR. CURTIS: Was this information included in the PMA, that you have up here on the slide?

DR. ADELS: This information that you are seeing now is from the EGS, and this breakdown specifically was not included in the PMA, no, but the data is all in there.

DR. CURTIS: Then you need to submit that to the FDA.

DR. STUHLMULLER: As a point of clarification, it is okay to present alternative analysis of the data in the PMA, but all of that has to be submitted as an amendment to be reviewed by the FDA.

DR. ADELS: Okay. Dr. Deaton, do you want to comment more on the female issue?

DR. DEATON: I will agree with Dr. Perler that the issues regarding women largely relate to native vessel size. For a given population of men versus women, the femoral and external iliac diameter is going to be smaller.

While there are clearly patients who have adequate access -- and they are relatively easy to determine -- and some who are too small, there is a gray zone, if you will, where our current diagnostic techniques to size the femoral and external iliac arteries, the standard of measurement is not such that you can totally predict when it is going to be easy or not.

You may think that you have adequate size and you can run into difficulties with access, and it is more likely to happen with women than it is in men.

The other subjective issues that relate to access that include tortuosity and calcification basically apply in both men and women, as do these access issues. They apply in men and women. It is just more common in the female population.

When access is not an issue, women benefit in pretty much the same way that men do.

DR. PERLER: Dr. Roberts had talked a little bit about perigraft flow, which obviously is one of the central issues and I think a relative unknown.

About 50 percent of the patients in the trial, as

I mentioned, had no change in aneurysm size at 12 months. What is a little bit concerning to me is that, while perigraft flow and increase in aneurysm size is not good, of the patients, in fact, who had no change in aneurysm size, 19 of the 52 tube patients and 25 of the 62 bifurcated patients with no change in aneurysm size at 12 months still had persistent perigraft flow.

I think we just don't know what the natural history of that is going to be, but clearly, it is a concern to me.

Have you got any data on a case by case in terms of aneurysm size as to persistent graft flow, and as that relates to changes in aneurysm size.

Were the larger aneurysms more likely to have perigraft flow and more likely not the change in size?

DR. ADELS: Dr. Caricarini(?) can probably review the results of the logistic regression analysis on that topic.

DR. CARICARINI: I am Dr. Richard Caricarini. I am a paid consultant to Guidant EVT on statistics. I have no financial interest in the company other than my fee-for-service basis.

When we did an analysis for the size of the aneurysm, there was a statistically significant relationship with size and the incidence of flow.

We did a GEE analysis, which is a longitudinal analysis, accounting for the time of the multiple and repeated nature of the observations.

We did see that patients with a higher diameter at baseline had a slightly higher risk of increase in size and flow.

DR. PERLER I guess one question that is out there that may relate to labeling or training issues is, what is the recommendation now? How are you going to train folks in terms of how they should address a persistent leak in these patients at six months or 12 months or 18 months, with an aneurysm that perhaps has not shrunk or perhaps has not increased.

DR. ADELS: We have an extensive training program planned, which is going to include specific training for the physicians on how to identify perigraft flow and how to evaluate post-operative diagnostics.

The labeling does recommend that patients with persistent perigraft flow be followed every six months with a contrast-enhanced CT. If, for some reason, that is contraindicated, that they have an ultrasound every six months.

DR. PERLER: In my trial, was my sense in response to Dr. Roberts' question, that some of the patients with perigraft flows had interventions performed or attempted

during follow up to seal those leaks; others didn't, even those patients with no change in aneurysm size.

I guess what my question is getting at is, is there a consensus -- do your investigators have any feeling as to who should or should not undergo an attempt to seal a leak, particularly perhaps as relates to the four types of leaks that Dr. Deaton described.

DR. DEATON: I think with regard to the types of leaks, if one feels that there is a direct communication to the aorta and that aneurysm sac is exposed to the same aortic pressures that it was before, that even with no change in aneurysm size, most would be predisposed to address that problem.

For branch perigraft flow, there is no convincing data what the natural history of that will be, only the implications from physiologic studies, given the acute change that those branch vessels have after you place an endovascular graft, since they are turned into basically a collateral circuit.

