

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL

This transcript has not
been edited and FDA
makes no representation
regarding its accuracy.

Pages 1 thru 241

Gaithersburg, Maryland
October 27, 1998

MILLER REPORTING COMPANY, INC.

307 C Street, N.E.

Washington, D.C. 20002

(202) 546-6666

sgg

AT

1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY SYSTEM DEVICES PANEL

Tuesday, October 27, 1998

8:00 a.m.

Gaithersburg Hilton
Salons C, D, and E
620 Perry Parkway
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

PARTICIPANTS

Tony W. Simmons, M.D., Acting Chairperson
John E. Stuhlmuller, M.D., Executive Secretary

VOTING MEMBERS

Michael D. Crittenden, M.D.
Francis R. Gilliam, III, M.D.
Gulshan K. Sethi, M.D.

CONSULTANTS APPOINTED TO TEMPORARY VOTING STATUS

Robert M. Califf, M.D.
Michael J. Domanski, M.D.
Thomas B. Ferguson, M.D.
Cynthia M. Tracy, M.D.
Janet Wittes, Ph.D.

CONSUMER REPRESENTATIVE

Robert A. Dacey

INDUSTRY REPRESENTATIVE

Gary Jarvis

C O N T E N T S

Call to Order, Tony W. Simmons, M.D.	4
Conflict of Interest, John E. Stuhlmuller, M.D.	4
New Business:	
The Year 2000 Impact on Medical Devices, Tom Shope, Office of Science and Technology, FDA	6
Panel Introductions	20
Company Presentation:	
Premarket Approval Application P970029 Eclipse Surgical Technologies, Inc. TMR 2000 Holmium Laser System	
Introduction, Mr. Murphy Chutorian	21
Study Design and Methodology, Linda Fenney, M.D.	25
Data Collection and Analyses, Anne-Marie de Merlier, M.D.	32
Clinical Results, Keith Allen, M.D.	35
Risk/Benefit Analysis, Eric Topol, M.D.	56
FDA Summary, Michael Berman, Ph.D.	61
Panel Discussion	73
FDA Questions for the Panel	165
Open Public Hearing:	
Sam Consul	216
Panel Recommendations	217

P R O C E E D I N G S

Call to Order

DR. SIMMONS: Dr. Stuhlmuller will now read the conflict of interest statement.

Conflict of Interest

DR. STUHLMULLER: The conflict of interest statement: The following announcement addresses conflict of issues associated with this meeting, and is made part of the record to preclude even the appearance of an impropriety. The conflict of interest statutes prohibit special government employees from participating in matters that could directly affect their or their employers' financial interests.

To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The agency has no conflicts to report.

In the event that discussions involve any other product or firm not already on the agenda, for which an FDA participant has a financial interest, the participants 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 firm 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 20th, 1995, I appoint the following people as voting members of the Circulatory System Devices Panel for this meeting on October 27, 1998: Michael Domanski, Thomas Ferguson, Cynthia Tracy and Janet Wittes. 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, signed Bruce Burlington, M.D., Director, Center for Devices and Radiological Health, dated 10/22/98, and Dr. Simmons is appointed as Acting Chairperson for today's meeting.

Another appointment to temporary voting status, pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiologic Health, dated October 27th, 1990, as amended April 20, 1995, I appoint Robert M. Califf, M.D. as a voting member of the Circulatory System Devices Advisory Panel for the October 27th, 1998 meeting. For the record, Dr. Califf is a voting member of the Cardiovascular Drug Advisory

Committee for the Center of Drug Evaluation and Research. He is a special government employee who has undergone the customary conflict of interest review, and has reviewed the material to be considered at this meeting, signed Michael A. Freedman, M.D., Acting Commissioner of Food and Drugs, dated 10/19/98.

DR. SIMMONS: I don't believe there is any old business, is there?

DR. STUHELMULLER: No.

DR. SIMMONS: Tom Shope, from FDA, is going to give a small presentation on Y2K problems under new business.

New Business

MR. SHOPE: Good morning. I am Tom Shope. I am with the Office of Science and Technology at the Center for Devices and Radiological Health, and a group there known as the Division of Electronics and Computer Science.

[Slide]

A couple of years ago, we started talking about the issue of the impact of the year 2000 on medical devices, and because I guess I was involved in those discussions, I seem to have inherited the role to be a spokesman for that issue, here, at the Center.

So, the purpose of my discussion this morning is to share with the panel, as well as with the audience, what

the situation is as we currently know or understand it with regard to the Impact of the year 2000 on medical devices; to provide the panel with an opportunity to give us some feedback, if it is appropriate, with regard to other products that might need attention or consideration, issues associated with this problem that the Center might want to address in terms of educational activities, etc.

[Slide]

The panel has a copy of the overheads that I am going to be using, but I will just speak for a few minutes. At the end, I will certainly be glad to entertain any questions the panel may have.

So, we are doing this with each of the panels this year to try to just update folks on what is going on with regard to our activities, as well as a chance to air some of the issues. You might have known that last week was "National Y2K Awareness Week" as organized by the President's council on year 2000 conversion. So, it is an issue that is in the minds of lots of people these days, and I guess the real question that comes up is, you know, what kind of an event is this going to be? What is going to be the impact? And, we are doing our best to make sure the impact on medical devices and the delivery of healthcare is as modest as one might make it.

[Slide]

Certainly, there are medical devices that will have problems, that are designed in such a way that there will be problems. However, I think for the large majority of those it is a very minor type of problem, particularly associated with disclaim dates, but very little of the problems that we have learned about to date have a real impact on the functionality of the devices.

Certainly, in the whole healthcare arena there are considerable problems. Hospitals and healthcare facilities have a tremendous job to do to deal with their internal software applications, their databases, their record-keeping, billing, payments, patient records--you name it. There is a potential there for Year 2000 problems associated with it. So, I am hopeful that all healthcare facilities are busily working on this issue currently and, as members of the panel, you might want to inquire as to what is happening at your facility when you get back there, just to make sure that it is getting the attention that it needs.

This is really not a bug, as one of the physicians from the Department of Veterans Affairs coined the phrase, "millennium bug syndrome," to describe this problem in one of his discussions, but it is due to the way systems were designed.

Basically, it is the problem when a computer system fails to accurately represent or use a date because

it only used two digits to represent the year. That hasn't been a problem recently because the "19" for the century was pretty well understood but as move into the year 2000, then there is a potential for confusion. One cannot tell 2000 from 1900 when all you get are the two zeroes. In some systems even the two zeroes don't appear because of the way the system was designed. The characters printed may not even be zeroes, and so it really can lead to some confusion as to what exactly was the date; what was the date format; what is happening there.

If it is only a display, it is perhaps not a significant problem. But, when that date is used in some kind of algorithm; when it is used in a calculation; when it is used in a comparison; when it is used to compare a person's birth date with today's date to determine age, and then that age is used in some medical decision process there is a potential for problems.

[Slide]

This is from a couple of years ago. As I started looking at this issue a little bit and started seeing some of the ads and some of the information technology trade press, and this one sort of was an interesting impact on me in the fact that at that time, a year or so ago or three years ago, there were a lot of PCs, the previously manufactured personal computers, that, due to the way their

basic input/output system or their real-time clock was designed, had problems and, since PCs were used in many medical device designs, there is a potential then for that impact on the use of the medical devices that are controlled by PCs.

I have listed here just a couple of the kinds of products that might be of that nature, pacemaker controllers, systems that collect data from monitors on patients and provide that to a central location; perhaps computer systems in the clinical lab that collect data from a number of different instruments, perhaps from different manufacturers, and compile that information. So, those are the kinds of problems that might arise if the PC is not working properly.

A couple of years ago we were also seeing these kinds of quotes, trying to raise awareness of a healthier industry to deal primarily with their information technology issue, not so much their medical device issues. As a way of trying to get some attention to this problem, I thought these quotes were pretty good as an impact when we started talking about this in the Center a couple of years ago.

The point is this is probably the largest computer initiative in history and it is not a date that will slide and slip. It is a date that is fixed and we have to meet it in order to be successful in preventing any adverse impacts.

The second quote there about the healthcare system was really focusing not on medical devices but on information technology infrastructure in hospitals, but it gives you some idea of the potential magnitude of the problem.

[Slide]

Well, medical devices are potentially subject to this problem. Listed here are some applications or some types of medical devices that might be considered as potential sources of problems. Anything with a microprocessor or control that involves a data time-keeping process; anything that is controlled by a PC if that PC has problems. Basically, the problem with a PC is that it can't keep track of date it is so when it goes to file a record it may associate the wrong date with that record. If the date information in the PC is input into the algorithm, then the algorithm wouldn't be correct.

There is a large number of medical devices that are nothing more than software applications, just software programs. Probably the most striking example of this is the computer programs used to do radiation therapy treatment planning. These are basically just large software programs that run on a work station that input data from some of the imaging systems, such as computer tomography x ray systems or MRI systems, that use that patient information to plan

the therapy and to develop a treatment plan. There are radiation treatment planning systems that have been in use recently that were designed for the process of planning treatment for teletherapy or brachytherapy. These are ways of doing radiation therapy where the source of the radiation is a radioactive isotope, either cobalt 60 in the case of teletherapy or some other radioactive isotope that is implanted in the tumor during the brachytherapy treatment.

If the planning system can't keep track of when the radioactive source was calibrated and compare that date to the date on which the therapy is going to be administered, the strength of the source calculation will be incorrect, and inappropriate therapy could be delivered. There are, in fact, radiation treatment planning systems out there that have that problem, that will need to be corrected. The manufacturers have identified them, and the software corrections are being developed. But that is an example of just a software program where the algorithm can go astray because only two digits were used for the year.

Any device that interfaces with another device where there is transfer of data for record-keeping purposes, such as perhaps the clinical laboratory systems, has a potential for problems.

Then, there are a lot of products with imbedded chips. These are really programmable electrical devices or

microprocessors or other specially designed chips that are part of the medical device. In many cases, these chips are like the little chip in your microwave oven that allows you to put in the time and get a date displayed, but it really doesn't have anything to do with the functioning of the microwave oven. Your date there can be off--your power goes off, your light starts to flash but the microwave oven will still work. There might be a function or two of the microwave that depends on the timing but that really doesn't usually depend on the date.

So, there are a lot of medical devices that have that kind of a feature. They display a date or they print a date on a paper record that describes what the device has done or what kind of function it recently performed, but the date does not prevent, or the date being in error does not prevent that function from normally being carried out by the medical device. So, as you can see, there is a wide range of potential products.

[Slide]

At CDRH and FDA, we are starting to talk about this issue. We decided, of course, that the manufacturers are the only ones that have the real knowledge about their products to be able to determine if there is going to be an impact on the product, and what kind of measures need to be taken to deal with that.

So, one of the first things we did was develop a definition of compliance so we could all be speaking the same language. What do we mean when we say that a product is compliant? That is, it doesn't have the year 2000 date problem?

We developed this definition which is based on a federal requisition reg. definition of year 2000 compliance, the definition the federal government uses currently in purchasing products. We have used this in our activities so far. Basically, the definition says if there is any ambiguity about what the century is, i.e., if there are only two digits being used, displayed, printed, used in calculations, if there are problems of leap year because year 2000 is a leap year and some of the devices have ignored that particular aspect so there are some calendar functions that don't work right in some products.

[Slide]

We developed this standard definition and have been using that. We have worked with manufacturers and are providing a mechanism for manufacturers to provide information to the healthcare community and to the public and to the federal agencies that buy healthcare products via the worldwide web. We have provided an opportunity for manufacturers to post information on our worldwide web site for the products that they manufacture, both current and

past production, that have a problem.

Let me just mention that we are here today for these three reasons: To ask the panel or to solicit from the panel any suggestions or advice that you might have about products in your domain of expertise that may have a potential for a problem that we may not be aware of.

Although we have been in communication several times with all the manufacturers about this problem, and I think it is one that all the manufacturers are aware of, if there are some problems that could present a risk to patients if the problems are not addressed, we would like to be able to focus specifically on those, and if you have suggestions for us, we would like to provide a vehicle for getting those either through the Dr. Stuhlmuller, the executive secretary or the committee, or directly with me.

[Slide]

Our database that we operate is on the worldwide web. This is the web site. It takes you to the FDA home page, and on that home page there is an icon for the Year 2000 which will take you to the web site. There, one can see information for currently over 3000 manufacturers, and the information displayed there is either a statement from the manufacturer that their products don't use dates, because we had no way to know initially which manufacturers had products that might use a date in a computerized

product. So, we started out by asking all 13,000 or so manufacturers with a request of information. So, we heard from a lot of sunglass manufacturers or wheelchair manufacturers that they had no computerized products. So, that information of vital interest to many people is available on the web.

We also gave manufacturers an opportunity to tell us that none of their products they make, even though they may be computerized, are impacted by the year 2000 date problem in a way that would make them non-compliant with the definition that I gave earlier.

So, those two statements are there for manufacturers. In addition, if a manufacturer has a problem identified with one of their products, then they provide to FDA for posting on the web site the specific make and model, serial number, software version number, description of the problem with that kind of product, and the kind of solution the company plans to offer to deal with that problem. In some cases the solution is nothing. They say this is obsolete or this is such a minor inconvenience and doesn't have any real impact on the use of the product that we don't plan to offer a solution. All that type of information is available on the web site.

In addition, if a manufacturer has not completed assessment of their products, in other words, they are still

in the process of looking at all their past production to determine which products have a problem and which ones don't, they can list by product, along with the ones they have identified as having problems, those products whose assessment is still under way.

We think this information then will give the hospital engineers, the clinical engineering community and the hospitals the ability to look at their inventory in their healthcare facility and determine which products need remedial action, what the manufacturer is going to be doing about that, and which ones they need to worry about for replacement perhaps because of the lack of compliance and the age of the product if there is not going to be a solution offered by the manufacturer.

What can the FDA do here to encourage manufacturers to offer solutions? Our authority at this point is if a product, due to a date problem, would present an unreasonable risk to the patient, the type of problem that we have in Section 518 of the Food, Drug and Cosmetic Act that gives us the authority for mandatory recalls, then we would exercise that type of authority to deal with that problem. It is an authority we seldom have to use because the manufacturers normally will volunteer to recall a product that presents a risk to patients and we expect manufacturers to take those types of actions. But for the

vast majority of medical devices that have year 2000 date problems, they don't rise to that level where use of the product is likely to cause death or serious injury that required medical intervention, which is sort of the criteria that we use. Therefore, the manufacturers are going to have to make a decision as to whether they deal with this problem on an economic basis, on what does it cost to fix this problem basis, versus the good will of the customer or meeting the needs of the customer for corrections to a product. So, the vast majority of medical devices I think are going to fall into that category, and these are decisions that the manufacturer is having to make individually based on their market situation.

[Slide]

Just to give you an example of what is on our web site, I think this one may not be in the handouts, but this is just the page you get to. Basically, you can go there and get an introduction about some of the information that is available on our web site. We have some congressional testimony. We put out a guidance document in June which was addressed to manufacturers, giving them our expectations of what they needed to do under our current regulations under our good manufacturing practices or under our quality system regulations which require manufacturers to assess all their past production for Year 2000 date problems impact, and then

to take the appropriate corrective action to deal with that. As a minimum, that corrective action would involve notifying customers about potential problems that are uncovered.

You can go to this web site then to select and get a report, either by manufacturer name or by type of reports, and the whole database is available for downloading by healthcare facilities that want to use that database and compare to their own inventory. So, there is a lot of information available on the web site. It will continue to grow as we get more and more submissions from manufacturers. We are actively encouraging, along with the assistance of the Health Industry Manufacturers Association, the Medical Device Manufacturers Association and other groups, to encourage manufacturers to further share information.

Some of the things we have done over the last couple of years about this problem to try to make sure that the right activities are under way to deal with it were several letters to manufacturers, beginning last June, where we put manufacturers on notice that this could be a problem. We have developed a guidance for manufacturers. We have established our database. We continue to monitor reports of products with problems, and we will be undertaking some educational activities in the future to alert physicians, consumers, the appropriate audiences with the appropriate messages. We will be looking into that I think in the next

few months.

[Slide]

As a closing remark, this is my name and phone number if anybody would like to provide information directly to me or to contact me. You can also communicate via the executive secretary.

There are a few more slides in the handouts that I left with the panel which give some details about some of our past activities, but I won't go into detail on those. You can take a look at those if you are interested.

That is the quick and dirty story.

Introductions

DR. SIMMONS: Maybe we should have introductions of the panel now. Do you want to start off?

DR. CALLAHAN: My name is Tom Callahan. I am Director of Cardiovascular, Respiratory at the Food and Drug Administration.

MR. DACEY: I am Robert Dacey, the consumer representative.

MR. JARVIS: Gary Jarvis, the industry representative.

DR. GILLIAM: Roosevelt Gilliam, from Richmond, Virginia. I am a clinical cardiac electrophysiologist.

DR. CALIFF: Rob Califf, from Duke University.

DR. STUHLMULLER: John Stuhlmuller, medical

officer at FDA and executive secretary for the panel.

DR. SIMMONS: Tony Simmons, Wake Forest University.

DR. DOMANSKI: Mike Domanski, NHLBI.

DR. FERGUSON: Tom Ferguson, Washington University, St. Louis.

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

DR. WITTES: Janet Wittes, Statistics Collaborative.

DR. SETHI: Gulshan Sethi, University of Arizona.

DR. TRACY: Cynthia Tracy, Georgetown University.

DR. SIMMONS: I guess at this time we have an opportunity for the open public hearing. Is there anybody that would like to speak?

[No response]

Nobody requested any time so I think we will move on to the regular panel discussion of the product. As the company representatives comes, could you introduce yourselves and declare your financial status?

PMA P970029: Eclipse TMR 2000 Holmium Laser System

Introduction

MR. CHUTORIAN: Certainly. My name is Doug Murphy Chutorian. I am the founder of the company and I have financial interests as an employee and as a shareholder.

[Slide]

Good morning, ladies and gentlemen. We appreciate the opportunity to present our data to the panel today, and we appreciate everyone also coming to this particular panel to hear the Eclipse application for premarket approval for its products for TMR or transmyocardial revascularization.

I have mentioned my name, and it will be my pleasure today to introduce the presenters who are assembled to answer your questions and provide data to you. I also have the opportunity of describing the Eclipse products.

For the introductions first, let me start with Dr. Linda Fenney who is in the audience. She is the Vice President of Medical Affairs at the Eclipse Surgical Technologies, and is responsible for the study design of these protocols and the conduct of these protocols through their entirety. She will present the study design and methodology.

Anne-Marie de Merlier, also seated in the front row, is the Director of Clinical Regulatory Affairs at Eclipse. Anne-Marie de Merlier was responsible for data collection. She prepared the panel packets that you have and also wrote the premarket approval application. Today she will discuss data collection and analysis.

Seated at the table at the far end is Dr. Keith Allen, the primary investigator for this study. Dr. Allen

is a cardiothoracic surgeon at St. Vincent's Hospital in Indianapolis, Indiana. He has been involved in three of the Eclipse TMR studies.

Seated closer to me, here, is Dr. Eric Topol, Chairman of the Cardiology Department at the Cleveland Clinic. Dr. Topol has been an advisor to the company and has reviewed the data set, and will present to you his risk/benefit analysis.

[Slide]

There are additional experts that we have invited here today, seated in the audience, to answer any questions that you might have. Dr. Charles Du Mond, seated in the second row, is a biostatistician from the Pacific Research Associates Company, in California. Dr. Du Mond prepared the statistical analyses that we will present today.

Seated in the front row is Dr. Tom Fudge, an investigator and a cardiothoracic surgeon from Terrebonne Regional Medical Center in Louisiana. Dr. Fudge has participated in three of the Eclipse TMR protocols.

Finally, I want to introduce Dr. Philip Schoettle, who is an investigator and cardiothoracic surgeon from Methodist Hospital in Tennessee. Dr. Schoettle has participated in two TMR trials with Eclipse Systems.

[Slide]

Here is the Eclipse TMR device. As you can see,

the laser system is a solid state holmium laser which operates at 6-8 watts, or 1.2-1.5 joules per pulse. The wave length of it is 2.1 microns, which is in the mid infrared range, and it is a pulsed laser so it gives a set of pulses at a repetition rate of approximately five per second. Each pulse is quite short in length. It is only 200 microseconds long, and they will be delivered as the laser fiber tip goes through the myocardium. The fiber is actually a unique part of this. It is 1 mm diameter fiberoptic delivery system. You can see a picture of it here. This is the advantage of fiberoptics, showing the flexibility here as it is wound around a surgeon's hand.

But the goal of these fibe optics is to be able to be flexible enough to access parts of the heart that may be difficult to reach, in particular for example, the posterior aspect of the heart.

[Slide]

In use, these devices are displayed as follows: We have a malleable steel handpiece with a tip that is placed on the surface of the heart. The fibreoptic is placed just underneath the upper myocardium. Then laser energy is delivered as the fiver is advanced into the left ventricular chamber.

As you can see here, one channel will be made and then approximately 1 cm away a second channel will be made,

and this will continue until the procedure is over. Dr. Keith Allen will present more operative details to you.

I would just end here by saying that these devices have been presented in a number of clinical trials. Today we will discuss TMR versus medical management, and Dr. Linda Fenney will describe that protocol to you. Dr. Fenney?

Study Design and Methodology

DR. FENNEY: Good morning.

[Slide]

I am Linda Fenney, and I am a member of the company. I would like to start by putting the TMR procedure into some context this morning.

[Slide]

Six million Americans are treated for chest pain in this country every year.

DR. SIMMONS: Can you speak more clearly and from the microphone, please?

DR. FENNEY: I am sorry. There are 885,000 PTCA or CABG procedures performed annually. Despite this large number of procedures, which has been growing over the last few years with an aging population, it is estimated that there are 12 percent of patients that are now referred for procedures and are still judged to have no interventional option.

[Slide]

This is the population that we target with the TMR procedure. These are patients with class IV angina as judged by the Canadian Cardiovascular Society classification, those that are unable to perform any physical activity without chest pain, and may even have chest pain at rest, the sort of patient who has pain brushing their teeth, etc. They are not candidates for further revascularization attempts.

[Slide]

The study in which we chose to look at these patients was entitled a prospective, multi-center, randomized comparison of transmyocardial revascularization versus medical management.

[Slide]

This study enrolled from March of 1996 through February of 1997, by which time we had enrolled our originally planned cohort of 160 patients. As you see, it was a prospective, consecutive randomized controlled trial. The follow-up time points were at 3, 6 and 12 months, and it was monitored throughout by a data and safety monitoring committee. This committee was independent from our company, and was blinded to the randomization arm of the patients. They looked at data at various intervals as blocks of patients entered the study.

By our 12-month follow-up time point we had

achieved 100 percent follow-up for mortality on all patients, obviously, and 97 percent follow-up for the angina endpoint.

[Slide]

We continued to enroll in this study whilst the FDA had an opportunity to look at our data, and this was at the investigators' request, and we continued to randomize. We had entered a total of 275 patients by the end of July, 1998. We have 97 percent follow-up for eligible patients at 12 months for both angina and mortality endpoints in this group of patients.

[Slide]

Patients were included in the study if they had class IV angina, as I mentioned, but also if they had an ejection fraction above 25 percent, if they were not a candidate for other interventional therapies, and if they had an area of ischemia which was located in the lower two-thirds of their left ventricle, more than ten percent of which was reversible.

[Slide]

They were excluded from the study if they had had a Q-wave MI within the previous three weeks, or a non-Q-wave MI within the previous two weeks; if they were severely unstable, which was defined in the study as being unweanable from IV anti-anginal medication; and if they had an

uncontrolled ventricular tachyrrhythmia or decompensated cardiac failure.

[Slide]

They were, likewise, excluded if they had severe COPD, defined here as an FEV1 of less than 55 percent of their predicted value; if they are required chronic anticoagulant medication, such as coumadin; and if they had ventricular mural thrombus which could, of course, be dislodged during the procedure; also if they had a contraindication to dipyridamole, which was used as our stressor in our thallium stress tests.

[Slide]

We looked at several outcome measures in the study. Our primary ones were angina improvement; treatment failure, the definition of which we will come to shortly; and perfusion as measured by dipyridamole thallium stress tests.

Our secondary endpoints were those of mortality; event-free survival; rehospitalizations for cardiac causes; myocardial infarction; and medication usage.

Two further endpoints were added later in the study, those of exercise treadmill tests and functional status as judged by the Duke Activity Status Index, or DASI questionnaire. The addition of these two further study outcome measures was consistent with the later discussions

of the panel meetings.

[Slide]

Our initial primary endpoint then was that of thallium perfusion scans judging the thallium endpoints. The thallium perfusion scans were initially chosen based on the assumption of the mechanism of action of TMR, that is, that it acted primarily by patent channels and the channels remained patent.

Over time, other theories as to the mechanism of action came into view, and at that point we decided that thallium scans may not be the optimal way of looking at our endpoints. We went back and discussed with the FDA changing our primary endpoint to that of angina and treatment failure. Following these discussions, we moved to amend our protocol. We made an IDE amendment in December of 1996, and discontinued collection of thallium scans at that time. So, at that time thallium scans were eliminated as our only endpoint.

[Slide]

We then had three endpoints, those of angina improvement, treatment failure and thallium perfusion scans.

[Slide]

I would now like to discuss the collection of data around our major clinical endpoints and our methodology. Angina improvement in this study was judged according to the

Canadian Cardiovascular Society classification. Improvement was designated as two classes or more improvement. If you will recall, patients were class IV at baseline and so they were to have improved to class II or better to be judged as to have improved in the study.

Approximately a year ago we attended one of these panel meetings, and the emphasis was put on the need to have masked angina assessment. So we, at Eclipse, went forward and did a second assessment of angina endpoints in a masked fashion. We used an independent core lab at the Cleveland Clinic where we had two masked interviewers. They followed a script which has been used in several acute ischemia studies in the past at Duke University. This analysis took place at 12 months or beyond.

[Slide]

Thallium perfusion scans in this study were dipyridamole stress thallium scans. We obtained three images using SPECT technology and a standardized protocol at all sites. The images were stress, rest and six-hour delay. These are obtained at 3, 6 and 12 months after baseline. Perfusion improvement was defined as greater than ten percent improvement in the extent of any of our perfusion variables. Again, we used a core lb, this time at Brigham and Women's Hospital. They used computer quantified masked analysis of the data, which is more rigorous than the usual

visual analysis of thallium scan data.

[Slide]

Event-free survival in this study was defined as freedom from one or more of the following: Death; Q-wave MI; cardiac hospitalization; or revascularization attempts, such as PTCA or CABG.

[Slide]

For our functional status endpoint, as I mentioned, we used the Duke Activity Status Index, or DASI, questionnaire. This is a validated questionnaire and correlates well with oxygen consumption. It consists of 12 questions which are weighted, and enable a judgment of the functional status of a patient by summing the weighted score based on these questions. A higher score means that you have a better functional capacity. Again, we used a core lab, the same core lab we had used for the masked angina evaluation, and the DASI questionnaire was administered in the same fashion as the masked angina evaluation.

[Slide]

Medication use in the study was evaluated in comparison to pre-enrollment levels. The core lab that we used this time was at Stanford University Hospital, and the medications were again scored in a masked fashion. We used three categories of anti-anginal medication; nitrates, calcium channel blockers and beta blockers. The core lab

scored these changes in medication using five grades. They were either initiated or increased, stayed the same, decreased, or were discontinued.

I would now like to hand over to Anne-Marie de Merlier, who is Director of Clinical and Regulatory Affairs at Eclipse, and she will talk further about the methodology and the analyses.

Data Collection and Analyses

DR. DE MERLIER: Thank you very much.

[Slide]

Treatment failure in this study was defined a priori in consultation with the FDA, our scientific advisors and investigators in the study. It was an objective measure of when patients had failed the treatment to which they were originally randomized. It was defined in this study as the occurrence of one or more of the following events: Death, or Q-wave myocardial infarction; two cardiac hospitalizations within three months; or three cardiac hospitalizations within a year; or if the patient was unweanable from IV anti-anginals after at least 48 hours and two attempts at weaning.

[Slide]

It is important to understand treatment failure in this study because some of the patients in the medical management arm who met this endpoint ended up becoming

unstable, and withdrawing from this study and enrolling in a separate study for unstable patients.

These patients to which I refer were called rollover patients in this particular study. To roll over, not only did the patients have to meet the treatment failure criteria in the study, but they had to meet a second set of criteria to enter the unstable study. These criteria were either that the patient be, as I mentioned, unweanable from IV anti-anginals after at least 48 hours and two attempts at weaning; or, that they be too unstable to undergo a dipyridamole stress thallium scan.

Because patients were required to meet two sets of criteria, one to leave a study and a second to enter the unstable study, not all patients who met the treatment failure criteria ended up rolling over from medical management to TMR.

[Slide]

I would now like to describe the randomization in the study. A total of 275 patients were randomized in the study from March, 1996 through July, 1998, and 132 were randomized to TMR and 143 were randomized to medical management.

[Slide]

Of the 143 patients who were randomized to medical management, 46 patients met the treatment failure criteria

and withdrew from this study, became unstable and enrolled in the separate study for unstable patients. Thus, at the time of the analysis we had 132 patients who were originally randomized to TMR and who received that therapy; 97 patients who were originally randomized to medical management and who remained on medical management for the duration of the study; and 46 patients who were originally randomized to medical management but who eventually received TMR.

[Slide]

It is because of these patients who rolled over from medical management to TMR that we were required to perform three different methods of analyses on our data. Those methods were intent-to-treat and what we will refer to in this presentation as rollover censored analysis. In the intent-to-treat analysis, the 132 TMR patients were compared with the 143 patients originally randomized to medical management. This analysis was used for endpoints which were definitive prior to the patient rolling over and which could, therefore, not have been impacted by the fact that some of the medical management patients eventually received TMR.

The endpoints which were analyzed according to intent-to-treat include event-free survival, treatment failure and cardiac rehospitalizations. The rollover censored analysis was used for endpoints which were measured

at 12 months and which, therefore, could have been impacted by the fact that some of the medical management patients eventually received TMR.

To account for this, patients in the medical management arm who rolled over to TMR were censored from the analysis at the time that they rolled over to TMR.

Therefore, in this analysis you will see that we compared the 132 patients originally randomized to medical management with the 97 medical management patients who remained on that therapy for the duration of the study.

In these analyses, you will also see that we have presented the data from the 46 rollover patients for descriptive purposes only as they were not included in the statistical comparison between the two groups.

The rollover censored method of analysis was used for the following endpoints: Mortality, angina improvement, perfusion, medication usage, functional status as measured by the DASI survey, and exercise treadmill tests.

At this time, I would like to turn the presentation over to Dr. Keith Allen, from St. Vincent's Hospital in Indianapolis, who will present the clinical results of this study.

Clinical Results

DR. ALLEN: Thank you very much.

[Slide]

I am a cardiothoracic surgeon at St. Vincent's Hospital in Indianapolis, Indiana. I am the primary investigator on this study, and was the largest enroller of patients in this particular study.

DR. SIMMONS: You have to declare your financial status as well.

DR. ALLEN: I am sorry. The trip was paid for by the company but I have no other financial interests.

[Slide]

As previously mentioned, this is a multi-center, randomized trial that was divided among 18 centers across the United States.

[Slide]

The baseline characteristics between these two patient populations were very similar. Age average, 60 between the two groups. Preoperative ejection fractions were only slightly reduced at 47 in both groups. The predominant makeup of this patient population was male. Approximately two-thirds had a history of a myocardial infarction. Of note is that close to 85 percent of patients in both groups had had one or more previous coronary-artery bypass operations.

[Slide]

Cardiac risk factors were also similar between the two groups. We looked at diabetes, history of smoking,

hypertension, hypercholesterolemia, and a family history of premature coronary-artery disease. Once again, no differences between the two groups were noted.

[Slide]

This is a typical angiogram of a patient that was enrolled in the study. This is one of my patients. You can see by the broken wires this was a very obese patient. He had had two previous coronary operations. Left main ejection demonstrates no distal targets that could be grafted, and all of his bypasses were occluded.

[Slide]

The surgical technique is relatively simple to perform. I would love to stand up here and tell you this is a complicated operation but it is really not. It is performed in the operating room. It is done under general anesthesia. We use a very limited left anterior thoracotomy incision and, for the most part, patients are extubated at the conclusion of the case before they leave the operating room.

[Slide]

This is a typical patient of mine, showing the positioning to prepare for the limited left anterior thoracotomy.

[Slide]

This is the operative photograph showing one of

the laser fibers that can be used, demonstrating how the laser fiber penetrates the ventricle from epicardium to endocardium, and these laser channels are placed one square centimeter apart in the distal two-thirds of the left ventricle in areas preoperatively identified as being ischemic.

[Slide]

Among the 132 patients who were randomized to receive TMR, an average of 39 laser channels were placed in each patient. Laser procedure time was 25 minutes, and total procedure time was approximately an hour and a half.

[Slide]

What I would like to now do is go through in some detail of these clinical results that we obtained during the collection of data. We will discuss adverse events, mortality, myocardial infarction rates, the results of thallium scans. We will spend a fair amount of time on angina improvement. We will look at event-free survival, treatment failure, the use of medications, exercise treadmill tests and functional status, and the incidence of rehospitalizations for cardiac causes.

[Slide]

As a surgeon, the number one thing that I am interested in is am I hurting my patient, and can I do this safely and with complications that are reasonable? This is

the listing of perioperative complications that occurred either in hospital or within 30 days of surgery in the 132 patients randomized to receive TMR.

Overall, there was a five percent perioperative mortality rate. Seven patients died. Ventricular arrhythmias--these are all arrhythmias not just tachycardias or ventricular fibrillation but any ventricular arrhythmia that required a treatment, either chemical or electrical, within the first 30 days--occurred in 17 percent of patients. Atrial arrhythmias occurred in ten percent; hypotension, ten percent; non-Q-wave myocardial infarctions occurred in five percent. Congestive heart failure was seen in four percent of patients; respiratory insufficiency in three percent. Q-wave myocardial infarctions were very rare in this study and occurred in only one patient, for a one percent incidence. Transfusion due to blood loss from the TMR laser channel occurred in no patient.

[Slide]

I think there are two of these complications that warrant some more in-depth analysis, and these include death and ventricular arrhythmias. The death rate overall for this very sick group of patients with inoperable coronary-artery disease was five percent which, considering their comorbidities and their inoperability, I think as a clinician is quite reasonable.

There was an investigators' meeting, however, that was scheduled three months into the start of this study when data was presented regarding the early results. At that time, the investigators became aware that the mortality in the initial 25 patients that were enrolled in the study appeared higher than we would have expected or had desired. At that time, a discussion was carried out as to whether some patient care modifications could be made to improve that early mortality.

It should be noted that that early mortality was consistent with previously published mortalities for other TMR procedures at that time. So, it was not out of line with what we were expecting but, as a surgeon, you are always trying to do your patients better.

[Slide]

There were three issues that we discussed, and the consensus at the conclusion of that investigators' meeting was that we could perhaps improve our mortality by adopting these three minor patient care modifications. The first included stopping fluid loading patients. The concept of requiring fluid loading in patients was predicated on the history with the use of the CO2 laser.

I was trained by an investigator who started using TMR using the CO2 laser, which requires fluid loading and a full ventricle so that the collimated beam of the CO2 laser

is appropriately dispersed. It was apparent that fluid loading in our patient population perhaps was increasing subendocardial ischemia by increasing LVDP and, at the same time, was perhaps leading so some of the respiratory complications that I pointed out earlier.

A second area that we thought was important to look at was the rapidity with which you could drill laser channels with this device. As I mentioned earlier, this is a very, very simple device to use in the operating room. When I am showing or teaching somebody how to do this, it is much like eating bon-bons. You almost can't get enough because you can drill these laser channels so quickly. Clearly, early on in the study we were probably drilling these laser channels in groups quicker than we should have been doing, and not allowing the heart to recover in between bursts of lasers. So, the technique that we thought should be adopted was to place three to five laser channels and then allow the heart to recover rather than drilling 15 or 20 laser channels very quickly.

The third area was to minimize mechanical manipulation of the heart. I have been in practice now for five years and I am not used to operating, or was not used to operating on hearts that aren't cardiopleged and arrested, as some of the older cardiac surgeons are. But what we found was that you are now operating on a very

ischemic ventricle through a limited incision, and all of these patients, for the most part, had had one or more previous operations. Thus, minimizing mechanical manipulation of the heart to prevent arrhythmias is very important and needed to be stressed.

[Slide]

What we found was that if you break out the patients prior to that investigators' meeting in June of 1996 and compare it to the subsequent patients, after initiation of those three patient care modifications you saw a dramatic decrease in the 30-day operative mortality. Prior to these modifications operative mortality in the first 23 patients was five, or almost a 22 percent incidence. After these simple modifications were instituted at the investigators' meeting in June of 1996, in our last 109 patients we have had two operative deaths, for an incidence of less than two percent.

[Slide]

Similarly, using this same time frame of the investigators' meeting in June of '96, ventricular arrhythmias in the first 30 days following surgery prior to that investigators' meeting occurred in 34, almost 35 percent of patients. Once again, this is all ventricular arrhythmias that required some form of either chemical or electrical treatment. After the investigators' meeting,

with those simple modifications our ventricular arrhythmia rate declined to just under 13 percent.

[Slide]

I think it is important to specifically look at ventricular fibrillation that occurs in the operating room with this procedure. Once again, prior to those patient care modifications, probably most importantly pausing between channels and minimizing manipulation of the heart, operative ventricular fibrillation occurred in almost 22 percent of patients. After the investigators' meeting this was reduced to 5.5 percent.

[Slide]

If we look at freedom from all-cause mortality using Kaplan-Meier analysis at one year, and an intent-to-treat analysis, we see that there is no statistically significant difference despite the early initial mortality in this subset of patients that got TMR at one year, and 91 percent of patients in the MM group were alive at one year compared to 87 percent in the TMR group.

[Slide]

Once again, if you look at a little different analysis using a rollover censored, those patients that were originally randomized to medical therapy but rolled out of that therapy because of treatment failure and becoming unweanable from their IV anti-anginals, with this different

analysis the Kaplan-Meier one-year survival was the same as with the intent-to-treat analysis, 91 percent versus 87 percent.

[Slide]

Clearly, it is important that we are again not causing harm with this operation with regard to myocardial infarction. Q-wave myocardial infarctions were very rare in this study and, at one year with rolled over censored analysis, freedom from Q-wave myocardial infarctions were not statistically different, 98 percent versus 96 percent.

[Slide]

If you look at non-Q-wave myocardial infarctions, once again with one-year Kaplan-Meier, at one year the freedom from Q-wave myocardial infarctions, similarly with log rank analysis, were not statistically different, 93 percent versus 88 percent.

[Slide]

Angina is our main primary clinical endpoint that we looked at, and it is important that we define how we looked at this. Because it is difficult to determine an angina class change of only one class, we defined angina improvement as being an improvement of two or more CCS classes.

What I am going to show you in the next several slides are several different ways of looking the angina

data. I do this because the angina data with the rollover patients is difficult to interpret. What you will find at the conclusion of these slides is that regardless of how you analyze the data, angina improvement was always dramatically in favor of the TMR patients.

[Slide]

What you see in this slide is angina improvement, showing those patients who were randomized to TMR and got TMR. These are the patients that were randomized to the medical arm of the study and remained in the medical arm of the study. This third bar shows you patients that were randomized to the medical arm of the study but became unstable and rolled out of this study into an unstable protocol.

[Slide]

What you will see on this slide is that regardless of the time frame that angina was assessed, whether at 3, 6 or 12 months, angina improvement was dramatic and consistently improved in the patients that received TMR compared to those patients that remained on medical therapy. Interestingly, those patients that were in the rollover group, similarly, had a very consistent improvement in their angina.

You might note that what this slide appears to show you is that the patients who received medical therapy

and remained in the medical arm of the study appear to be getting better, going from 13 percent improvement to 32 percent improvement at one year. What is actually occurring here is that the rollover patients who were the sickest group in this category are leaving that arm of the study and are being treated with TMR. So, the medical arm of the patients are not getting better; it is simply that they are being biased by the rollover population leaving their arm of the study.

[Slide]

If you look at angina improvement in a purely intent-to-treat way so even somebody who rolled over and got TMR, he is still counted in the medical arm, you will see that you have a statistically significant difference in angina improvement in those patients in the TMR arm versus the intent-to-treat medical arm.

[Slide]

One way that I think is good to look at this is to do an analysis where patients aren't censored. It is important to include deaths, patients that were rolled over, or patients that were unavailable for follow-up. This next analysis is going to show you that we counted all deaths as class IV. So, if you died on the medical arm you were class IV, and if you died on the surgical arm you were class IV. Anybody who got a repeat intervention was classified as also

having class IV. If you are a rollover patient you are classified at whatever your angina class was at the time you rolled over to get TMR. If you were unavailable for TMR follow-up you were classified as class IV. If, however, you were unavailable on the medical arm we classified you as having class zero.

There were 58 patients who were excluded because they were not due for their 12-month follow-up data, leaving 217 patients that could be analyzed.

[Slide]

What we see with this analysis is that 58 percent of patients who got TMR had a dramatic improvement in their angina compared to only 19 percent of patients in the medical arm of the study.

[Slide]

Because angina is a subjective endpoint, something that an investigator or a validator has to ask questions about, there certainly can be room for bias. The company undertook masked validation to assess how closely we were validating patients from an investigator standpoint.

What this slide shows is the masked validation compared to the investigator's assessment. Of those patients that got TMR, investigators were very good at matching the masked validators. They were even. I think that is pretty easy to understand since most of the TMR

patients had either class zero or class I. Even as a cardiac surgeon, if nobody is having angina it is easy for me to say that they are having class zero.

It is a little bit more difficult to decide whether a patient is class II or class III. I think you see that in the group of patients that were in the medical arm of the study. Masked validators tended to classify the medical patients as having a little less angina than the investigators.

As you will see in the rollover patients, once again, if you got TMR the concurrence between masked and investigator assessment was very close. Obviously, the question that you should ask is, well, does this difference that you see here make a difference in angina assessment? And, the answer is no.