There is no a strong consensus, I don't believe -- I guess I would like Dr. Moore to comment as well -- among the investigators as to when it is appropriate to intervene with coils or other adjunctive procedures pre-operatively or interoperatively or post-operatively. So, that practice is variable and that is basically in the body of evolving

knowledge about this.

DR. MOORE: I think that probably is the bottom line. Obviously, when a leak is identified, that patient becomes flagged and followed.

Since a number of these leaks -- at least half -- have sealed over a period of time, it is reasonable to follow them on a regular basis to ascertain that that is a completed issue.

On the other hand, after a reasonable length of time, if the leak fails to seal and/or if the aneurysm enlarges, then that is an indication to do an angiogram, to try to better define exactly where the leak is coming from, whether it is an attachment site leak or a branch back-flow.

That can be dealt with by endovascular means, usually percutaneously, whether it is coiling of the perigraft attachment site leak, or whether it is coil embolization of a branch.

Clearly, those are adjunctive measures which can be used and which can be helpful.

DR. PERLER: We noted that the incidence of leaks among the whole study population decreased with time. I was just wondering, were there patients in whom a leak sealed at one year, but other patients who previously had no leak, one was identified in?

I guess the question is, what is the incidence of

new leak among patients in whom, on initial post-discharge study, they had no leak?

DR. ADELS: We do have that data for both tube and bifurcated patients. There was some incidence of late leak in both patient populations.

There were some patients who experienced new perigraft flow at six or 12 months. Only one of these patients -- this was of two patients who had an increase in aneurysm size as a result of that late leak.

In some cases, some of that late perigraft flow, there is no perigraft flow at discharge, then there is perigraft flow at six months, and then it is gone again at 12 months.

I think to some extent the core lab was very conservative in reading perigraft flow. If either the CT scan or the ultrasound indicated perigraft flow, if there was any indication on either test, they called it flow.

Sometimes those things might have been false positives and, hence, went away, so it is a little difficult to look at it. We did see some occurrence of late leaks, both branch and attachment site.

DR. PERLER: As I look at the data, late conversion was performed on three patients for a leak and an increased in aneurysm size.

I believe there were six tube and three bifurcated

patients who had persistent leaks and increase in aneurysm size. I wonder how those three patients were selected for conversion or, conversely, why the others were not.

DR. ADELS: Let me clarify. The three patients -- the data that you see on increase in aneurysm size comes from the core lab.

In fact, to complete the picture, I must tell you that the three patients who were converted were not included in those increases.

Two of them were converted prior to their six-month visit, prior to that point. One was converted late, and the increase in aneurysm size in that patient was actually less than the five-millimeter cut-off for an increase.

Of the nine patients who had an increase in aneurysm size late, and were not converted, the one subject without a leak has received no treatment.

When I have concluded my summary of this, I will ask Dr. Moore to comment. That is a patient of his.

Of the eight subjects with perigraft flow and increased aneurysm size, three have been treated with coil embolization of branch vessels successful. One has been treated with a stent and PTA successfully.

Two subjects have had a second endograft place, which was successful in treating the flow, and two have not

received any treatment.

DR. DEATON: A bit of clarification on those early conversions. Those were patients that had clearly very large attachment site related problems.

The investigator, the surgeon, did not feel that the aneurysm was isolated and didn't feel that any protection from the natural history of an aortic aneurysm had been provided. That is the reason they were converted, not waiting for the disease to progress.

DR. MOORE: In the one patient that had aneurysm enlargement without visible leak, we have actually recommended to that patient that he undergo conversion to open repair. At this point, he has declined.

DR. PERLER: Most of the acute conversions were done, as you said, for failure to access or basically because of anatomic problem.

I think it was just under eight percent in the tube and just under 10 percent in the bifurcated patients.

It sort of raises, I think, an issue that hasn't been really covered this morning. A large part of the game is the pre-operative evaluation of these patients in terms of their appropriateness for the technology as well as the imaging studies and assessment of those imaging studies and prosthetic size.

Have you correlated the conversion rate with iliac

artery diameters or angulations retrospectively, to see whether there were errors in judgements in selecting patients for this approach, or are they purely technical issues, perhaps more related to a learning curve type phenomenon.

DR. ADELS: I would like Dr. Caricarini to address the results of the analyses to look at the risk of this, and then the physicians can comment.