[Slide]

What we clearly see is that if you look at simply angina assessed by a masked validator, there continues to be a dramatic improvement in angina in those patients who got TMR. Similarly, the previous analysis that I showed you with the investigator's assessment once again confirms this.

[Slide]

We looked at dipyridamole stress thallium scans in three ways, looking at ischemic or perfusion defects, rest defects and delay defects. We defined an improvement as a

greater than ten percent improvement. We did this on the initial cohort, or the initial 160 patients randomized in the study. Paired baseline and follow-up scans were available in 79 percent of the TMR patients and 65 percent of the medical patients. Computer quantified pairs, which I think is the more rigorous way to evaluate thallium scans, were available in 67 percent of the TMR patients and 59 percent of the medical patients.

[Slide]

What these computer quantified thallium scans show was that there was no change in any of these three areas that we looked at, either ischemic, rest or delay defects, at 12 months compared to their baseline scans.

What this data shows me as an investigator is that we are not harming patients by creating microinfarcts and getting angina improvement by creating destruction of myocardium because we are not showing increase in rest defects. As we pointed out earlier, the selection of thallium scans was predicated on a presumption of mechanism. Clearly, at this time I don't know how this procedure works and, for me, the important of the thallium scans is that I am not creating increased perfusion defects.

[Slide]

If you look at event-free survival with a pure intent-to-treat analysis, and you define event as either

death or Q-wave MI, cardiac rehospitalization or repeat intervention, you see a dramatic divergence of these curves at one year with a Kaplan-Meier analysis, and 55 percent of patients in the TMR were event free compared to only 31 percent in the medical arm.

[Slide]

Treatment failure, as previously noted, was defined a priori. It included one or more of the following: death or Q-wave MI; two cardiac hospitalizations within three months; three cardiac hospitalizations within 12 months; or you were unweanable from IV anti-anginals after 48 hours and two attempts at weaning.

[Slide]

When you look at a Kaplan-Meier intent-to-treat analysis from freedom from treatment failure, you will note that if you were randomized to the medical arm of the study you were two times more likely to meet this treatment failure criterion than if you were randomized to the TMR arm.

[Slide]

The rollover patient characteristics in that particular population certainly complicate the analysis of the data, but I think it is important to specifically look at the characteristics of those rollover patients, and 87 percent, or 40/46 of the patients that rolled over were on

IV anti-anginals at the time of their TMR. Also, at the time that they were rolled over they had been on IV anti-anginals in a coronary care unit for over four days. In fact, almost 20 percent of these patients were transferred from a referring facility because of their inability to care for these patients.

[Slide]

What you will see here is a comparison of the rollover patients with those patients who remained in the medical arm of the study and who did not roll over, demonstrating that they clearly are, from an angina standpoint, more ill. Of the rollover patients, 96 percent had been hospitalized compared to only 42 percent of those patients who did not roll over in the medical arm, and 93 percent were on some form of IV anti-anginals compared to only 25 percent in the medical arm.

If you will also look at the mean hospitalization of patients, the mean hospitalization of patients was 1.7 for the rollovers in a three-month period compared to only one in a nine-month period for the medical group that remained on medical therapy.

I think then if you annualized it or did it on a per month basis, you will see that a rollover patient had an average of 0.6 admissions per month compared to only 0.1 for those patients who didn't roll over. Clearly, the rollover

patients, from an angina standpoint, were a more ill group.

[Slide]

I think an interesting analysis is to look at the rollover patients as their own control. You see here the 46 patients who were ultimately rolled over. Prior to them rolling over, in a three-month period they had 82 hospitalizations spread among 44 patients. After they rolled over and received TMR you had a dramatic decrease in the amount of hospitalizations, down to 19 from 82, and these were spread over only eight patients.

[Slide]

In order to do a statistical analysis we annualized this rollover rehospitalization rate, and prior to rolling over 7.1 admissions per patient compared to only 0.7 after they rolled over and got TMR--a dramatic difference.

[Slide]

Let's spend a moment on medication years. When we look at the medications it is important to ask did these patients simply get better because--even though they were on maximal medical therapy, did they get better because you somehow reduced medications in the medical patients and increased them in the TMR arm?

What we saw was that medications, from a calcium channel blocker standpoint, beta blocker and nitrates, were

not increased significantly different between any of the treatment arms, but what we saw was that despite the TMR patients having an improvement in their angina, they had a significant reduction in the amount of calcium channels and the amount of beta blockers that were used. Nitrates stayed the same. So once again, despite an improvement in their angina, TMR patients were actually using less medications.

[Slide]

Twelve-month exercise treadmill tests and the functional status using a DASI or, once again, not part of the original design of this study and collected after the study was initiated, we collected 90 treadmill tests, 81 of which were not in protocols. Because you are unable to pool different protocols with regard to exercise time, we analyzed those 81 patients who at 12 months had a Naughton protocol. What you saw was a trend for the TMR patients being able to exercise longer, 1.7 minutes longer, compared to the medical patients.

When you analyze METS you are able to pool all the protocols. So, with all 90 of the protocols pooled, TMR patients were able to statistically do more METS than patients who were on the medical arm.

[Slide]

The Duke Activity Status Index, as Dr. Fenney previously pointed out, is a validated questionnaire. It

was administered by a core lab with masked, trained interviewers at the Cleveland Clinic. The results of this functional status at 12 months show you that TMR patients had a significant improvement in their functional status compared to the medical patients also at 12 months.

Interestingly, the rollover patients, once again as outlined by this blue bar, also had a significant improvement, or had a very good functional status at the 12-month analysis.

[Slide]

Freedom from cardiac rehospitalizations I think is an important element to look at. Once again, you are able to do this on a pure intent-to-treat analysis. If you were randomized to the TMR arm you were 61 percent free from cardiac rehospitalizations at one year compared to only 33 percent free from cardiac rehospitalizations in the medical group.

[Slide]

Adverse events requiring cardiac hospitalizations are summarized on this somewhat busy slide but what it shows you is that you were more likely to have a cardiac hospitalization and to require IV anti-anginals if you were in the TMR arm compared to the medical arm and, furthermore, if you got readmitted you were more likely to be readmitted for angina and chest pain if you were in the medical arm

compared to the TMR arm.

The rest of these are sundry readmissions for the TMR and MM patients and were not different between the two groups.

[Slide]

In summary then, regardless of whether you use an intent-to-treat analysis or a rollover censored analysis, the incidence of death, Q-wave myocardial infarctions, non-Q-wave MI, and the results of thallium scans were not different between the two groups.

[Slide]

If you look, however, at angina, treatment failure, event-free survival, hospitalizations, quality of life, and exercise tests utilizing METS, regardless once again of how you analyzed the data, with the exception of METS for the intent-to-treat, all of these categories were markedly in favor of patients randomized to TMR.

[Slide]

In conclusion then, TMR significantly reduces angina symptoms. It reduces treatment failure. It reduces cardiac rehospitalization. It reduces medication use, and it increases event-free survival. It does that without a significant change in mortality compared to continued medical therapy.

I would like to now introduce Dr. Eric Topol,

Chairman of the Department of Cardiology at the Cleveland Clinic, for a brief risk/benefit analysis.

Risk/Benefit Analysis

DR. TOPOL: Thanks very much Keith. I would like to first point out I have been working as an ad hoc advisor for the company Eclipse. I have been compensated for my time. I do not hold any equity stake in the company.

[Slide]

I have been asked this morning to try to put some of these data that you have just heard into perspective.

[Slide]

First let me discuss the clinical problem that we are confronted with. As mentioned earlier, these are patients with inoperable coronary disease. They represent patients who have a very diffuse pattern of atherosclerotic involvement throughout their coronary arterial tree, and are really at an end-stage point in their coronary disease. These patients, for the most part, have profound physical limitations due to their angina and, because of this, they are truly suffering and desperate. They convey to their physician a sense of hopelessness, and up until recent times physicians have had a parallel sense of hopelessness. It is only through the newer developments of TMR and in the more nascent stage angiogenesis that we have technologies that may be offered to these patients to try to improve upon

their clinical status.

[Slide]

Recently, because of the opportunities to treat such patients that are burgeoning, we, at the Cleveland Clinic, performed a systematic review of the clinical problem. Dave Mukherjee and his colleagues at our institution reviewed 500 consecutive patients who had been referred to our institution for evaluation and management of their coronary-artery disease.

DR. STUHMULLER: Excuse me, is this information that is in the PMA? Because your discussion needs to be limited to information that is in the PMA.

DR. TOPOL: Slides were provided but I don't think it was in the PMA.

DR. STUHMULLER: All right, as a point of clarification, your discussion has to be limited to data that is in the PMA.

DR. TOPOL: Okay, if you don't want me to go through it, I won't. It was just the scope of the disease.

[Slide]

Typically, when we are confronting patients for evaluation of bypass surgery, which is performed in the U.S. in over 400,000 patients per year, we are comparing the risks for these patients perioperatively with respect to the potential incidence of death, stroke or myocardial

infarction with a tradeoff of patient benefit insofar as reduction of angina, and in certain patient subgroups there is an improvement in survival, such as those with left main coronary disease or poor left ventricular function. This typically would not even manifest until years into follow-up.

So, for the most part, there is a tradeoff that we have commonly accepted with a procedure that is very frequently performed and represents the standard in surgical vascularization today of a risk of mortality and stroke and MI versus the benefit in anginal reduction.

[Slide]

Now, with TMR the question is what is the tradeoff? We recognized the potential that there could be an excess perioperative mortality risk. In many respects, this project, this protocol and the antecedent one represent pioneering efforts in the field. The apparent difference in mortality at one year of 9 versus 13 percent by intent-to-treat analysis, or an absolute difference of four percent, needs to be weighed in perspective that, indeed, there was an early initial mortality, as Dr. Allen reviewed, but this was radically decreased when the technique was refined by a very early investigator meeting, not even three months into the initiation of the project.

By the changes in the protocol for fluid loading,

decreased manipulation of the heart, and by less aggressive use of channel creation, there appeared to be a very marked change in outcome for patients and all subsequent patients enrolled in the trial.

In addition, it is worth noting that over time the survival curves do not suggest any divergence with respect to mortality and, indeed, there main problem, if there was an excess mortality risk which was particularly localized to the early patients in the trial, was an early phenomenon, that is, in the perioperative phase.

In addition to these two points, a key point is that there has been subsequently a randomized trial that has been comparing TMR with bypass surgery as compared to bypass surgery alone, which does not show any excess in mortality but, rather, showed just the opposite for TMR, the same technique.

[Slide]

The benefits of TMR are quite substantial. As has been reviewed, the marked decrease in angina, which was quantitatively an 84 percent reduction at three months into the follow-up. This is a highly durable finding. It was rigorously determined. That is, it was validated through a masked system, and it was adjudicated, and it is highly consistent with the parallel, that is the antecedent trial performed with TMR before the current project. Clearly, it

is the most relevant patient focus endpoint because these patients are presenting because of intractable angina.

[Slide]

As has been reviewed, the treatment failure, which is a key endpoint in this trial, was very substantially reduced, from 74 down to 48 percent, as was the need for cardiac rehospitalizations, decreased by half, from 61 to 33 percent.

But I also would like to point out that the difference in the curves as the follow-up proceeded became further divergent so that at the first 30 or 60 days while there is an absolute benefit in these key endpoints, this has been widening throughout the extent of the follow-up.

[Slide]

So in conclusion, TMR represents a new technology for patients without therapeutic alternatives. The initial risk in this randomized trial, in the early cohort specifically, appears to be titrated by the refinement in the technique. There appears to be overriding evidence of clinical benefit for decrease in angina and ischemic-related hospitalizations. Thank you.

DR. CHUTORIAN: Ladies and gentlemen, that completes the company presentation.

DR. SIMMONS: We will now go to the FDA presentations. Maybe the company could step back and let

the FDA come in.

FDA Summary

DR. BERMAN: Good morning.

[Slide]

My name is Michael Berman. I am the FDA team leader for TMR and PMR device systems in general and, in particular, I am the lead reviewer for this particular PMA and I will be presenting the FDA Summary.

[Slide]

These are members of the FDA review team. These are the folks who wrote the summary memos, which were included in the panel pack, for their particular specialities. As well, there are other folks involved, who have been involved at one stage or another, either during the IDE process or the PMA process.

[Slide]

This morning I will present the FDA view as follows: I will give you a brief device description. I will talk about the preclinical testing that the sponsor did to support their claims for safety and efficacy; summarize the clinical evidence to support safety and efficacy claims. I will talk to you about possible limitations of the clinical trial, and I will remind the panel that FDA has proposed to them, included in the panel package, specific questions which we very much ask that you keep in mind

during your deliberations regarding this PMA application.

[Slide]

Very briefly, the device has three components.

The first is a laser which functions solely as a source of energy. The second is an optical fiber cable which conveys the energy from the laser to the operative site, which is the heart. The third piece is the hand piece which allows the surgeon to precisely position the tip of the optical fiber and to advance it through the myocardium as the laser fires.

[Slide]

Basically, what the device does is to create approximately 1 mm diameter holes through the left ventricular wall of a beating heart, going from the epicardial surface to the endocardial surface. The penetration is clean through from the outer surface of the heart into the ventricle.

[Slide]

The sponsor has provided data for bench testing to support claims of safety and efficacy for this device system. In particular, they have done electrical safety testing, which was done according to international standards. They have tested the software which controls the device. They have tested device functionality and performance. They have tested for electromagnetic

compatibility, which is important; the hospital environment is becoming more and more hostile that way. They tested for device symptom reliability; for the biocompatibility of those portions of the device which are in patient contact, which include the optical fiber and the hand piece; and for packaging and sterility. The sponsor provides the patient contact portions of the device sterile, as packaged and shipped, and they have verified the integrity of the package and they have verified the suitability of the sterilization procedure.

In the final memo, the lead reviewer memo that is in the panel packet, at the time of that writing there were still outstanding issues regarding electrical safety. Those issues have been resolved by the sponsor and there is no outstanding issue.

There is an outstanding issue regarding software. The sponsor is in the process of addressing that issue. There is no concern that they won't be able to. We are quite confident that by the time of approval this issue will be resolved.

At the time of the writing, there was an issue of electromagnetic compatibility. That issue has been resolved. There is still an issue as to the device symptom reliability. It is an issue of testing. The testing is being done. The sponsor is in the process of responding.

We are quite confident that the response will be provided and that it will be acceptable.

[Slide]

This is a brief summary of the clinical evidence that is provided. The sponsor conducted a randomized, unmasked comparison of treatment, transmyocardial revascularization versus medical management. They looked at a 12-month endpoint. They looked at improvement in anginal score which, as they have described, is defined as an improvement of at least two CCS classes, beginning with class IV. They looked at changes in myocardial perfusion by assessment of thallium scans. They looked at mortality and at major adverse cardiac events.

[Slide]

This is the way the data is presented in the panel pack. The FDA focused on 12-month endpoints. We presented data based on the treatment received. We compared that analysis to intent-to-treat analysis and to others, as you will see in the panel pack.

For our comparisons, we based the statistics on patients who completed the 12-month endpoints. We did not do last observation carried forward. We also present 95 percent two-sided confidence intervals, which I will show you in a bit, and we give the completeness of the follow-up at each outcome.

This is extracted from the panel pack. We want to show you a data display page that consists of two parts. The upper part of the page is a graphic. It will be either a bar chart or a figure, as appropriate. The bottom part of the data display page is a table. Together, these allow you to look at the data either at a glance or, if you are interested in specific numbers to see where this data came from, which patients were or were not included. This is from the pack. This is figure 9 on page 25.

[Slide]

This is a blow up of the graphic of the data display page. What it shows you on the left is the improvement in the percent of patients with angina improvement, defined as two CCS classes, in the treated group versus the medical management group, based on an intent-to-treat analysis. So, all of these patients are patients who had initially been assigned to medical management. It didn't matter whether they were rolled over or not; they were initially medical management so they stayed in for the analysis.

Here we show the difference in the percent of patients who received improvement and we show the 95 percent confidence bars. Since the bar does not include zero, it means that this difference was statistically significant.

Here we show angina improvement at 12 months

accounting for rollover. These are patients then who remained in the medical management group for 12 months. You can see that there is a difference in the percent of those patients which improved. Here is the difference showing that the difference is statistically significant.

[Slide]

This is a more detailed look at the graphic. This is the intent-to-treat analysis. It is what was on the left in the graphic. Here is the percent improvement for treated, for medical management. Here is the difference that is statistically significant. There is at least a ten percent difference and not more than 39 percent difference. We have 95 percent confidence in that. Here is the follow-up completeness. You can see that for the treated patients 95 percent completeness, 76/80, and 91 percent completeness, 87/96. So, this tells you that for this particular comparison in both groups the follow-up was about the same.

This is the second part of the tabular display. This is what we call the primary angina comparison. Again, it shows you the same information, 76 percent improvement versus 32 percent. Yes, there was a difference; yes, it was statistically significant. These are the limits of that difference, and this is the completeness of the follow-up. You notice in this instance the follow-up was not quite as complete for medical management as it was for treated.

[Slide]

We have extracted some of the conclusions of the clinical study that we are highlighting. This is angina improvement, improvement of at least two CCS classes at 12 months. For TMR patients, the treated patients, 76 percent of those patients are defined as improved; 32 percent of the medical management patients. The difference was 44 percent. It is at least 28 percent, not more than 60 percent. So, there is a statistically significant improvement in angina classification for this treatment based on controls.

[Slide]

These are the results of the imaging study which was performed only on the original cohort, as was intended. What it shows is that there is no change in the change and extent of ischemia or the change in rest defects for the TMR versus the medically managed group. This can be interpreted, as the sponsor pointed out, as showing that no harm was done. It can also be interpreted as saying that no improvement was made. It doesn't matter; the numbers say that there is no difference in perfusion as measured by thallium scan.

[Slide]

This is survival, all-cause mortality at 12 months based on a Kaplan-Meier estimate. In the treated group, 86.5 percent survival; in the medically managed group, 91.4

percent survival. There is no statistical difference at the 12-month endpoint. This treatment did not affect survival.

[Slide]

This shows freedom from major adverse cardiac event, as was defined, at the 12-month endpoint. This shows that there was 55 percent freedom from major adverse cardiac event in the treated group. A bit more than half of the treated patients were free from any major event at 12 months; 31 percent of the medically managed patients were free at 12 months. There is a statistical difference.

[Slide]

We would like to discuss briefly with the panel possible limitations of this trial. This was a real clinical trial that was done with real investigators and real patients. There are going to be limitations. We are not implying that there is anything wrong with the trial, we are just suggesting that in reality nothing is perfect. We ask the panel to consider the effect of these possible limitations on interpretation of the results and on their recommendation.

As regards the 12-month follow-up, in the original patient cohort, the original 160 patients, the angina follow-up at 12 months was 98 percent for treated and 97 percent for medically managed. In all of the patients, the 275 patients, 95 percent follow-up for treated, 89 percent

for medically managed. The masked follow-up for angina at 12 months, 91 percent of the original cohort; 78 percent of the original cohort in the medically managed group. The masked follow-up was only supposed to be done for the original cohort. The thallium perfusions which, again, were only supposed to be done for the original cohort, 67 percent of the treated and 59 percent of the medically managed. This last, roughly two-thirds in each group, this is about average for this kind of follow-up.

The study by design included patients with class IV angina only. Class III patients were not studied. So, there is a question as to whether the results from this study are applicable and, if so, to what extent to patients with class III angina. We note that patients who have class IV angina cannot get worse.

[Slide]

As noted by the sponsor, angina assessment is subjective, and patients are not masked as to their own treatment. So, there is possible patient bias in answering the questions. Often in a study, patients who are treated expect to get a benefit and react as if they do, and patients who are randomized to the control group often feel unloved and feel as if nothing was done there is no improvement. So, that is a problem in interpreting angina assessment.

[Slide]

This is a graph of the percent of patients that was rolled over as a function of time at which they entered the trial. Roughly a third of the medically managed patients rolled over to treatment. So, there was significant loss to the control group. Time to rollover was not short. That is to say, you can see that patients rolled over fairly evenly during the course of the study so there was not an issue with admitting patients and then immediately rolling them over. That was not a problem.

You cannot see from this slide, but we have looked at this data and we find that the rate of rollover is similar between the first half of the study and the last half of the study. There wasn't a change in the rate at which patients rolled over during the course of the study.

[Slide]

We have provided some questions for the panel which we will ask them to please consider during their deliberations with regard to this specific PMA application. I am going to go over them briefly now for the record. We will come back to you later in the proceedings and go over these questions one by one.

Of course, in the beginning we need to know is the data presented adequate for evaluation of safety and efficacy.

As regards labeling, are the indications for use as stated in the labeling, which is in your panel pack, adequately define the patient population? Are there contraindications which should be included in the labeling?

Do we want to warn physicians of the increased mortality observed in patients with unstable angina who were treated with TMR? And, we want to know does the proposed labeling provide an adequate warning for physicians.

[Slide]

The sponsor presented evidence, based on their investigator meeting of June, '96, that the perioperative mortality seen early, before that meeting, may have been related to the fluid loading of patients. The incidence of ventricular arrhythmias in the early patients may also have been related to fluid loading. There may be an influence, as sponsor noted, of the rapidity at which channels or groups of channels were made, and as to how much the heart was handled. All of those may have affected those ventricular fibrillations and mortality early on.

The sponsor made a change in their protocol and they showed you that the incidence of FV and 30-day mortality declined. Does the proposed labeling regarding fluid loading, handling of the heart and pausing between channels appropriately represent the state of the knowledge?

Should an additional informed consent, over and

above the usual surgical informed consent form, be required specifically for the TMR procedure?

[Slide]

In Section 11.4 of their manual, the sponsor presents a brief outline of the possible mechanisms of TMR. Does that material adequately summarize the current state of knowledge?

Do you, panel, have any other suggestions for the labeling? Should there be things in it which aren't? Should things which are in it--do they need to be changed or clarified? And, does the data presented adequately demonstrate safety and efficacy of the device as it is labeled?

[Slide]

We will ask you some follow-up questions about this particular PMA application. In particular, what type of long-term follow-up, in addition to anginal class and mortality data, would be appropriate for the TMR-treated patients, and how long should those patients be followed?

Are there any other issues of safety or efficacy which are not adequately covered in the labeling which need to be addressed in further studies, either before or following device symptom approval?

I remind you, panel, that we have additional questions after you have finished your consideration of this

PMA application. We have some questions regarding the future development of TMR and PMR which we would like to have answers for. Those additional questions will be presented following the deliberations on this application.

DR. SIMMONS: I think we are scheduled to start the panel portion of this presentation now but I think, because of the time, we will take our break now. I guess we will take a 15-minute break.

[Brief recess]

Panel Discussion

DR. SIMMONS: The primary reviewer from the panel's standpoint will be by Dr. Califf. He will start with the questions.

DR. CALIFF: First of all, let me just say that I think the presentation has been extremely clear, and somewhat refreshing maybe compared to some of the others that I have heard, in terms of the clarity of what was done with the analyses and how the patients were counted, and all those kinds of things. I am particularly happy with the subjective endpoint, that there was some independent assessment done by others than those who did the procedures.

My understanding is that we are going to ask general questions first and not get to the specific questions until afterwards. Is that right?

DR. SIMMONS: That is correct.

DR. CALIFF: I only have a couple of questions. The first is just a point of clarification. I understand from what was stated that none of the investigators in the study own stock or have stock options in the company. Is that correct?

MR. CHUTORIAN: None of the investigators were given stock options by the company.

DR. CALIFF: Do any of them own stock?

MR. CHUTORIAN: I believe that some may have bought stock after the investigation. We have no record of that, and have never asked the investigators that question.

DR. CALIFF: Just a point of clarification that may be a point of discussion with other panel members and the FDA, I strongly believe, particularly in an unblinded study that doing a pivotal investigation and owning stock in the company is a huge conflict of interest. I don't know now one could ever resolve that difference. So, I would urge that that be asked in any clinical trial, and especially in an unblinded trial, and I think that information should be made available to those who are reviewing the data.

DR. STUHLMULLER: Dr. Callahan, do you want to clarify that from an agency perspective?

DR. CALLAHAN: Generally, the policy is that we just believe in truth in advertising, that they make it

known. Certainly we ask all the presenters here to do that. We haven't asked that of each of the different investigators. Maybe, as you suggest, that is something that is worth doing. Not to deny it or not, but just to make you aware.

DR. CALIFF: So, maybe that should be a point of future discussion but, certainly for me, when I review unblinded clinical trial data that would lead to substantial profitability and money made, I like to know what the situation is with regard to those who did the assessment and enrolled the patients.

The main question I really have I think is around the difficult issue of how to view the mortality data in this study. I just want to make sure I have it correct. If we take the tabular summary that you provided, which is the one sheet which is sort of all the work that you have done and I think it is a nice document, it reads that the 30-day mortality in the randomized trial was 5.3 percent in the TMR group and 1.6 percent in the medically treated group.

MR. CHUTORIAN: That is correct.

DR. CALIFF: And what you stated is that within this randomized trial, in the early phase of the trial you had an excess of mortality. There was an investigators meeting called, and you changed the technology. If you could just restate how many patients were enrolled after the

investigators meeting and what the 30-day mortality was?

MR. CHUTORIAN: Certainly. Dr. Allen?

DR. ALLEN: After that investigators meeting, which was not called because of what was perceived to be an early mortality but was a scheduled meeting. It was just apparent at that time that there was perhaps a higher mortality than the investigators would like to see. As I mentioned in my presentation, that was the mortality though that was consistent with published early operative mortality in other TMR patients at that time. After June there were 109 patients who were enrolled, with a less than two percent mortality. There were two deaths out of 109, 1.8 percent.

DR. CALIFF: And, when you say two deaths, you mean 30-day mortality?

DR. ALLEN: Correct.

DR. CALIFF: Well, then if we go to the FDA summary--I just want to get the time frames correct, there is a diagram--let me get the right page so we can all be looking at the same thing. It is page 5-17. By the way, again, I want to commend you on giving us some pretty clear information to follow here. If we look between three and six months of follow-up, there are seven deaths in the TMR group and no deaths in the medically treated group. Do you know how those deaths break out in terms of the time frame before and after the investigators meeting?

MR. CHUTORIAN: The randomized investigation started in April. The investigators meeting was in June. So, all those patients would be after the investigators meeting.

DR. CALIFF: Are you sure about that?

MR. CHUTORIAN: Yes. I think all three-month follow-up would have been afterwards.

DR. CALIFF: Would the patients have been enrolled after then?

MR. CHUTORIAN: Oh, I am sorry, you asked about enrolled. Dr. Topol?

DR. TOPOL: I think there is definitely some difference, and that probably only would become evident by going through the seven patients systematically.

DR. SIMMONS: We can't hear you.

MR. CHUTORIAN: He was saying that the follow-up would have occurred afterwards, but the question was, was the enrollment of those patients done before or after April, and we would have to go through individual patients to tell you that.

DR. CALIFF: I just want to ask a few more questions about the deaths because I think it is the issue that I am most concerned about. What I am trying to get at here is that it may be tenable to accept that a change in operative procedure resulted in a lower mortality in the

first few months, but if there were a bunch of deaths between three and six months in that same cohort that was enrolled after the investigators meeting, then that would be of some concern.

DR. TOPOL: Looking at all the patients who died after the first 30 days in the TMR group, there is a total of nine, of whom seven are in those three-six months. Only two of those patients had their enrollment before the investigators meeting on June 20, '96.

DR. CALIFF: Okay. I guess the next question about the deaths is when you did the analysis to show the before and after effects, did you do any analyses to separate out operator experience from the specific techniques that were changed? In other words, if the issue really is that inexperienced operators have a higher mortality, that would lead to I think a lot of interest in having very specific labeling that may be requirements. If it is that you can just tell any operator not to give so much volume, then that would give us a different perspective. Were you able to do any analyses to sort these out?

DR. ALLEN: Unfortunately, I think it is very difficult to pinpoint which of the three modifications that the consensus was that we change as to how that would affect mortality. They are very simple modifications that at the

time were not thought to be major. I think the consensus among the investigators was, well, if we do these things the patients may benefit. In retrospect, those minor modifications resulted in some dramatic improvements. It is difficult now to go back and do a specific analysis as to which one of those specifically resulted in the decrease in mortality.

As a surgeon, these are very simple things to teach. It is not a complicated operation to do. So, simply instructing somebody on how to modify their care of the patient and how to do the procedure I think, in my mind, is quite sufficient.

DR. CALIFF: Well, not to be confrontational but I want to be technically correct here --

DR. ALLEN: Sure.

DR. CALIFF: What you have done is a correlation analysis with time, and things got better, and there may be some things in your mind, as a surgeon, but we can't really say, based on evidence, that we really can tease out, based on what you have told me, operator experience from particular maneuvers that may be useful.

DR. ALLEN: Correct. I think though what you would expect to see, if it were truly operator experience, the curves would continue to diverge over time, for example mortality curves, and you don't see that. It appeared very

early on, and with just simple modifications in how the procedure was done, that aren't complicated and aren't difficult to pass on to somebody, I think that is what we are seeing here. But you are absolutely correct though in that it is very difficult to tease those things out and, unfortunately, I don't think we are able to do that.

DR. CALIFF: I want to get a perspective from you as an investigator, and maybe from Eric and also from the company. I am concerned both about your own portrayal and the FDA's portrayal that there is not a higher mortality, and I think other panelists will have perspectives on this, but in a study this small, an insignificant p value tells us nothing about whether the mortality is higher. It is just not an adequate study to assess mortality, and I think it is a critical area and I am surprised that in the FDA presentation, which otherwise was a great presentation, but I am surprised that the comment was made that there is not a higher mortality.

I think that, you know, if one looked at the power to detect even a 50 percent higher mortality, it is just not there in a study of this size. Maybe even taking into account operator inexperience, our point estimate is at the one-year follow-up that there is up to maybe 40 percent higher mortality in these patients. The curves did not come all the way together; they stay apart. How much higher

mortality do you think would be acceptable, or how much of a higher mortality you think you should have to rule out in order for a patient to get the greater benefit that you demonstrated in angina?

DR. ALLEN: And I think that is a very valid concern and a good question. Clearly, in the latter part of the study after the investigators meeting, when those modifications were made, the mortality of 1.3 percent in the last 109 patients was very similar to the mortality seen in the medical arm. Patients were dying in the medical arm also.

Clearly, there is a risk/benefit tradeoff. Patients have reduced treatment failure, improved event-free survival, reduction in cardiac rehospitalizations, and a dramatic improvement in their angina. You do have some up-front risks, as with any surgical procedure, whether it is coronary-artery bypass, a pneumonectomy, whatever.

I think the operative mortality overall of five percent, even including those early patients, is pretty reasonable considering the inoperability and the disease state that these patients are in.

DR. CALIFF: So, you would say that it is reasonable, and you would have no qualms about a patient signing consent that there was maybe a 25 percent increment in risk of death, that the curves did not come together in

the data that we have, and that the benefits in terms of reduced angina would be an acceptable risk to take? See, the difference in bypass surgery is that the curves do come together and, in fact, they cross and there is a benefit in terms of survival. So, if we were purely empirical based on the data we have before us, we would say that the difference here is that we are asking patients to take a true hit in terms of higher risk of death, not just transiently but for the total duration of follow-up, in return for a symptomatic benefit.

DR. ALLEN: I think that is true but, for example, in coronary-artery bypass patients the curves only come together for a certain subset, the patients that have left main or severe left ventricular function. We operate on patients on a daily basis that have angina and who don't have left ventricular functions and the curves don't come together on those patients.

DR. CALIFF: We have a disagreement on that. I think I have spent a lot of time looking at those data. The curves do come together. They may not become significantly different in favor of surgery but they do definitely, definitely come together. I would be interested in the company's perspective and in Eric's perspective on this.

MR. CHUTORIAN: Certainly. There are a couple of aspects to this. Number one, we had a rollover population

in this study. The sickest of the patients in the medical arm dropped out and went into the rollover arm of TMR therapy. Therefore, the impact that would have on the medical arm if that wasn't happening is something you have to consider.

If you take a look at the mortality in the patients who rolled over, you see at 12 months in the Kaplan-Meier that it actually did cross over and, therefore, the rollover patients in the medical arm had a lower, not a statistically significant lower but just a crossover that you are looking for.

All the rollover patients rolled over after that investigator meeting. So, that would take into account the changes in technique that seemed to have modified the perioperative risk that you see in the overall numbers.

DR. TOPOL: I think it is a central point, and certainly deserves discussion. There are a few points though that I will try to put into perspective. One is that the absolute difference in mortality, the worst case scenario by intention to treat, is a 13 versus 9 percent or absolute 4 percent. Well, that could represent as much as 40 percent higher than the medically managed mortality. I think these are patients with advanced disease who are in a hopeless situation. In fact, some of them will say they would rather die than have to live with this type of angina.

So, taking that into consideration, I think such risk of four percent, which is largely confined to the perioperative phase and in this cohort in the early phase of the study, perhaps represents the worst case scenario.

I think a couple of points also are that because it is a new technique, the change in the way the technique was performed really did seem to have a very marked, quite a substantial impact on subsequent perioperative as well as late outcomes. So, perhaps that really does represent the worst case scenario.

Notwithstanding that, in reviewing these data, I remain somewhat concerned about what the mortality risk is. Of course, that four percent absolute is just a point estimate. It could be wider than this. And I think it really was a review, at least for me, of the other randomized trial that is not the subject of discussion today but in which over 260 patients were randomized to the same technique, TMR --

DR. STUHMULLER: Excuse me, your discussion needs to be limited to the data set in the PMA. The data outside the PMA can't be discussed.

DR. TOPOL: It was submitted with the PMA.

DR. STUHMULLER: I am sorry then.

DR. TOPOL: Yes, and the 265 patients in that data should not be suppressed. They were randomized between TMR

and bypass surgery versus bypass surgery, and there was a substantially lower mortality among the patients who received TMR. This helped, to me, mitigate concerns regarding mortality. And, in the discussion about mortality and the new technique, all data that were available, which also extend the window of the operative technique--there was a longer temporal experience--need to be factored in to the evaluation of the technique.

DR. CALIFF: I am going to just touch for a second more on this in a minute but I want to divert to the question of refractory angina. Can you review what medical therapy these patients were on?

DR. ALLEN: These patients were felt to be by the cardiologists on maximal medical therapy.

DR. CALIFF: Do you have it quantified?

DR. ALLEN: If I could have the slide on medications?

[Slide]

What I can show you is that in the TMR group over 40 percent of patients were on three or more drugs; in the medical group, once again, over 40 percent of patients were on three or more drugs, and those drugs were classified as either calcium channel blockers, beta blockers or nitrates. We also looked at analgesic-narcotic use in these patients, and approximately 22 percent of patients in both groups were

on some form of an analgesic or narcotic.

DR. CALIFF: Let me just persist on this for a minute. So, only 40 percent were on three drugs?

DR. ALLEN: Correct, 42 percent in the TMR group, 49 percent in the medical group.

DR. CALIFF: I mean, I am having a little trouble with that being called refractory end-stage.

DR. ALLEN: There were also additional patients on four drugs. So, if I add them up, 51 percent were on three or more drugs; 57 percent were on four or more drugs. So, those are the numbers. I left out those patients that were considered on four drugs.

DR. CALIFF: Do you have any information about why over 40 percent of the medically treated patients were not being treated with full anti-anginal therapy?

MR. CHUTORIAN: We do have information on the drugs. There were 36 percent on two drugs.

DR. CALIFF: Again, I am just going to throw out some things here. I know it will be a topic of discussion with other panelists, but typically if you talk about people being hospitalized multiple times we think of three classes of drugs, nitrates, beta blockers and calcium channel blockers. These are people with good left ventricular function who didn't have severe other comorbidities. So it is hard to understand why the cardiologists wouldn't have

maximally treated their angina rather than allowing them to keep coming back into the hospital. I would have thought it would be worthwhile to know what was happening there. But you don't have any further information about why patients weren't treated with three drugs fairly often?

MR. CHUTORIAN: No, we just have that 90 percent or more were on two drugs, and we presumed that there was either inability to tolerate a third drug or that we caught them at a period of time when they came in when they were only on two medications or this wasn't listed on their form.

DR. CALIFF: I have one more. I know this is an impossible question, but the last time I looked at a device like this it was said the treatment worked by relieving the ischemia and making the thallium defects better. Now we hear that it has nothing to do with that but we don't really know why it works. So, what is going on here?

DR. ALLEN: I think the last time that you looked at this the assumption was made that the thallium was improved and that relieved angina. As you will recall from that presentation, there was no clinical correlation between angina improvement and thallium improvement. There was a statistically significant difference in thalliums but there was no clinical correlation to that.

Once again, as an investigator, we clearly don't fully understand how this procedure works, and there are a

number of theories. So, the selection of thallium as a way to evaluate how this works is probably not appropriate. For me, as I said in my discussion, the important thing that thallium shows me is that these patients aren't getting their angina relief by creating microinfarcts or worsening their defects.

DR. CALIFF: So, we know some things that it is not but we don't really know what it is. Is that a correct interpretation?

MR. CHUTORIAN: We could talk about several of the mechanisms that have been proposed and discuss some evidence if you would like.

DR. CALIFF: Maybe you could just summarize on the what the leading theory is.

DR. ALLEN: I think there are generally four theories or really three theories that people hold. One is that the channels remain patent. A second is that the procedure stimulates angiogenesis. A third is that it denervates the heart. I think those are probably the three leading theories, and I have been at meetings where you can spend all weekend discussing the pros and cons of each of these, and that is why I think at this stage of the science we simply don't really understand how this procedure works.

DR. CALIFF: Let me just say that I am delighted that you have actually gone to the trouble to show that

patients lives are improved by the treatment, and I would like to know why the treatment works but it is not the most important issue to me.

But in that vein, if we could turn to page 5-23, I understand why you presented the masked assessment as being consistent between the investigator assessment and the masked assessor, but I would urge people to at least come away with a slightly different conclusion. I think this is actually a great data set. I hope it gets written up to make the case that we need masked assessment. Although it doesn't change the answer in this particular trial, it certainly could change the answer in trials where the magnitude of the difference is less because if you look at the top panel, if I am interpreting this correctly, what I see is that out of the three cases in TMR where the masked assessor said it was class IV angina, there were two cases out of those three where the investigator said it was much less than class IV. Essentially, what you see is sort of a downgrading in the TMR group by the investigator, and an upgrading in the medically treated patients.

Also, it is interesting that you end up with a correlation coefficient of 0.66 for the experimental patients and correlation of 0.39 for the medically treated patients. So, if anything, to me this is really a pretty important statement that we need to have unbiased assessment

of subjective endpoints. I think you have done a good job of showing, through a variety of analyses, that the fundamental answer doesn't change. But I think a note of caution for other people in the audience is that the fact that there is a reasonable correlation coefficient does not mean that you would get the same answer if there was less of a treatment effect. Do you agree or disagree with my diatribe on that?

MR. CHUTORIAN: I would agree.

DR. ALLEN: I would agree.

DR. CALIFF: So, just to come back, the final issue for me, and I will not dwell on it too much more, is that while the actual hard core assessment of how patients felt is critical, I think in order for patients to put a therapy that offers symptomatic therapy in perspective, it is useful--at least if I were a patient I would want to know what the tradeoff is in terms of the potential of death.

I think we end up with a data set that has a fairly broad confidence interval on that estimate, and you have some arguments based on the change over time that are certainly reasonable and rational arguments, but I will probably just leave it to the rest of the panel here to try to ask questions to sort of sort through the feelings about that. If I am just out of line on my concern about this, that is okay. It might be useful to turn it over to others

at this point.

DR. SIMMONS: Dr. Domanski?

DR. DOMANSKI: I would start in two ways. First of all, I certainly compliment the company on a long and arduous process, clearly executed, and on their choice of consultants. I think that has been good.

I do have some concerns and I would like to take them from perhaps the more specific to the more general. I would like to explore first of all that rollover mortality. You told us that they were sicker patients, but I wonder if perhaps you could go through the numbers of mortality in the rollover TMR group compared to the mortality in the group that got TMR and the mortality of the medically treated patients. If you could just go through those numbers. I want to make sure mine are correct.

It looks to me like actually the group that rolled over and got TMR had the lowest mortality of the whole lot. It belies your claim that they are the sickest. It sounds like they were not only not the sickest but may have been less sick.

MR. CHUTORIAN: Could we have slide 90, please? I think we can show you the Kaplan-Meier. Dr. Allen?

[Slide]

DR. ALLEN: The first part of your question is that, as I pointed out in my talk, from an angina standpoint

40/46 of these patients had been on intravenous anti-anginals in a coronary care unit, refractory to being able to wean them for, as I said, over 4 days prior to rolling over. We, fortunately, in our rollover patients were able to treat them quite effectively.

What you see here is Kaplan-Meier one-year survival using the three-group analysis, those patients who got TMR, those patients who were randomized to medical management and remained in medical management, and those patients who were randomized to medical and rolled over. What you actually see is that this group of 46 patients had the best one-year survival, followed shortly thereafter by the medical group and then by those patients originally randomized to TMR.

DR. DOMANSKI: I guess that is the point, and I apologize for being obtuse. The numbers I wrote down, and this probably came from a table--well, I wonder if that doesn't make the point. It looks like the mortality is actually lower in the group that rolled over and got TMR. I am not sure I see why that doesn't make the point I made originally.

DR. ALLEN: You are absolutely right, but I think all of the rollover patients rolled over after the modifications were made in the surgical technique.

DR. DOMANSKI: Well, I am not sure I know what the

modification in surgical technique tells me. I mean, you sort of changed your technique in the middle and there are other things that could explain the difference, including I guess operators being more effective.

I think actually those data are probably better explained by the fact that your rollover group was not as sick because you wouldn't expect that having somehow rolled over conferred a protective effect on them. So, it is probably not absolutely central to the application, but I guess I am persuaded that that was a less sick group, for whatever reason. It is obviously subjective in terms of rolling over and assessment of anginal status.

MR. CHUTORIAN: We can show you slide 61, and that will perhaps clarify a little our opinion about it. Dr. Allen?