DR. CARICARINI: In every analysis, we screened a number of variables. Because the baseline anatomic characteristics of the aneurysm were different between the control and treated populations, we always included those in our analysis for possible inclusion into the model.

The size issue is kind of tricky, because there was not a consistent response to any of the parameters. For example, one of the more important parameters that we did find significant in two particular cases were the difference in the size of the graft relative to the size of the artery.

In this particular situation, we found that for attachment site leak, this was significant, and the undersizing, if you will, led to a higher probability of attachment site leak, as might be expected.

The other situation was in the case where the difference in size between the graft and the artery, there was an over-sizing issue.

If there was an over-sizing issue, it was more highly associated with the possibility of having an intervention for limb flow or patency.

Otherwise, there were no consistent relationships between the size of the graft. There were a couple of analyses that indicated that the size of the limb itself was an issue.

The differences in the size between the successful patients and unsuccessful patients was extremely small, between a half and one millimeter.

DR. DEATON: I think it relates to the issue the FDA raised in terms of labeling and indications and contraindications.

Should there be a statement related to anatomy in terms of iliac artery tortuosity, as well as sizing of aortic neck angulation, that sort of thing.

Is that something that this panel should be thinking about, and should be formalized in writing for the practitioner who is considering putting this device in a patient out in the real world.

DR. ADELS: I would like to ask Dr. Deaton and Dr. Katzen to both comment on that.

DR. KATZEN: I think you have identified all the salient issues with regard to access. The study looked at diameters of the common iliac artery. Therefore, it is

difficult to judge exactly the common femoral external iliac artery diameter, although those were evaluated by physicians.

The differences that I described before in terms of the standard of measurement, or the exact sizing of an external iliac artery along its entire length, can be difficult in a borderline zone where it is just the right size to accept the device.

The issues of tortuosity, calcification and other pathology that can affect the external iliac are more subjective, but they clearly are issues that deserve a great deal of attention and are part of the learning curve involved with applying and using this device.

DR. PERLER: I think it is important to note that when the trial began, there was no experience with endovascular treatment of abdominal aneurysms.

Some of the issues that are of concern relate to a body of knowledge that we have acquired during the course of the trial.

I think that, despite attempts to quantify statistically some of these variables, there are clearly issues that we have learned and I think are planning to incorporate into the training physicians in terms of patient selection and part of the company's planned physician training program, even though they might not necessarily be

quantifiable.

DR. PERLER: I want to leave sufficient time for the other panel members. Let me ask one more quick question in one more area, renal insufficiency, that caught my attention.

I think the rate of acute renal insufficiency was about eight percent in the bifurcated patients, 3.2 percent in the tube patients, and that was sort of attributed to contrast load.

I must say, eight percent of acute renal insufficiency seems quite high, even back in the days when we were doing aortograms and run offs with older contrast agents and without digital subtraction angiography.

First of all, how did you define renal insufficiency, and secondly, have you correlated the incidence with the actual dye load.

Thirdly, in terms of the acute renal insufficiency, and then another 10 percent of renal insufficiently long term, have you actually analyzed the renal arteries to make certain there were no cases in which renal artery flow was compromised by the prosthesis.

DR. ADELS: Let me clarify the definition of renal insufficiency for you, and then I will have the physicians response to the remainder of your questions.

We considered renal insufficiency a rise in

creatinine greater than 30 percent above the established preoperative level, lasting 24 hours. Our threshold for renal insufficiency was pretty low. We called pretty much anything renal insufficiency.

I would also like to point out that the vast majority of the patients who had renal insufficiency did not require dialysis.

DR. PERLER: The vast majority didn't. How many did?

DR. ADELS: I think there were three patients who required dialysis. Yes, there were three bifurcated subjects who required dialysis, one of which had preexisting renal insufficiency, one of which had a very complicated procedure and multi-system failure, and one was off dialysis within three days. So, a very low rate of actual dialysis required in these patients.

I would like Dr. Moore to possibly comment on the renal insufficiency, but it is important to note that when we controlled for pre-operative renal insufficiency, the differences between groups went away.

DR. PERLER: Is that a labeling issue?

DR. ADELS: There is a discussion in the labeling. There is a precaution in the labeling, that patients with pre-operative renal insufficiency might have an exacerbation of this condition as a result of the procedure.