[Slide]

DR. ALLEN: Once again, this is the slide that I showed to you. From an anginal standpoint, I mean, these patients were in a refractory state. I understand what you are saying.

DR. DOMANSKI: I mean, I will stipulate that your data are what you showed, but I think the mortality difference is a little bit easier to measure.

DR. ALLEN: In the talk I also outlined that the patients in the rollover group had been hospitalized

significantly more times than those patients in the medical arm. So, I understand what you are saying. All I can do is tell you, you know, the data we collected would imply that the rollover patients, at least from an angina standpoint, were in dire straits. Fortunately, they got a good result and we were able to treat those patients effectively.

DR. DOMANSKI: The other question I have is just a point of information, I suppose, and I couldn't find it in there, did you have any patients who were put into this protocol and then subsequently were revascularized by angioplasty or CABG?

MR. CHUTORIAN: Yes, there were. Dr. Allen?

DR. ALLEN: I think that is a good point. There were actually three patients that ultimately got coronary-artery bypass grafting. Two of those patients had progression of disease in previously undiseased vein grafts. So, they had recurrence of their angina. They then had a period of time in the study when they had their angina come back. They underwent catheterization and they had new disease in their vein grafts. They underwent bypass operation and their angina subsequently resolved.

We did have one patient, and he happened to be my patient, who was randomized to the medical arm of the study and continued to have refractory class IV angina, did not meet any of the rollover criteria and sought coronary-artery

bypass surgery, in Milwaukee, and died on the table.

So, I think that illustrates that these patients don't have a lot of alternatives. Even though this operation carries with it, as we said, five percent mortality, the alternative is that some patients that will go out and find a surgeon that is willing to operate on them in a desperate situation may be much, much worse.

DR. DOMANSKI: Well, I think also that in many patients there is some subjectivity, some very real subjectivity about what represents an inoperable patient. Actually, the fact that you didn't have more is of interest. I mean, it sort of suggests that in fact you picked a population that probably was inoperable as a group. I mean, I would have expected, frankly, more rather than this small number that you had.

I guess the larger point, and we talked about going to larger points, is if one looks at these data one could say that what you have--there is a very nice article published in the "Science" section of The New York Times a few weeks ago on placebo effect, and one could look at your data and say, "gee, they didn't do anything, at least objective, with regard to providing more blood flow to the heart." I am not a surgeon and I don't profess expertise relative to denervating the heart; I know you can do it with a transplant, but I am not sure that you have a procedure

that is necessarily effective in denervating the heart. One would not expect early results to be based on angiogenesis, although maybe later results could be.

I see no mechanism demonstrated at all. Now, there are certainly times when we accept, without mechanism, a treatment. But one mechanism that does clearly present itself, in fact, in the presence of objective demonstration of lack of better perfusion--one mechanism that certainly rears its head is placebo effect. And, one can look at these data, and I am going to ask you to argue differently, and say that what you have is a placebo, a rather elaborate placebo that, in fact, may increase mortality although your study, in fairness, doesn't have the power to demonstrate either an increase or decrease, although I must say it seems unlikely that it is going to decrease given the data that are there. But it looks like a mortality inducing placebo. That works like a champ as a placebo. Why isn't it that?

DR. ALLEN: Clearly, you do have to be concerned about placebo effect. I think there are several arguments that would mitigate against a placebo effect. At least with a surgical procedure, once the patient that has had the operation becomes separated temporally from the surgeon, whom he obviously wants to please, the placebo effect becomes much less, and at least with operations typically you start to see the placebo effect disappear at 6-7 months.

DR. DOMANSKI: I am not sure that is true. I think there are data to suggest otherwise in terms of the duration of placebo effect.

DR. ALLEN: Additionally, I think the next argument is that we looked at, for example, angina at multiple points during the course of the procedure and at each time point the angina improvement was consistent.

The third point is that if you will look at curves such as cardiac rehospitalizations, event-free survival, treatment failure, those curves continue to diverge at one year by Kaplan-Meier analysis. It would be my impression that if it were purely placebo you would tend to have those curves become parallel.

DR. DOMANSKI: But doesn't your event-free survival include subjective things relative to hospitalizations and people coming in with angina that could be explained by placebo?

DR. TOPOL: I think what you raised, Dr. Domanski, is intriguing and I have certainly thought about whether this is a possibility in light of historical data like the Beck procedure and Vienberg procedure, going way back, multiple decades, could this have induced changes by a surgical procedure, not a real placebo but, rather, the operation per se?

I think there are many things that mitigate

against that theory. The thing to me that is quite impressive is that these are cardiac surgery veterans. In this series of patients, 86 percent have already had bypass surgery at least one time, many two or even three times. So, if an open chest operation was going to have such a pronounced effect on their subjective perception, and not just subjective but also by independent assessment, on angina and their need to go back to the hospital again this would be quite surprising because they should have derived this from prior major cardiac open heart procedures. So, they are not cardiac surgical naive in that respect. They have already not endured one or more operations but have had intervention in a continuum of their coronary atherosclerotic disease.

So, I think the marked difference in angina, the marked reduction in the need for hospitalizations, and all the other things that have been presented really argue strongly that just doing the procedure per se without any mechanism that has not been fully elucidated, of course, could have induced the benefit.

DR. DOMANSKI: Well, this is going to be an interesting question as the FDA and the FDA panel consider a device that has little objective demonstration--objective demonstration, physiologic benefit--in a setting where we may just not understand the mechanism. It may be there but

we don't understand it. It is actually an interesting and complicated question. I think we have been through this before, obviously, with other devices.

I guess the last thing that I would say is I agree with Dr. Califf's concern about unmasked studies in general with investigators who hold an equity position relative to that device. There is a lot of money to be made in that business. I, frankly, don't think disclosure in any way mitigates the conflict in that sort of setting. Just saying you did it doesn't mean you didn't do it.

I don't know about this particular device but in general where it is unmasked and where there are major public health implications, I think that sort of investigator really is not acceptable. That is all I have.

DR. SIMMONS: Dr. Ferguson?

DR. FERGUSON: Well, I would echo the remarks that have been made about the presentations. I thought they were excellent.

I am only going to query you about one part which is really troubling me, and it is very important because it is going to ultimately go into labeling. Dr. Allen, at the beginning even you said that the first case for each of the investigators in the aggregate had an exuberant, let's say, mortality rate for that group. At three months you had a meeting and you made some changes which you want to put into

your warnings on the label that I don't really think you have proved have anything to do with the fact that over time the mortality rate is decreased. I mean, I have to be convinced that the lack of fluid loading and waiting between the laser hits has made that kind of dramatic difference.

Now, I am not against your putting those in there, but I don't think the data has been presented to show that that, in fact, is the reason that your mortality has come down. I think that is an important point for another reason, and that is, since you have introduced the CO2 laser in your own presentation here, the issue comes up because those are not issues that are recommended, or precautions that are recommended with CO2 devices. So, the question comes up if these, in fact, are really, truly important because there is a difference between your laser type and the CO2 laser--that is a critical question to me. But first you have to demonstrate to me that those are important enough to put in the warnings as proven.

DR. ALLEN: I share your concerns, Dr. Ferguson, and I wish I could stand here as an investigator and give you some concrete statistical analysis that would give you that reassurance, but I can't.

What I can tell you is that those three modifications in technique are what we felt, among the investigators, were the important changes that led to a

reduction in mortality. I think also if you will look at --

DR. FERGUSON: Excuse me for interrupting, but this was done three months into the study. Right? Why was it not related to the learning curve, if you will?

DR. ALLEN: Well, a learning curve, to me, implies that it is something that every operator has to go through, and I don't think that these minor modifications represent a significant challenge to most surgeons, and can be passed on quite easily, as the company has done in their labeling.

DR. FERGUSON: I am not talking about the modifications as being part of the learning curve. I am talking about the whole procedure as part of the learning curve because I think you will admit that, in spite of the fact that you say it is a simple procedure and so forth, there are certain critical elements of the operation, like not dislocating the heart if you can possibly do so--I am just asking the question.

DR. ALLEN: Sure, and I absolutely understand. I guess I would use the comparison that there clearly is a learning curve, for example, in doing a Ross procedure. There is no question that that needs to be done repetitively and several times to get good at it. This operation is not difficult to do, and by simply verbalizing some simple patient care modifications, I think the mortality can be dramatically decreased.

DR. FERGUSON: I think that is true of any operative procedure, and I think that there is no simple operative procedure that doesn't have a learning curve. That would be my guess about it.

DR. ALLEN: Yes, sir.

DR. FERGUSON: But, as I say, these have two implications I think we need to resolve. The panel has to deal with them, and those are, are these modifications that are your impressions among your group, which may certainly be correct, are these things that we need to put in the warning material?

Number two, do they relate somehow, because that question inevitably is going to come up--do they relate somehow to a difference in the way that this laser beam works as compared to CO2?

DR. ALLEN: I think if you will look at the Kaplan-Meier one-year, for example, mortality between the CO2 and the Eclipse laser--and I don't think we are here today to compare lasers but yours is a very valid question, TMR performed with the CO2 laser, at one year, with a Kaplan-Meier, has a mortality of 15 percent. TMR at one year, performed with the Eclipse laser, has a mortality of 12.5 percent. So the mortality at one year, regardless of which you laser you utilize, is the same.

DR. FERGUSON: But the issue is not whether they

are different procedures, because I agree with you, I think they work in a similar way except for channel size and a few things like that, but I am getting back to the issue of whether this package has to come with these conditions and the other one doesn't. That is the point.

MR. CHUTORIAN: Dr. Ferguson, as you point out, there are some differences between the laser types. In the CO2 there is just one big beam. So you need to have the heart full of blood to try to block that beam. In this case, as you point out, because of the fiberoptic, the beam here diverges so it is not a requirement to have fluid loading because you can just go through the heart and with the divergent beam it does not take as much blood to block the beam. So, this enables this device to be able to operate without fluid loading.

As you pointed out, the way the labeling reads now, for the committee and the panel, is that we say under precautions: avoid excessive fluid loading prior to the TMR procedure, unless clinically indicated, as fluid loading may contribute to an increased risk of mortality. We further say that the operator should pause after the creation of every few TMR channels, as such pauses may reduce the likelihood of ventricular arrhythmias. I guess it is up to the panel to decide if you want to put that in. We felt that that would be reasonable.

DR. FERGUSON: Right. I think that I don't have any problem with that. I have another problem, which is going to get to the specifics, and that is what is fluid loading and how much is needed to not overload the patient to fulfill these requirements, and so on and so forth.

But I think I would like to stick with the issues I brought up first, and I guess I would have to say that at the moment I don't hear any really valid answer to my question about why the whole group of investigators started out with a very high mortality. Very early in the series you got together and changed a bunch of things and things got better, and so you attribute the improvements to those particular things that you decided upon.

DR. TOPOL: Perhaps I can help on that, Dr. Ferguson. I think there are a couple of points to underscore. Firstly, we are talking about the first 23 patients who had been assigned to TMR in the randomized trial. So, that only constitutes 17 percent of that random assignment. Moreover, if one adds the patients who ultimately went to TMR in the course of the project because they went into this rollover category, it only constitutes 13 percent of the patients.

So, the point here is that the early experience, with those patients who died in the first 30 days, the seven patients with perioperative death, five of those had

occurred before the June 30th, 1996 meeting. But many of the patients had their procedure done, the TMR procedure, by an operator surgeon for the first time after that juncture.

DR. FERGUSON: Their first case?

DR. TOPOL: Yes, it was their first case because it was such a small proportion, as I said, between 13 and 17 percent, so that somewhere between 83 to 87 percent of the remainder of the TMR patients were being done, and by the time of that early assessment at that pivotal meeting in the project, many of the operators had not even done their first surgery.

So, I think that strongly argues that this is not an operator learning curve--and, of course, I think one key assessment is that you cannot say which of these three major changes in refinement, whether it be the fluid, whether it be the cardiac manipulation, or whether it be the markedly lower aggressiveness of the channel creation, you can't say which of these, but I think you can make a very strong case that this change or refinement in technique led to a marked change in outcome for the duration of this product and, as I have been alluding to for the duration of this project beyond this randomized trial well into another 266 patient randomized trial.

DR. FERGUSON: Thank you for your explanation.
That is all I have, Tony.

DR. SIMMONS: Dr. Crittenden?

DR. CRITTENDEN: Can you tell me, Dr. Allen, you were selected as the principal investigator because you contributed most of the patients? That was it, or was it an a priori designation?

DR. ALLEN: I don't believe it was an a prior designation. I think it primarily involved a very busy center and I accumulated the most patients in the study.

DR. CRITTENDEN: So, in this group of 23 patients that have been much debated, how many of those did you contribute?

DR. ALLEN: The first patient that I operated on died. So, one of those deaths was my patient.

DR. CRITTENDEN: And the remaining deaths were distributed among others equally?

DR. ALLEN: Correct. No center had more than one, one early death. Correct.

DR. CRITTENDEN: And, can you be more specific about the manipulation that you are talking about? I mean, I assume you do an entry thoracotomy and then you expose the pericardium, and if there are some adhesions you have to dissect the adhesions to expose the myocardium. How much more manipulation do you need? You say this is a simple procedure and it seems that reflecting the pericardium is all you really need to do.

DR. ALLEN: You are right. In a virgin case reflecting the pericardium is not a hard thing, but in some of these that had one or more cardiac operations, reflecting the pericardium can be difficult. You also have to expose the distal two-thirds of the left ventricle, including the inferior posterior wall which, through a limited thoracotomy, as I am sure you are familiar with, can be difficult. So, as a surgeon, I am used to operating on a heart that is arrested and cardiopleged, and I can move it about and dissect it and remove the adhesions without fear of causing arrhythmias or problems with the heart. In this operation, much like doing a beating heart operation, you have to have a little different mind set, and I think that just needs to be reinforced to a surgeon that is going to be doing this.

DR. CRITTENDEN: So, you are saying maybe you can push but not push so hard. Is that what you are saying by "less manipulation?"

DR. ALLEN: Correct.

DR. CRITTENDEN: And, is there an occasion where you decide maybe not to push because that is causing a problem and then you have to abandon that area?

DR. ALLEN: Certainly.

DR. CRITTENDEN: Do you think that affects the effectiveness, if we really know about the effectiveness of

this?

DR. ALLEN: You know, if, as an investigator, I thought I had to do undue manipulation of the heart to drill two more laser channels, in my mind, I probably wouldn't place those two extra laser channels. Does that answer your question?

DR. CRITTENDEN: Yes. Now, you talk about letting the heart recover between channel creation. What is the heart recovering from specifically?

DR. ALLEN: Clearly, when you are discharging a laser, and because of the simplicity with which it can be done with this device, it is very easy to fire many, many laser channels in a very short period of time. I know you are a cardiac surgeon, and it is simply manipulating the heart and tapping on the heart very vigorously and frequently that can cause problems. So, what was very apparent early on, after the first case, was that you needed to drill three or four or five channels and simply then allow the heart to recover. Actually, it works out very nicely because during that period of time it takes maybe 30-45 seconds for these channels to stop bleeding. So, actually it is a good thing, and you are just allowing the heart not only to recover but the bleeding from those channels is easily controlled at that point.

DR. CRITTENDEN: The panel pack said that the

incidence of cerebral embolism, and that is a problem associated with this procedure, is less with this laser than with the CO2 laser. Is that really true?

DR. ALLEN: If you have that page in the panel pack --

DR. CRITTENDEN: I am sorry, I didn't mark it. I just remember from reading.

DR. ALLEN: Okay. We actually had no cerebral vascular complications in any of the patients that had TMR, and I don't believe that in the panel pack we made a comparison to the CO2 laser. I think the incidence of cerebral embolization with the CO2 laser, if not zero, was very, very low also. So, I don't think that this is a problem.

DR. CRITTENDEN: Do you think the best technique is with the anterior thoracotomy? Can this be done thoracoscopically? Must it be an anterior thoracotomy?

DR. ALLEN: No, it can be done through a sternotomy. It can be done through an anterior thoracotomy, and it can also be done thoracoscopically.

DR. CRITTENDEN: And the effectiveness, do you think, would be the same regardless of the exposure?

DR. ALLEN: I think, yes.

DR. CRITTENDEN: But there is a certain amount of territory, you have to cover the two-thirds?

DR. ALLEN: Right now, it is lasering areas that are ischemic. So, if the posterior wall, for example was ischemic, you would at least need to try--let's say you were doing it thoracoscopically, you would have to get to the posterior wall thoracoscopically. I am sure you do some thoracoscopic surgery, and that would be difficult in somebody who has had multiple operations.

DR. CRITTENDEN: But most of these patients are going to have multiple areas at risk, aren't they? They are not going to be just single territories, I don't think.

DR. ALLEN: Right.

DR. CRITTENDEN: Do you have any idea in terms of mechanism whether endocardial initiation of the channel versus epicardial initiation of the channel makes a difference, from your perspective?

DR. ALLEN: You know, I am not sure I can comment on that. I think there are a lot of theories with regard to some specific mechanisms but, at this point, we didn't evaluate that.

DR. CRITTENDEN: Were you ever tempted to combine this with some of your open coronary-artery bypass procedures? Do you think that is a worthwhile thing to do?

DR. ALLEN: I am involved in a parallel randomized, prospective trial that was looking at coronary-artery bypass grafting combined with TMR versus coronary-

bypass grafting alone in patients who could not be completely revascularized with CABG alone. So, I have experience with that procedure.

DR. CRITTENDEN: But I think the labeling for this advice is that it only be done as an isolated procedure, not in combination--

DR. ALLEN: We are here today to look at TMR sole therapy compared to medical therapy. When those other trials have been adjudicated and properly presented, then there may be other indications.

DR. CRITTENDEN: And one final question, what was the 30-day mortality for the rollover group?

DR. ALLEN: Four out of 46. I think that is about 8 percent.

MR. CHUTORIAN: I think you were asking after TMR was performed on a rollover basis. So, the number is 4/46. In the first 30 days two of those patients had rolled over and were part of that.

DR. CRITTENDEN: I guess what I am trying to work out is for unstable angina patients.

DR. ALLEN: Well, in 46 patients who rolled over, their operative mortality was approximately eight percent. So, if you looked at the overall operative mortality of the TMR patients for the entire study, it was five percent. So, in answer to your question, yes, it was slightly higher.

DR. CRITTENDEN: That is all I have.

DR. SIMMONS: Dr. Wittes?

DR. WITTES: I have a few more questions related to the mortality. Let me first echo what has been said before about the clarity of both the company's presentation and the FDA's presentation. It makes it so easy to review when everything is clear. So, that was great.

Another just slight comment, just because there aren't alternative therapies, it doesn't mean this treatment is effective, and I think we need to evaluate this on its merits and not the fact that there is nothing else.

I have five topics that I want to bring up. The first is the placebo effect. The second is mortality. The third is the rollover. The third and fourth are rollover and treatment failure, and finally a little bit about drugs.

Let me say that we talk about the placebo effect as if it is all or nothing, that either there is a placebo effect and this is all placebo effect, or it is a treatment effect. But, in fact, what one would expect is that some of the effect is placebo and some of it is real, and then in this kind of situation it is impossible to tease out the magnitude.

Similarly, as Rob pointed out, one of the things that is so interesting about the concordance or lack of concordance in the blinded and the unblinded reading is the

trend that the investigators had toward thinking that the TMR people had lower anginal class and the medical management had higher. So, again, what you have, it seems to me is that one of the things that we have to deal with is that the effect that is estimated, the "naive" effect, just the observed effect, is almost certainly--that is too strong, is probably an overestimate because it incorporates whatever placebo effect there is and this bias in classification. I think part of the whole risk/benefit analysis, whether it is explicit or implicit, is what is the effect, how large is that.

So, the question that I put on the table is have you thought about how to modulate your estimated effect by the likelihood that there is some placebo effect and by this bias in reporting?

DR. TOPOL: I think your point is a good one. Firstly, there is maybe some admixture of having gone through a procedure. I don't think that actually would be classified as placebo effect, but just that the procedure per se could influence the subjective outcome of the patient. Indeed, even in bypass surgery this has been thought to have some role in why patients have a sense of better well being after conventional bypass surgery. It is impossible to ferret that out.

This goes back to Dr. Domanski's comments as well,

and I think that the most cogent evidence that this is well beyond any type of placebo effect comes from this technique in the randomized trial as an adjunct to bypass surgery, where there is a reduction in mortality. That can't be from a placebo or from the procedure itself. That is a very hard endpoint.

Now, with respect to the adjudication, I think that Dr. Califf's points and yours are really vital. That is, any assessment of angina when we are doing a procedure for angina and we have really short-term follow-up, the angina assessment becomes critical and it needs to be done in a masked way, and these data certainly support that. But the masked data in a sense validate but also demonstrate the discordance. I think that while it is a highly significant difference still, it is less than for future studies using angina as an endpoint that masked validation is a key ingredient of evaluation outcomes. That is objective. It is being done truly in a blinded fashion with respect to no knowledge of treatment assignment. And, it is a natural thing, indeed, by investigators whether it is evaluating a lesion after angioplasty or surgical success, to sway in a very subtle way their views of a subjective endpoint. That is why that independent assessment is really just critical.

DR. WITTES: Thanks.

DR. CALIFF: Janet, can I just ask you, I mean,

you have been doing clinical trials for a while, how would you look at it? I mean, I don't know of any objective way to sort it out.

DR. WITTES: I don't either.

DR. CALIFF: Okay.

DR. WITTES: I mean, it seems to me that if there weren't that placebo effect, I would actually prefer to estimate the effects on the basis of the masked data rather than the investigator data. How to factor in this other, who knows. But I think what I am saying is that it is reasonable to suspect that the observed difference is an enhanced rate rather than a true rate.

Let me touch on mortality. We are obviously all concerned about it, and part of the nature of the concern is that we can't get our hands around it because the study is too small to be able to tease anything out of it; to be able to know what is going on.

Maybe I am looking at the wrong page because I was looking at page 4-30, which said to me that, for example, it was not true that all the mortality in the TMR patients was occurring in the very beginning. I mean, it looks to me as if there are deaths throughout the year. Is that right? Am I reading this wrong?

MR. CHUTORIAN: No, you are reading it correctly. There were deaths before 30 days and also deaths in the

follow-up period.

DR. WITTES: Okay, because I heard something that said that nearly everything was in the beginning and that is not what I am seeing here.

Again, I think there is no good answer to this, and the only way you can do a trial when you are worried about mortality is to make sure that the size is large enough so the probability of having an excess, if there really isn't, is small.

DR. TOPOL: If I could speak to your point, the issue here is that the difference, the absolute difference in mortality at 30 days between the TMR and the medical management group is 3.6 percent, that is, 5.3 versus 1.7, on the page that you are referring to, whereas at one year there is 4.9 percent. So, the absolute difference of 3.6 over 4.9, approximately 80 percent of the difference, is occurring in the first 30 days. That is what I was referring to when I was trying to sum things up.

DR. WITTES: Okay, that has clarified it.

But now let's get to the definition of treatment failure and rollover because for me this is the most difficult part. I agree with Mike that you can't tell just because of outcome--you can't look at outcome to deduce how sick people were. You need to look at baseline and, of course, one never has enough data to do that. But it is not

the outcome that tells you how sick, it is who they were.

And, one of the questions that I have--let me ask you first a question of fact and then I will tell you why I am concerned. In order to go into rollover you have to have a treatment failure. One of those pieces is not death, but I would imagine most of it is coming from at least two hospitalizations. Is that right?

MR. CHUTORIAN: You would like a breakout on why the patients' treatment failed?

DR. WITTES: Yes.

DR. ALLEN: As you pointed out, Dr. Wittes, yes, certainly treatment failure primarily wasn't death, it was cardiac rehospitalizations and, most importantly, unweanability from IV anti-anginals. That is probably one of the largest single reasons for treatment failures, unweanability.

DR. WITTES: Let me ask the clinicians here, is that subjective? How subjective is that?

DR. SIMMONS: Very.

DR. WITTES: It is? Okay. And, I assume that the hospitalization for the rollover TMR does not count as one of the hospitalizations.

DR. ALLEN: Correct. You know, I can't argue that unweanability from IV anti-anginals isn't subjective. I would feel very uncomfortable as an investigator if we kept

patients on IV anti-anginals. We admitted them, and put them on IV anti-anginals for 24 hours and the cardiologist called and said, "hey, I can't wean these patients; you've got to take them to the operating room," or even at 48 hours, which is what the protocol suggested. The average time the patients were on IV anti-anginals was over four days. I think the longer the patient is in the hospital and in an intensive care situation on IV anti-anginals, the less likely it becomes subjective and the more it becomes somewhat more objective. You certainly can argue that, but that would be my position.

DR. CALIFF: Janet, just for full disclosure here, let me say what happens in environments I have been in. I don't think this mitigates the good effort made to measure things and the measurements that were made, but we all know that, particularly with a new procedure like this, there is a very delicate balance between what the patient subjectively wants and the interaction between the doctor and the patient that can lead to, you know, keeping somebody in the intensive care unit. We all see it waiting for transplantation, for example, bumping people up to inotropic therapy so they move up on the list. It is very clear as I have gone to other medical centers and seen the trials with this type of device, not this particular trial because I never can remember which device is which. But with this

type of device, it is another reason to think that the estimate may be a little over what the reality is because patients who are having symptoms would like to get a new treatment if they think it is going to help.

DR. WITTES: That was exactly the input of my question, is that a mechanism, and if the patient wants the TMR or the doctor wants the patient to get TMR, and the angina is a little bit worse than it has been, and they will pop you into the hospital and then you are eligible.

DR. ALLEN: It required two points. They had to meet eligibility requirements to be enrolled in an unstable angina protocol. So, they simply couldn't fail treatment. As Anne pointed out in her talk, there were patients that had treatment failure but didn't roll over. So, what allowed you to roll over was that you had to be unweanable from IV anti-anginals. The protocol specifically stated it had to be for at least 48 hours and when two attempts had been made to wean patients off. Our average was four days, not two days.

But Dr. Califf's point, you know, I can't argue against that, and unfortunately that is the reality of clinical medicine. We try to do the very best job we can at putting together a study like that, and I cannot tell you that that wasn't going on but we tried to avoid it as much as possible.

DR. WITTES: I have just one more point on this. I understand the intent-to-treat analysis just fine, so I can look at those and I know what those mean. As soon as we get to the medical management with and without rollover versus the TMR, I don't know how to read those. It seems to me that the least one needs to do in doing that kind of analysis is to say this is outside the realm of the randomization; this is an epidemiologic comparison, and these analyses need to be corrected for all kinds of variables and they really need to be what I call aggressively modeled analyses because, otherwise, any kind of data selection that is going on, any kind of imbalance-- you can't separate that out from the effects.

So, again, my own reading as I look at intent-to-treat is that it is nice and clear so this is not a problem, but I think if it worked, if there weren't such a clear difference even in your worst case analysis, I think the analysis comparing those two medical management groups is really problematic.

Finally, I need to ask you a little bit about these drugs. You presented today those people who had decreased their usage of calcium channel blockers, beta blockers and nitrates, but I think there were those who increased as well. Isn't that right? They were in both directions?

MR. CHUTORIAN: Yes, on figure 5-48 in your panel pack is where you will see patients who increased. There were no significant differences between those numbers.

DR. WITTES: But if you are separating increase and decrease, they need to be put together in some way.

MR. CHUTORIAN: Yes, there are difficulties in putting them together in this kind of analysis, but since there was no difference in patients who increased their medication but there was a difference in those who decreased it, so those are the ways we took a look.

DR. WITTES: Okay. That is all.

MR. CHUTORIAN: Thank you.

DR. SIMMONS: Dr. Sethi?

DR. SETHI: I just have a few questions, and mostly they are technical so maybe Dr. Allen can help answer some of those questions.

Do you have a breakdown of patients who just had anterior versus posterior and inferior creation of channels? I think it is difficult to make a lot of channels posteriorly and inferiorly, and you mentioned that you don't want to dislocate the heart very much. Do you have a breakdown of that, how many patients had creation of channels anteriorly versus posteriorly-inferiorly?

DR. ALLEN: We have collected that data but I don't have that at my fingertips. I can't give it to you

right now. I understand the point you are making though.

DR. SETHI: Are there patients where you wanted to create channels posteriorly and inferiorly and you couldn't do it?

DR. ALLEN: No, in my personally experience, I enrolled 64 patients in the study and I was able to create channels where I wanted to. Sometimes I had to take a little more time to expose that particular area of the heart and do things a little slower, and be a little gentler, but I ultimately could place channels where I wanted to have them placed.

DR. SETHI: And you sect the heart completely in the pericardium?

DR. ALLEN: Actually, what we tried to do is just dissect the distal two-thirds. If there are patent vein grafts, we try and avoid manipulation of those patent vein grafts, just as you would in a redo operation. Oftentimes you will dissect an anastomosis. For example, a lot of these patients had patent mammaries and so, rather than trying to dissect out the mammary artery to expose a little bit more of the high anterior wall, you will go up to where the mammary is inserted and so you are able to expose the distal two-thirds pretty effectively.

DR. SETHI: And, you say you have done 64 patients in the whole study. Has any investigator gone through a

coronary artery or coronary vein, and what happens to those patients with a bleeding heart?

DR. ALLEN: Actually, I can't tell you that I have never drilled through a coronary vein or a coronary artery. I would assume that if that happens you could have some serious events. When I have done this operation in conjunction with bypass, I have placed a channel through an artery and it didn't cause any problem.

DR. SETHI: I would think putting a 1 mm hole in a patent coronary artery or vein would cause significant bleeding, especially with a beating heart. I am surprised that you don't see that problem.

DR. ALLEN: With this particular laser, bleeding is not a significant problem. It really takes 45 seconds to a minute for your series of three to five laser channels to stop bleeding. I have never had to place a stitch on a sole therapy patient to stop a channel from bleeding.

DR. SETHI: And how do you know that you are through the endocardium? Is there any way to demonstrate that, maybe by echo?

DR. ALLEN: Sure. When you are using sole therapy in just a TMR patient, you can confirm your hits, as I call them, with TEE but TEE actually isn't necessary. It is both an acoustic noise that you hear, the channel changes as you are drilling it, ch-ch-ch, you can actually hear the channel

when you are into the ventricle, and there is also some tactile but primarily it is acoustic. I did a study that looked at a comparison, my ability to hear and feel channel penetration, and compared that blindly with the anesthesiologist looking at the TEE, and there was almost 100 percent concordance. So, it is pretty easy to tell when you get into the ventricle.

DR. SETHI: On a slide you showed the operative procedure and a balloon pump in the patient. I just wonder how often you use a balloon pump in these patients.

DR. ALLEN: You know, in our experience there is a tradeoff between the benefits of a balloon pump versus using some inotropic support. A lot of these patients have peripheral vascular disease and diabetes and comorbidities that make complications from a balloon pump not necessarily minor. But I am not at all hesitant to put a balloon pump in a patient, particularly the patients that have unstable angina. Clearly, mechanical support rather than inotropic support and decreasing their oxygen consumption that way is better, but balloon pumps aren't without their complications. In my experience, I use a balloon pump about ten percent of the time.

DR. SETHI: And what is their use in the whole study? Do you know that?

DR. ALLEN: I am not sure that I can tell you for

the whole study, but in my center it is ten percent, and my balloon pump use is primarily in patients who have unstable angina.

DR. SETHI: The rollover patients, they were eight percent, right?

DR. ALLEN: Yes, sir. Correct.

DR. SETHI: In your experience, if you do use a balloon pump, does it make any difference in these patients? Do you think that you might be able to optimize their ischemic events during surgery better, or does it make any difference?

DR. ALLEN: You know, in my experience, having had some complications in these patients from balloon pumps, there is clearly a tradeoff. Your hypothesis is well taken, but I am not sure that, at least at this panel meeting with the data we have, I can honestly answer that question effectively.

DR. SETHI: And, about ten percent of patients had ventriclular fibrillation. How do you manage those patients most of the time?

DR. ALLEN: I am sorry, could you repeat that?

DR. SETHI: About eight or ten percent of the patients have ventricular fibrillation during the procedures. How do you manage those patients?

DR. ALLEN: You know, as I showed on my slide,

after the investigators meeting when we made some of those changes, our operative ventricular fibrillation rate was 5.5 percent, and those patients typically, in the operating room, are electrically cardioverted. Those patients have R2 pads on, particularly if they are redo. If they are not redo it is easy to put paddles in, but most of the patients are redos and they have R2 pads on.

DR. SETHI: That is all for the time being.

DR. SIMMONS: Dr. Tracy?

DR. TRACY: Just a few questions, and it is, at least in part, going to reflect some of the other members of the panel. I am still trying to get a handle on the mortality and then interpret it in light of one of the questions that the FDA has for the panel.

The bottom line is that in the original intention-to-treat TMR group there is a 4.1 percent mortality. Then, in medical management without rollover there was 7.2 percent mortality. So, those are probably, I would think, the best groups to be comparing. So, is that a significant difference?

Trying to then get a handle on taking out any effect that the change in the operative technique may have had, can you comment in any way on the 109 patients, I guess, who enrolled after the change in the procedure? Can you comment on their mortality?

DR. ALLEN: In the 109 patients after the June, '96 investigators meeting we had two 30-day mortalities. So, it was 1.8 percent.

DR. TRACY: Can you provide an annual mortality? That 12.1 percent I believe is the total one-year mortality. Can you provide the one-year mortality on that group that was done by the modified procedure?

DR. ALLEN: After the June procedure? Yes, if you will give us a minute to pull out a back-up slide. You are asking for, like, a Kaplan-Meier analysis out to one year after the June meeting?

DR. TRACY: Right.

DR. ALLEN: Give us a moment and we will get it. Do you have another question while we do that?

DR. TRACY: Yes, Dr. Sethi raised the question of the operative VF, and it was 5.5 versus almost 22 percent pre- and post-modification. However, the 30-day--there is still a fairly significant 7.3 percent, if I am doing the numbers right, of the patients even after the modification who ended up with fairly significant ventricular arrhythmias. I think that needs to be compared in some way with what happens in the medically treated patients who did not roll over. So, I am trying to interpret the deaths. There is not much information given in the individual patient information, it just says "cardiac death." What are

those deaths?

MR. CHUTORIAN: Sure, we can give you some information on those. May I have slide 146, please? Dr. Allen, perhaps you would like to comment?

DR. ALLEN: Could we have that previous slide up?
[Slide]

This is the analysis you were looking for, looking at one-year Kaplan-Meier after the June meeting. You see it is 93 percent versus 90 percent. Is that what you were asking for?

DR. TRACY: Yes.

DR. WITTES: Do you have the intent-to-treat one as well?

DR. ALLEN: Dr. Wittes, I don't have a slide prepared that shows that as intent-to-treat.

DR. TRACY: And the issue of the deaths? What is a cardiac death? Is a cardiac death non-sudden death? How was that categorized?

DR. ALLEN: As far as deaths were concerned, the cardiac deaths--and you can put up slide 146--

[Slide]

This lists the reasons for the 30-day mortalities in the seven patients. One of the patients got his thoracotomy and fibrillated prior to even getting the TMR, and he died in the operating room. One patient had an acute

MI with severe LV dysfunction and died. One patient had a pulmonary embolus in conjunction with an acute myocardial infarction and died on day five. One patient had a documented pulmonary embolus on autopsy and died on day four. This patient is mine, with LV dysfunction on day 11, with low cardiac output state. One patient, confirmed by autopsy, had a vein graft which acutely closed postoperatively, and had ventricular fibrillation related to that acute vein graft closure and died. Then, the final patient died of multi-system organ failure.

So, in answer to your questions, at least operatively, the one patient who didn't actually get TMR died of ventricular fibrillation as a primary cause. Is that what you are asking for?

DR. FERGUSON: Could I just ask one question?

DR. ALLEN: Yes, sir?

DR. FERGUSON: I just want to ask a question about that vein graft that closed. What was the target area for that? Was it right or somewhere else?

DR. ALLEN: Actually, that was a right coronary vein graft, and it was very badly diseased distal right but the vein graft was still patent.

DR. FERGUSON: That is the one that closed?

DR. ALLEN: Correct.

DR. FERGUSON: Okay, thanks.

DR. GILLIAM: I would just like to ask one question. LV dysfunction--these patients all had EFs greater than 45 percent. Is that not correct?

DR. ALLEN: The average EF was approximately 45 percent in the study. They had to have an EF greater than 25 percent, but there was a wide range in EFs in these patients.

DR. TRACY: Just a couple more points really. In the presentation, talking about the 30-day ventricular arrhythmias with modification of the TMR technique, there is still a significant number of patients who had ventricular arrhythmias and that is concerning. I don't know what else to say about it, other than that is concerning. There isn't information presented on the medical management group.

DR. ALLEN: There was a sudden death in the medical arm of the study. So, arrhythmias are presumably occurring in the medical arm that are resulting in deaths. I share your concern about arrhythmias. I think you have to look at the patient population you are dealing with. We are clearly not revascularizing these patients. As our thallium data shows, they still have some ischemia. So, arrhythmia is a known complication and problem in this patient population.

DR. TRACY: Looking through, the 21 who had perioperative VF, there were two who subsequently died, and

even if both of those were sudden deaths that would have been about 9.4 percent. So, I couldn't make a case that there was a clear correlation but it is concerning to see that percentage of patients who had ventricular arrhythmias and, just as a caution, I think that that should be raised.

DR. TOPOL: I certainly agree with the concern but one other factor is the ascertainment issue, and the patients undergoing TMR--and, of course, ventricular arrhythmia was fairly widely defined--were undergoing continuous monitoring, whereas the medical patients may have had such arrhythmias but unless they resulted in sudden cardiac death, it may have been under-diagnosed in that set of patients.

DR. TRACY: That is true. One of the contraindications to enrollment was if the patients required ongoing anticoagulation or had a mural thrombus. I would think that those should be listed as contraindications, I would think. I don't think you would want to put somebody back on coumadin. Any comments?

DR. ALLEN: Actually, in one of the other studies on unstable angina part of the protocol is putting patients back on coumadin and, actually, that was an early concern and we kept that contraindication throughout the study but you certainly can anticoagulate these patients fairly soon after surgery and, in fact, our experience using this on

patients that are undergoing coronary-artery bypass grafting where they are fully heparinized bleeding is not an issue. So, that is probably not a reasonable contraindication based on my experience.

DR. TRACY: All right. How about mural thrombus?

DR. ALLEN: That is clearly a reason. I can't argue against that.

DR. TRACY: Then really just one final point, again going back to the questions that the FDA has for the panel. Question four was dealing with unstable angina. I am still having a hard time understanding, do you or do you not have a worse outcome with TMR if you have unstable angina? If so, then how in the world did you end up having a rollover group that had unstable angina? Please clarify that for me because I am a little lost on that.

MR. CHUTORIAN: Unstable angina is defined as unweanable from anti-anginals. It is not a generic definition. This is specific. That is what unstable would mean in this case, unweanable from anti-anginals. Any further comments?

DR. ALLEN: The bottom line is that the early operative mortality in a patient with unstable angina, whom you take to the operating room on IV anti-anginals, is a little bit higher than somebody with stable angina. But if you look at that at one year, their survival actually, for

whatever reason, is better than for those patients who had stable angina and got TMR. So, once again, it is a risk/benefit. These patients are incapacitate in the CCU and can't get out of the hospital, and you offer it to them, and at one year you get very good results but you pay a little bit of an increased price on the front end.

DR. TRACY: Then really just one final comment. To me, it is not surprising that if you fluid load somebody who is very sick that they are going to have higher operative mortality. That just seems like a logical consequence.

DR. SIMMONS: Dr. Gilliam?

DR. GILLIAM: I think Dr. Tracy has addressed a couple of my concerns. Just some housekeeping, things that were absent, a lot of the patients who are not candidates for surgery with a lot of hardware in the heart, did you have any problems doing this procedure on people with, say, valves or pacemakers, or other type of hardware that may be in the heart as far as interference or any type of confounding problems with your procedure and implanted hardware?

DR. ALLEN: As we pointed out, one of the contraindications was coumadin. So, if you had a mechanical valve you were excluded from the study. So, I can't specifically tell you how many patients had, for example,

porcine valves that we operated on. In my experience, there were none. I have not done this procedure on somebody that has had a previous valve operation. With regard to the presence of an AICD, none of the patients had preoperative AICDs and so that wasn't a problem. I don't have the data in front of me for the entire centers as far as pacemakers. Once again, in my center I didn't enroll patients that had pacemakers. But, intuitively, those devices are all right-sided devices so drilling channels in the left ventricle shouldn't interfere with those devices.

DR. GILLIAM: Yes, I wouldn't think it should, but I think that is something that you may want to evaluate.

DR. ALLEN: Very good point.

DR. GILLIAM: One of the questions, specifically looking at ventricular arrhythmia, I didn't see this data anywhere, was there any protocol that specifically allowed prophylactic treatment prior to going to surgery for ventricular arrhythmias? Were people on anti-arrhythmics? Was that tracked in any way?

DR. ALLEN: The only contraindication was if they had uncontrolled ventricular arrhythmias. As I said, we didn't put these in patients that had AICDs. There have been cases where we have done this in patients who were well controlled and were on amiodarone.

DR. GILLIAM: I guess the purpose of my question

was, you know, after your investigators meeting, to explain why you had less events afterwards was if you brought up the fact that you are seeing 20-plus percent episodes of ventricular fibrillation. I mean, it doesn't take a rocket scientist to say, "well, maybe I can nip this in the bud," and give them a little hit of Lidocaine before starting the procedure.

DR. ALLEN: I understand. I see where you are going with that question, and prior to the investigators meeting patients were treated with prophylactic Lidocaine. So, that wasn't a change that was made after the investigators meeting. We were already doing that.

DR. GILLIAM: So, is that a recommendation you would have for someone going through the procedure, that they be treated prophylactically, or do you have any data on that?

DR. ALLEN: That is part of the training and that goes along with instructions to surgeons about how to do this operation.

DR. GILLIAM: I know it has been said many times today that the mortality is similar to previous groups and, you know, maybe I am just misreading something. In the study handout we have the PLC heart laser labeling, on 1-10 in our handout, where it says for mortality, surgery plus 30 days thereafter was one percent in the absence or unstable

angina in that group. As I understand the numbers that we are settling on here, it was 1.8 after the investigators meeting but over the 12 months we are looking at five percent.

DR. ALLEN: I think what I was referring to was that in 1996, when that investigators meeting was going on, the current published data on TMR, which was not in a large number of patients, the early operative mortality was in the 10-20 percent range. So, we weren't out of line in that respect.

DR. GILLIAM: Any idea why their surgery mortality is at least labeled as less in the PLC versus this particular surgery?

DR. STUHMULLER: Actually, that is probably an issue for FDA to address. You know, the sponsor shouldn't be required to explain somebody else's labeling. Dr. Callahan, do you want to address that, please?

DR. CALLAHAN: Your specific question is?

DR. GILLIAM: Well, in the PLC heart laser labeling, on 1-10, it just says mortality, surgery plus 30 days afterwards was one percent. If we are to take the data for this procedure, we have 30 days at five percent. So, it appears that at least this procedure is likely to be five times more.

MR. CHUTORIAN: Just a point of information. On

page 1-11, the mortality is listed as three deaths in the first days. The other one is different, and they had nine deaths in their crossover patients, in 60 crossover patients. So, the numbers would be a little over three percent, as you are saying, in the TMR group and approximately 15 percent at 30 days in the crossover group. That is on page 1-11.

DR. GILLIAM: I must be looking at something different. I see 1/102.

DR. WITTES: I think it has to do with whether it is in the presence of stable angina or not.

DR. GILLIAM: Exactly, and I am looking specifically for stable angina, which is presumably the group we are looking for, not the unstable angina patients.

DR. CALLAHAN: Yes, there are differences in the patient populations, for one. I mean, the PLC included class III and class IV angina, and the samples are so small anyway, I am not sure we can tell too much. But I am not sure the company could tell what PLC would be.

DR. TOPOL: I want to echo that point because the overall one-year mortality from that trial for the TMR assigned patients was 15 percent, and they start to fractionate them into even smaller subgroups. We already discussed the problems of the user point estimates and 95 percent confidence intervals. As Dr. Callahan is pointing

out, with the small subsets I don't know that you could interpret that. Also, I have a hard time interpreting that particular table, anyway.

DR. GILLIAM: One of the things that was listed as a potential placebo effect, at least a placebo type effect, was that in a person who was expert, if you will, at having several operative procedures this may be less notable. Do you have any data on how long the timing from the last bypass procedure to the TMR procedure on average was?

MR. CHUTORIAN: We will check.

DR. GILLIAM: Any autopsy data from any or the patients who died? Do you have any type of findings that may suggest what exactly the laser did to the heart?

MR. CHUTORIAN: May I see slide 92, please?

[Slide]

There were six patients for which there were autopsy results, as summarized on this slide. The TMR channels were occasionally patent in the 25-day period. As you can see, there is angiogenesis and sinusoidal-like channels, which is similar to what we saw in animals, and new blood flow in ischemic areas is represented by angiogenesis and neovascularization. This was usually seen both in the area of the channel and in an area appropriate a centimeter to a centimeter and a half from the areas of the channel. So, you see basically angiogenesis.

DR. GILLIAM: I presume that study will be continued and we will probably see that at a later date. I don't go into detail with that right at this point, but I glad that someone is at least looking at those things.

I just wonder, you know, I am not going to doubt the Cleveland Clinic data but I am very surprised that there were 12 percent or people presenting to anyone for treatment for coronary-artery disease, that there is no procedure available to them. I find the numbers are pretty high.

DR. TOPOL: Well, I wasn't allowed to present those numbers this morning but, actually, it was 6.6 percent that were deemed suitable for transmyocardial revascularization procedure.

DR. STUHMULLER: The issue is the data in the file.

DR. CALIFF: Just a point of clarification. It seems to me that you have data in the file which tells you about exactly what the device may or may not do, but to understand the implications of approval of the device, how can you exclude information about the relevant patient population? I mean, you would never get from a small randomized trial a picture of what the device might be used for and, yet, we are being asked to approve or not approve a device that is going to be turned loose on society. I am very confused by this policy.

DR. CALLAHAN: The problem is that the company has done, and is doing, multiple clinical trials, and the only indication that they are looking for right now is this indication. So, this study was devoted to this indication. What keeps being alluded to is that some of these folks have done other studies and they are accumulating that data from that as well, and that really was not put into this file. So they are drawing from their own experience from other trials.

DR. TOPOL: Yes, I would like to comment about that, Dr. Callahan, because the data I was trying to present from a systematic review of patients in the Cleveland Clinic had nothing to do with other randomized trials that have been done with this laser device. It was, as Dr. Califf was pointing out, just to try to give some sense of the proportion of patients who might be candidates for this procedure.

With respect to the randomized trial that was subsequently done that has been mentioned more than a few times--I served on the panel for several years, as you know, and I don't think it is appropriate, even if it is in a preliminary sense, mortality data from a randomized trial, to suppress and censor information like that. I just want that on the record.

DR. STUHMULLER: I think the other way to look at

this is the paradigm that we work under, under FDAMA, and that you have to evaluate the device relative to its proposed indication for use, and you need to look at the data set that is appropriate for the indication for use, and you can't factor in other data sets where you have inadequate data on the safety and the efficacy, and you can't factor in off-label use. You have to look at the data set relative to the proposed indication for use.

DR. TOPOL: I couldn't agree with you more, but for concerns about such an important event as mortality, we would like to gather as much data as possible to try to make meaningful assessments, and it is a very different endpoint than angina, a very different endpoint from anything else we have discussed. And, I think it is really important to try to have the amalgamated data as best we can. Of course, it can be considered preliminary and whatever, but I think active suppression of this sort of data--and, this is apart from any involvement of serving as an advisor to Eclipse. It is just that I have had the opportunity to come and visit after a year or two hiatus of having worked actively on the panel. I just think it should be reconsidered in the future when there is a novel technique and there are pivotal data about mortality. They should at least be made available in the discussion because in this particular case it really is a key balancing toward whatever excess there was in the

first randomized trial.

DR. STUHLMULLER: Yes, but part of the issue you get in that is that TMR is being used in a fundamentally different way. It is being done in a different patient population. And, just to put it in very simplistic terms, you have to compare oranges and oranges, or what the control is. The issue, again, is that the paradigm that we have to work under based on the regulations is what the proposed indication for use is and what the data set is that is relevant to the proposed indication for use. That is what is under discussion today.

DR. SIMMONS: In addition, the company did have the opportunity to put the data into the panel pack. I mean, we all know you and respect any work that you have ever published, however, anybody could come up here and try to start presenting data that nobody has actually had a chance to review, or look at, or have some idea whether it is good or not good. So, I think the idea that the data that is in the panel pack should be presented--you did bring up some other topics that I would like to address, maybe at the end of the meeting, on exactly what you are talking about, the suppression of some kinds of data. I have always been kind of an advocate that proprietary data on human experimentation goes contrary to anything I have ever thought of, and it should all be opened up, and we ought to

talk about that at some point in time, but let's not get into that now. Were you done?

DR. GILLIAM: Just one other thing. This may be a lot easier. In reading this, I think there is some suggestion that there is a learning curve of some sort in this because, as noted prior to the meeting, four of the initial deaths that occurred were the first case of the surgeon doing it, and that suggests that there is, early on, or the first case of the surgeon.

DR. ALLEN: I think the explanation of this, and I probably should have brought this up when Dr. Ferguson was asking his question, is that the investigators that had those deaths were trained by a single surgeon who was utilizing a different laser device, and recommendations from that single surgeon trainer were passed on to each of those four investigators who followed his advice on those first patients, which included fluid loading.

DR. FERGUSON: Could we talk what different device you are talking about?

DR. ALLEN: The CO2 device. So, you know, the pyramid is an inverted pyramid. The training came from one surgeon, and once the surgeons in our investigation got together and realized that that probably wasn't appropriate advice and made changes, mortality was less than two percent on the last 109 consecutive patients that were done. So, I

don't know whether that helps a little bit with the explanation but that would be one of the reasons that it is probably not necessarily a learning curve.

DR. GILLIAM: I think I will just say that the data are not available for us to make that judgment now. I can't say whether a learning curve exists or whether something you did at that meeting--it may be the three things you listed or something else, or maybe you all just got together and figured out things that each of you individually did, or did something better. I don't know. That is all I have for now.

MR. CHUTORIAN: Thank you very much.

DR. SIMMONS: Mr. Jarvis?

MR. JARVIS: Yes, I have just a couple of questions and a comment. One, do you have any data at all about the number of patients that, before they were actually enrolled into the study and assigned a treatment arm, actually had episodes or were hospitalized for unstable angina?

MR. CHUTORIAN: I don't believe we have the data in just the way you are describing.

MR. JARVIS: Okay. Actually, the next question is kind of more geared toward the FDA than it is toward you. There was a statement made in the April meeting that talked about as angina relief over time, that it makes it less

likely a placebo effect. Are you still backing that statement?

DR. CALLAHAN: I am not sure who made that statement, but I don't know that we have any data to address that.

MR. JARVIS: Okay. That is all I have.

DR. SIMMONS: Mr. Dacey?

MR. DACEY: Some of what I want to discuss we can save until later. It is interesting from the consumer perspective, patient perspective, because in reviewing this material I thought back to, I guess it was in '67, when CABG started. It was very easy to explain. The heart was a pump and you were providing detours for oxygenated blood, and this is what we told patients. And, I was very much involved in patient education throughout this period. When Dr. Grunzig came along with PTCA, that was very easy to explain. We opened up some detours or pathways.

But now, as a consumer, as a patient, I look at this and I have to say how does it work? It is not as easy to understand from the patient point of view. And, the patient, of course, puts an enormous amount of trust and faith in their cardiologist and surgeon. We can deal with some of this, of course, but my core issue in representing the public is how do we help them understand what they may have to endure as part of their continuum of treatment for a

killer disease?

DR. ALLEN: You know, as a surgeon who has dealt with a lot of these patients, in any physician-patient relationship you have to establish that relationship and, utmost, you need to be honest with the patients. These patients are a desperate lot. They don't have a lot of options. That doesn't mean we should necessarily do something simply because they don't have options but they are in a desperate situation. When I talk to these patients, I am just honest with them and tell them that I don't have at my fingertips things that I can do for you; I don't have things that can help you. I describe to them how we do the operation, and I honestly tell them I don't understand how this works but we seem to get good results with regard to angina. Patients are very accepting. I think a lot of times physicians don't give patients enough credit for understanding complex medical things. If it is simply put in language that they understand, they really understand a lot more than we give them credit for.

MR. DACEY: Well, I have a thesis called patient learning curve, but that is another issue. The only other question I have is that we address frequently the issues of quality of life and I always raise this question of the indicators that are used to explain or demonstrate quality of life because it is so terribly subjective. As you point

out, a patient comes in and feels quite desperate; their family is desperate. Some serious quality of life issues are at stake. But it is a very difficult area to paint a good portrait, and it has to be almost done one patient at a time on their own terms. So, at some point down the road here I would like to speak more to this quality of life indicator issue.

[Slide]

I guess I get to ask a couple of questions. Everybody has already asked all the good questions, but I am an electrician, not a plumber. So, from some respects, I am kind of an interesting position because I take care of patients with angina but I can't do anything about it. I can take care of their electrical issues. So, I am kind of at the mercy of people who do plumbing things.

It has been my impression that angina is an extremely vague thing. It is a very ephemeral thing. I have taken care of patients with very small vessels who have intractable angina, and people, like some of these marathon runners who have severe triple vessel disease and don't have any kind of angina. So, I am having a lot of trouble. I appreciate what you have done in trying to objectify angina and trying to do the masked studies. I think it is a valiant effort. But the bottom line is that it is still based upon a very subjective thing, and there is certainly I

think a very significant chance that there is a major placebo effect involved in all this that hasn't been teased out yet.

On the objective portion, I didn't see anything in there about the EKGs. These patients pre- and postop EKGs and things like that, did any of that change? I mean, did they have ST segment changes with their angina that went away? I didn't see anything in the protocol about just looking at simple things like EKGs, resting ST-segment depressions, resting T-wave inversions, anything like that.

DR. ALLEN: Good comments, but we didn't specifically look at those things.

DR. SIMMONS: There was a comment in the packet about patients, you know, voiding the conduction system. So, you don't know whether patients ended up with ventricular conduction defects, or patients who ended up with new pacemakers? Was that one of the comments or was that just a thought that somebody could end up with a permanent pacemaker? Did some of the patients end up needing permanent pacemakers from this procedure?

DR. ALLEN: I don't have that at my fingertips and I would have to get back with you on that.

MR. CHUTORIAN: We did look to see which patients have pacemakers.

DR. SIMMONS: I guess the other comment I wanted

to make is that my impression also is that thallium studies are pretty iffy. So, I would suggest that your confidence that you aren't doing anything because they didn't change--I am having a little trouble with that one. With 1 mm channels, I don't think you are going to pick up any changes, if you were causing microinfarcts. I guess I would be dubious with the comment that gives you confidence that you aren't doing something to the myocardium. I just don't think that thallium is sensitive enough to pick it up. Do you have a comment on that?

DR. TOPOL: The point that was made earlier was that there is no evidence of larger defects, or that there was infarction that was measurable, induced by the procedure. This goes along with the lack of Q-wave infarcts, which were systematically assessed via serial ECGs, and the lack of enzymatic infarction data. So, I think all these together give a sense that there is not measurable infarction, that is, it is not a significant hazard of the procedure. There is a very small incidence as compared to the medical therapy group.

DR. ALLEN: I have that data on pacemakers. There are two patients who received TMR who ultimately got subsequent pacemakers for sick-sinus syndrome. There is one patient in the medical arm that also got a pacemaker.

DR. SIMMONS: So, probably not procedure related.

DR. ALLEN: Probably.

DR. SIMMONS: On the autopsy data, you showed some slides but you didn't actually show the slides of the tissue slices. Was that data supplied to the FDA, those autopsy data slides for review?

MR. CHUTORIAN: No, I don't believe autopsy data slides were supplied. We have a few slides from the animal studies which we could show you, if you wanted to see what it looks like, but I do not have the autopsy slides.

DR. SIMMONS: Getting back to the animal data, there was a comment in the FDA package that they had requested some slides, I think, and that some of the animal data was never supplied. Was that all taken care of? We can look into that later. I don't really have any major other comments.

DR. CALIFF: Could I make three comments?

DR. SIMMONS: Well, I think Dr. Ferguson asked first. Could we let him go with his one question?

DR. FERGUSON: I have requested to ask one other question which I had flagged and I did not do it, and I apologize. It really sort of relates to Dr. Simmons'. If you will look on page 4-5, the assessment of the FDA summaries of the animal studies, and read the last two sentences of that, it indicates clearly that parameters for optimal operating conditions for the clinical trial should

be justified.

Now, I recognize, probably more than other people in the room, being a surgeon, that one of the softest areas about any transmymocardial revascularization done by any system or any technique, be it a hypodermic needle, is the issue of where to put the holes and how far apart they should be, and the total number to be utilized has never really, to my knowledge--maybe you can correct me--has ever been determined in a scientific way.

The reason I bring that up is because--I am not saying that you are the ones that have to have the onus of having all of those data for your machine, but if you look on page 2-5 again, under the precautions, it doesn't say how far apart the channels should be. Your recommendation, as I think you said, Dr. Allen, is a centimeter apart.

DR. ALLEN: Yes.

DR. FERGUSON: And that is what is pretty standard around the country I think.

DR. ALLEN: Yes.

DR. FERGUSON: And I think that has been determined or judged simply because that seemed to be a convenient distance. To my knowledge, there is no data at all. Maybe some of the revascularization data that is beginning to come out will show that if you put a channel in the myocardium you can expect some reverberations about a

centimeter. I guess that is a question. Is that correct?
Do you feel that way?

MR. CHUTORIAN: We believe that is the case in terms of angiogenesis.

DR. FERGUSON: Now, look at the issue of the numbers, and I have a little trouble on page 2-5 with bullet 8, only in that it says that you recommend a maximum of 45 channels. I would like to know how that was derived, and whether that is derived from animal data or simply the availability of space on a sick heart.

Then you make a statement here which I think really is the part that I have a little problem with. It says, "... can be created because safety and efficacy of more channels has not been studied." I don't think the level of the number of channels, anywhere to my knowledge, has been really shown. Do you want to comment on that?

MR. CHUTORIAN: I think Dr. Allen can comment about the first part, the number of channels in relation to the heart. We are studying in some of the protocols some of the issues that you are talking about, but if they are not the subject of this talk I really don't have data that I can show you as to how many channels would be absolutely optimal.

DR. FERGUSON: Yes, but you make a comment which we have to deal with as a panel. That is the reason I am

bringing it up. You recommend a maximum of 45. This is going to go to the users.

DR. ALLEN: You actually had it right on target in that if you look at the size of an average ventricle, 45 channels in the distal two-thirds of the left ventricle, spaced one square centimeter apart, is where that number derived from. But, you are absolutely right, there is not a tremendous amount of science at this point for the selection of that number.

DR. FERGUSON: Thank you. That is all I have, Tony.

DR. CALIFF: Sorry, I know everybody is hungry and it smells like hamburgers in here --

[Laughter]

but, first of all, Janet, I was disappointed. I was expecting an eloquent dissertation on three primary endpoints. I thought, first of all, how can you have three primary endpoints? But if you do have three endpoints that you are co-equally interested in, I think this is a matter that the FDA and panels need to be aware of. I mean, I like to play golf and if I can take three tee shots every time and pick the best one my score would be a lot better than if I had to just hit one and go with the one that I hit.

DR. WITTES: Well, let me tell you why I didn't respond to it, because although there was this list of

primary endpoints, several times it said that prior to looking at the data there was a decision with the FDA that angina was to be the primary endpoint. So, that is how I interpreted it.

MR. CHUTORIAN: That is right.

DR. WITTES: Is that right?

DR. CALIFF: Good. I am glad that is taken care of. The cardiac hospitalizations, who decided whether it was a cardiac hospitalization or not?

DR. ALLEN: You mean who decided whether the patient should be admitted or not?

DR. CALIFF: No, who classified the hospitalizations?

DR. ALLEN: Each center, based on collection of records on each event that occurred.

DR. CALIFF: So, unblinded investigators--I am just going to state this in the most austere terms --

DR. ALLEN: Sure.

DR. CALIFF: -- some of whom owned stock in the company were deciding whether the hospitalization was cardiac or not.

DR. ALLEN: It was a research nurse at each institution who collected data on that and then supplied it to the company.

DR. CALIFF: But I am sure you know there is a

federal law that says the person at the bottom verifies, and that is the physician and investigator.

Do you have the data on total hospitalizations, not cardiac hospitalizations?

MR. CHUTORIAN: We can get that for you.

DR. CALIFF: Yes, I would be very interested in seeing that because we have seen a number of examples recently where the total hospitalizations looked quite different than the cardiac classification.

The last point is that you don't really mean to use the term unstable angina? I think it is very important to come up with some other description of what you are talking about because we recently looked at this, and there are 108 definitions of unstable angina that have been used in clinical trials or textbooks. That includes everything from you have a little more chest pain when you walk up an extra flight of stairs to refractory angina requiring intravenous. You are really talking about unweanable intravenous therapy, and I think it is really important for us to distinguish those, otherwise if you just say unstable angina was a risk factor, then, you know, how on earth do you decide between terrible angina that needed the procedure versus unstable angina?

DR. TOPOL: That is a great point because all the patients in the trial had unstable angina by definition.

DR. CALIFF: Right.

DR. TOPOL: The other point though is that this refractory angina category that you are describing--we have already brought up that there is some subjectivity as far as whether or not the patient is weanable twice from IV medication. So, even refractory angina as a subcategory of the broad 108 definitions of unstable angina is problematic as well.

DR. CALIFF: And the last point, just to give people something to think about at lunch, is the issue about not objectifying the angina. I actually think that the Activity Status Index was developed for that reason. If you look at the score of 21 in the TMR group and 12 in the medical therapy group, on page 5-49, 12 basically means that you can do your activities of daily living like bathing and dressing; and you can walk around your house; you could walk a block or two on level ground; and maybe do moderate housework. That is about it. That is a very limited, objectively determine what can you do life style issue.

With 21, just to give you something to think about at lunch, probably the next thing on the list that comes up is having sexual relations. So, 21 probably is an patient life style improvement, at least for many people.

DR. WITTES: But, Rob, look at the denominators.

DR. CALIFF: They are lower.

DR. WITTES: Yes, 58 and 37.

DR. SIMMONS: We will break for lunch.

DR. STUHLMULLER: I would like to make three quick announcements. One is just a reminder for the panel that you can't have any file specific discussion over lunch. Second, there is company confidential information in the room. So, we need everybody to leave the room and the room will be secured. Third, there was a set of car keys for a '99 blue, Regal Buick rental car that were found on the floor, and they are at the registration desk. The meeting will start again in an hour, at 1:30.

[Whereupon, at 12:30 p.m. the proceedings were recessed, to resume at 1:30 p.m.]

Afternoon Proceedings

DR. SIMMONS: Let's get started. I think the first thing we will do is just go around the panel here and ask does anybody have any more questions or issues they want to bring up for the company?

DR. CRITTENDEN: One quick question. Was there any difference between the number of channels created before and after the June meeting, 1996?

DR. ALLEN: No.

DR. TRACY: The region of ischemia, was there a relationship between improvement in anginal score and region of ischemia that you could comment on?

DR. ALLEN: I am not sure I understand your question. Since we didn't show an improvement in our thallium studies, we obviously can't correlate that with ischemia.

DR. TRACY: Right. So, I guess it is the unanswerable question of how this thing really works. If you don't think that you probably can get too far into the septum, you may maybe drill holes into the anterior septum and maybe get a certain percentage of the way through but you are not getting posterior septal regions --

DR. ALLEN: Right.

DR. TRACY: So, it is part of the unanswered question of how this really works.

DR. SETHI: You mentioned that you did some assessment of CPKMB and some enzyme assessment following the TMR.

DR. ALLEN: That was not part of the protocol, to routinely assess CPKMB rises.

DR. SETHI: Do you have any kind of data to see how much they go up, and what happens to those CPKMBs? Can you share with us whatever data you have?

DR. ALLEN: I can share with you just at my center. Once again, that wasn't collected in all of the centers. You would obviously expect with vaporization of 1 mm channels a small rise in CPKs, and that is what you do see when you collect data, but it doesn't have any clinical correlation.

DR. WITTES: There was a slight excess in CHF in the medical management group, 16 percent to 17 percent. In the ejection fraction, I know the means were the same but did you look at the distributions of the ejection fractions in the two groups?

MR. CHUTORIAN: I believe we looked at the distributions and did note anything. We can get back to the group to see if there is anything --

DR. WITTES: In particular the low end, 25-35.

DR. SIMMONS: Anybody else want to ask a question? Does anybody have a question for the FDA?

DR. CALIFF: I don't know how much I want to get into this, but I don't know if you had a chance to do any homework at lunch, but it seems to me that in assessing whether a device should be on the market we ought to have access to at least all the safety data that is available about the device.

Just to cite an example that really had an impact on me in the last year, I was involved when the panel approved the drug mebefradil for the treatment of angina and hypertension. It works great for angina and hypertension, and it is totally harmless, or appears to be in people who have no comorbidity or complicated situations. So we approved it without labeling. It got out on the market and it killed a bunch of people.

DR. SIMMONS: Well, was there some data you didn't have access to?

DR. CALIFF: In that case, actually there wasn't more data but in this case it seems like there is more data. We know that when the device gets out there it is going to be used beyond the specified indication. It would be useful to have the total picture, at least with regard to safety.

DR. SIMMONS: I guess, as you have probably noticed, I get kind of emotional on this issue, and I think we probably ought to put this to the end because there are people who have things to talk about right now.

But one of the things that maybe we could talk about before we adjourn is the possibility of having some other meetings to discuss these issues. This investigators issue I think is a very interesting issue that maybe people would like to just express some feelings on in an open sort of forum. The other thing is the release of medical data.

I think an example would be like the calcium channel blocker data that has never been released. I mean, that is a group of data that may actually have had some value, but that was considered proprietary data. I mean, right now the FDA's hands are tied. I understand that. By law, that data is considered untouchable and there is nothing they can do about it. So, I think it is wrong to direct anger towards people that can't do anything about it. We need to direct our anger towards congressmen, and maybe we could have some open discussion on that at a later time.

Are there any questions relating to the project for FDA?

DR. CALLAHAN: I can try to answer at least one of them. The potential conflict of interest of the investigators which you talked about earlier, and whether or not they can have financial interests. The agency is addressing that, as it turns out. There is a regulation or guideline that is under development right now to address that and to say how many investigators in any given study

can have financial interests. So we will, hopefully, dilute any of that kind of bias.

But in the past there have been PMAs approved where the main data has come from investigators who have sole financial interest in the company. So, it is for those reasons that the agency is in the process of issuing guidelines on that.

But this company is in the same status as any of the other companies before them. The folks who are at the table have admitted what their financial conflicts are, and we don't have any guidance for any of the investigators yet. That is forthcoming.

DR. WITTES: But really the issue is if you were to analyze the data and were to discover that those centers, where the PI had substantial interest, had really big reductions in the angina and those others didn't, that would have changed our interpretation of the data.

DR. CALLAHAN: Yes, that is why we are trying to issue a regulation. But it brings up other things, of course. How do we enforce that regulation? We can tell the manufacturer that they shouldn't be offering stock but, as this company has said, they have not done that. But how would we know in the first place? We could ask the question, but we would have to ask the question either of the company, and they may not know, or we can ask the

investigator and then how would we validate that data?

DR. CALIFF: Well, it is pretty standard in most clinical trials, maybe not device trials, that you formally ask --

DR. CALLAHAN: The investigators themselves, yes. That is part of the guidelines that we are setting forth.

DR. SIMMONS: I think there are a lot of potential issues on this topic that I would like to sort of bring to the table, but let's move on right now.

So there are no more questions on this protocol for the company or the FDA?

MR. CHUTORIAN: We would just like to do two things. Number one, there were some data requests that we have not fulfilled. We have some of that information now. And we would like to thank everybody for allowing us to present the data. Dr. Topol, on Dr. Califf's question?

DR. TOPOL: The issue of total hospitalizations is a good one, and we have a slide that we just made to summarize these data.

[Slide]

These are total hospitalizations in the two groups. The difference was significant for total hospitalizations and this was, of course, just a hospitalization and many, of course, had multiple hospitalizations. This doesn't take that into account.

The other thing that skews these data is that the patients in the medical management arm went on, 46 of them, to have TMR. So their window of any hospitalizations is only up to the point that they had medical management, which is a median of six months, whereas the patients in the TMR group had the follow-up. So, even taking those two issues into account, a single hospitalization and the difference in the temporal window of observation, still are very significantly different.

I think these data are important in light of lack of adjudication that Dr. Califf pointed out with respect to cardiac categorization.

DR. CALIFF: Just as a comment, this is the acid test of hospitalization data. I think if you reduce all-cause hospitalization that is a very stiff test.

MR. CHUTORIAN: The other question was on ejection fraction. The minimums in both groups were 25 percent. The quartile, that is 25 percent lowest, started at 40 in both groups. The medians were 47.5 in the TMR and 45.9 in the medical management group. So the groups are very well matched in ejection fraction.

DR. WITTES: But that is not the group I asked for. I asked for 25-35. I asked specifically for the lows.

MR. CHUTORIAN: In those groups, in less than 30 there was seven percent in TMR and ten percent in medical

management. In the 31-40, there were 28 percent in TMR and 18 percent in medical management.

DR. WITTES: So it is a little bit consistent with history of CHF. I mean, it looks as if the medical management group was a little bit worse in heart failure.

MR. CHUTORIAN: No, it would be the other way around. TMR had 28 percent.

DR. WITTES: No, no, no --

DR. ALLEN: She is right.

DR. WITTES: Yes, and the very low ejection fractions were more in the medical.

DR. STUHLMULLER: As a point of procedure for the sponsor, any additional data analysis that you do that is not in the PMA needs to be submitted as an amendment to the PMA and verified by FDA.

DR. SIMMONS: If the company will step back, we will open the discussion now for panel members. Do we want to go through the questions now?

FDA Questions for the Panel

DR. CALIFF: Yes, let's go through the questions. The first question is, is the clinical data presented adequate for evaluation of safety and efficacy?

Briefly, the efficacy issue, to me, is very clear-cut. Patients who got the procedure were less likely to have limiting angina hospitalizations, and had better

functional status. That is clear-cut. To me, it is a clinically meaningful difference. I am sure we will discuss later whether it matters that we don't know why this occurred.

I am going to take the hard line position, at least to start, that I don't think the data are adequate to evaluate safety, and it may be remediable if the FDA had reasonable rules about this, but the data themselves right now at 12 months are compatible with 13/100 higher risk of death with the procedure. They are also compatible with 3/100 lower risk of death.

DR. SETHI: But after they modified their protocol and you take that second group, and I understand this is statistically not correct but clinically it might be correct. After they modified the protocol the mortality dropped, and then it looks like the mortality in both groups is identical and not significantly different.

DR. CALIFF: We have all been through clinical research experiences where we look at the data, and pick out the group that looks the best and the therapy that we are interested in and, lo and behold, it looks pretty good.

You know, my point here is that I would bet that there is other data out there about this device that would satisfy my concerns, but on the face of it, by the rules that we are given if we can only look at these data--and I

am taking a hard line here to elicit the opinions of the other panel members--is it good public policy in the United States to say that we will accept devices based on the confidence intervals for mortality, which goes the wrong way and could be associated with 13 lives lost per 100 patients treated in the first year? Is that the standard by which we should be approving products in the United States?

DR. DOMANSKI: I think, actually, there are a couple of pretty substantial policy issues here. One is that there is no question that if you look at this randomized trial that, as they ascertained their endpoints, there is a difference in angina. But we are presented with a device for which there is no medical rationale provided.

In fact, it is just the opposite. If you look for something that is reasonable, like increased blood flow, the one test that they used shows no difference in their randomized trial.

So, I think that the policy issue is if you come in and you want approval for subcutaneous injections of alcohol because they reduce angina, and you tell the patient that this is going to reduce your angina and you give them something that is terribly painful, they get over it and, by golly, their angina is gone. Are we then going to approve that for use in the U.S.?

Now, that is a pretty gross example because there

may turn out to be a very real mechanism with this, but it certainly hasn't been elucidated and, again, the reasonable ones lack evidence.

You know, this is a careful study. This is not a group of people who have come in without having carefully analyzed their data. We have certainly seen over the years very poor applications by inept groups but this isn't the case with this group. These people studied this thing carefully, and they simply have no mechanism that they can find for it. So, I think that is a major policy issue --

DR. STUHMULLER: I need to clarify a couple of things in terms of how to keep the discussion focused. First of all, understanding the mechanism of action isn't required for approval.

DR. DOMANSKI: Should there be a mechanism of action, or will you approve placebos? That would be worth clarifying.

DR. STUHMULLER: Well, part of what you are being asked to do is provide an interpretation of the data set. I mean, understanding the mechanism of action is not essential to approval.

DR. DOMANSKI: Well, let me just ask you about that. Is the absence of one grounds for disapproval?

DR. STUHMULLER: Say that again.

DR. DOMANSKI: Is the absence of a medical

rationale why something did what it does grounds for disapproving it? Because if it is not, then this thing has proven itself quite admirably.

DR. STUHMULLER: Well, you know, the discussion needs to be focused on is for this application does the data set support safety and efficacy for this device for its proposed indication for use? That is what you are being asked to assess, not a public policy issue on a global sort of abstract way.

DR. DOMANSKI: Well, I guess I am not trying to do it in a global sort of abstract way. I actually am considering this thing and I think what I am saying is that there is no obvious mechanism for this, other than placebo. I guess all I am asking, and it would be helpful to know this, is would you accept a placebo if, in fact, it appears to reduce angina?

DR. CALLAHAN: The way you phrase that, it makes it difficult to answer you. But we certainly can approve something without knowing its full mechanism its action. Without knowing its full mechanism of action, does that mean it is necessarily just a placebo is the area we are struggling with.

DR. DOMANSKI: It is not "fully" understanding its mechanism. You don't understand its mechanism at all, or even that it has one. In fact, there is some suggestion

that maybe it doesn't.

DR. CALLAHAN: But I think what we all try to do is we wrestle with what is medically rationale, but then we still may fall short of anything shy of a mechanism.

DR. CALIFF: Well, I guess Dr. Domanski and I have staked out totally opposite points of view here. You know, mechanisms are nice but in the end people take therapies because it makes them live longer or feel better. A great mechanism, if you don't live longer or feel better, is not very useful.

DR. DOMANSKI: No, but there is some question of an increase in mortality here. We don't know that it is and we don't know that it isn't. This is a big operation that is done. So, it is not just like my subcutaneous injection of alcohol.

DR. STUHMULLER: And the issue of safety, you know, safety is defined as reasonable assurance based on solid scientific evidence that the probable benefits to health, under conditions of use, outweigh any probable risk. Right. Efficacy is defined as reasonable assurance that in a significant proportion of the population the use of the device for its intended use and conditions of use in the label will provide clinically significant results. And those are the issues.

DR. DOMANSKI: Right, and placebo can meet that.

So I take it that that would be okay.

DR. WITTES: It seems to me that we have almost nothing about mortality. I mean, what we see us very much consistent with chance, and I guess the way I read it is, therefore, it doesn't really speak to us much about whether there is harm or not. And, again, I leave it to my clinical colleagues, are there therapies that you use in absence of knowledge of effect on mortality?

DR. GILLIAM: I think we do things every day and we don't know how it works. You know, I told someone earlier that I get in my car every morning and put the key in the ignition, and I don't know how it works but I know I can drive.

DR. DOMANSKI: But somebody knows how it works, Roosevelt --

[Laughter]

DR. GILLIAM: Well, my care I am not sure about. But I think your point is well taken. It goes against all we have been trained to accept, that we can essentially have a device or a procedure or a medicine that we don't have a first clue of why it works, yet, we are willing to say that it works. I am not convinced that it necessarily is safe but I think that it does keep people out of hospital. When I say I am not convinced that it is safe, all I can say is that more people died who were in the group that got the

procedure than who were in the group that did not.

DR. TRACY: I think not knowing how it works--I wish we did know how it works, and I am personally convinced that it is more than a placebo effect but I agree that there is nothing that is presented here today that would give us even the remotest clue of how this thing works.

But that issue aside, the question of are there other clinical correlates where you do something that might be a detriment, I think these very patients are at centers where they might have had some last-ditch angioplasty, last-ditch stent, last-ditch bypass operation where you very much want to say, "well, I can get you off of nitroglycerine, there is a 50-60 percent change that you are going to die with what I am going to do to treat you." I mean, that is the alternative that these people face.

So, you know, just to be realistic, we are playing numbers a little bit. I mean, the worst case scenario was 12 percent versus 7.3 percent, I think.

DR. CALIFF: No, that is not the worst case. The worst case scenario is the confidence limits about those point estimates which are very broad.

DR. WITTES: Yes, they are broad, but these are the numbers that we have and I think that we have to make a decision based on these numbers, and I think it has to be put into perspective of alternative treatments that are

available. Somehow I think we have to take that into account.

DR. CALIFF: Well, I have obviously state the position to provoke discussion. I think there is always a fairness issue and precedent. You know, if you ask me should we be satisfied, if a 200 patient randomized trial with 20 deaths could give us any estimate of safety of any device, I would say the answer is absolutely not. Relative to what has been done before with this panel in this arena, this is a great study.

[Laughter]

So, those are the two things that we have to weigh against each other, and I just feel like there needs to be some consideration of a higher standard when it comes to safety.

DR. FERGUSON: Can I ask a question? Given the constraints under which we have worked in the past, which John has outlined very well, is it fair or is it all right for us to approve a very good study that has been done here but there are a lot of missing data, and put a codicil on the approval that would say you have to continue to look at this and provide, if you can--I mean it doesn't mean that you have to, but provide real physiologic data that is going to contribute to the understanding of the device? I don't know if we can even do that or not.

DR. CALLAHAN: No, there is nothing in the law that says we have to understand the mechanism. But the first part of your question, and that is why we are coming to you, is that, yes, you can make a benefit/risk decision. You can also make the judgment that you don't have enough data to make that but, as Cynthia is pointing out, we have the data as it is and to the extent that there is a lot of variability between it but, nonetheless, you have to adjudge if that is enough--is the unknown in the data creating enough of a problem of risk that it is not outweighed by the potential benefit.

I would agree, if the study were bigger in the case or mortality you could probably nail that down but we don't have that data, nor do we have that data in house either.

DR. GILLIAM: Is it out of bounds to have the FDA or the company do an equivalent comparison between the already approved device for this procedure? I mean, my feeling from the investigators is that this is somewhat different from the previous one. They fluid loaded and it was good at first but now it is not good, and so on, but there seem to be some differences between these two. Is it fair to say that obviously you can do postmarketing and in two years, three years, four years we will have something on, you know, how long this procedure lasts or makes a

difference, but should we be able to compare this data as an equivalent procedure?

DR. CALLAHAN: No, each submission stands on its own and the data stands on its own. So, you wouldn't be able to do that kind of comparison and, indeed, the studies that were done were quite different. As we heard, this is class IV instead of class III and IV. So, it is not valid for us to compare the two, and the lasers are totally different. But your other statement about can we follow it up and ask for more data, if you feel the benefit/risk is sufficient now to go forward with the decision, I assume they can collect more data postmarket.

DR. SIMMONS: I think one point that is important that the panel needs to recognize is that it is not uncommon for multiple sponsors to be conducting studies with similar types of devices simultaneously. One gets approved and then another one gets approved. You need to evaluate it based on its own data set and, yes, you can't do a comparison to another recently approved device.

DR. CALIFF: I would certainly agree that any indirect comparison is almost a complete waste of time, even if you wanted to do it or it was legal. I think Dr. Gilliam might have been asking could we encourage a direct prospective trial but I know that is another issue.

DR. CALLAHAN: Actually, that is the issue after

we finish discussing this particular submission.

DR. SIMMONS: It might make a difference in how you think about it and how you eventually want to put forth a proposal, you know, given the knowledge that if you have an inadequate base you can direct a study to answer the particular question that is really bothering you the most. I guess my sense is that we are all struggling with the academic issue that we don't like the idea of approving a device when we haven't got any idea of how it works. I guess we have to get over that and move on.

DR. CALIFF: I am not struggling with that at all.

DR. SIMMONS: Oh, I am,

DR. CALIFF: It doesn't bother me in the least.

DR. SIMMONS: It bothers me a lot. So, I think we need to move on past that and say is it possible--I mean, are you comfortable enough with the data that you think that some sort of a postmarketing study would help answer the questions to ease your mind on the mortality?

DR. CALIFF: It is amazing because we are struggling with exactly diametrically opposed issues. I am struggling with a non-academic issue. Are we going to approve a device which is going to be used in thousands of people and could result in a excess mortality of 4/100. So if it was used in 10,000 people it could result in 400 extra deaths in the United States. That is what I am struggling

with, and the question is what level of certainty should be required on that score? I guess what I keep wondering is if the company is doing other trials with this device, at least in somewhat similar circumstances, by looking at the totality of the information, we could probably become either much more comfortable or more uncomfortable with the safety issue.

DR. SETHI: But those are different patients. Those are not patients who have no other alternative. Those are the patients, if I understand correctly, are getting artery-coronary bypass and the laser is part of that and a complement and supplement to revascularization. So, we are not talking about safety in that respect because probably patients are doing well because they have a patent graft.

DR. CALIFF: So, the only other data with this device in patients that are simultaneously getting bypass surgery. Is that right?

DR. SIMMONS: I don't even know if we know that. I am not even sure if we can address those issues.

DR. STUHMULLER: You raised two issues earlier. The one that Dr. Callahan addressed was the issue of a financial conflict. The second one was with, you know, off-label uses of the device with different patient populations. The issue, again, today to keep the discussion focused is what is the proposed indication --

DR. CALIFF: My main issue is how does one scientifically evaluate safety of a proposed therapy? That is the question that is before us right now. And, it is not just the law; it is silly to take a tiny little data set out of a universe of data and say that is all you can look at to evaluate the safety of a treatment.

DR. STUHMULLER: But that is the regulatory construct that we have to work under.

DR. GILLIAM: To put it bluntly, Dr. Califf is simply saying that if we only can look at this study it is very clear that it is not possible for us to say this is a safe device. We can't say that it is unsafe but we don't have enough data to say that it is safe or unsafe.

DR. SIMMONS: Well, what would it take for you to say it is safe? What do you want?

DR. GILLIAM: Let's get one of our statistics people to say that.

DR. WITTES: I guess the conundrum that I feel is that to really answer the questions about mortality is a huge study. If we said the only way we would be convinced that this device is safe is that we need a randomized study of not 200 people but 1000 people, whatever it is to get an answer, it seems to me that that is one problem. But the other is to say, and I don't know if this is okay, in the label state the confidence intervals.

DR. DOMANSKI: You mean when you are going to do the procedure you open the thing and read that, or at least have the nurse read it to you since you might be gloved at the time?

[Laughter]

That doesn't really protect the public.

DR. SIMMONS: What kind of a mortality would be an acceptable mortality for this kind of a procedure?

DR. CALIFF: I think that is a great question that the clinical community is going to be dealing with more and more with other therapies which may improve quality of life but may decrease longevity. You know, just my clinical gestalt, having seen this data, would be that a sustained mortality in excess of about three or four lives per 100, I think, for most people would offset the degree of anginal relief that we are seeing here but, you know, it is hard to know that without actually presenting it objectively to a group of patients that have the condition.

DR. TRACY: But I think it is important to remember that the people who do clinical medicine have all said there is a very good chance that you will not survive this intervention. We have gone in there and we have said that, and we know they say, "I cannot live like this anymore."

DR. CALIFF: I think this is worth a few more

minutes of discussion because it is a critical issue. We are not talking about absolving people of their angina. We are just talking about an increase in function, roughly equivalent to going a minute longer on the treadmill or going up one more flight of stairs than you could go up before. That is the level of difference that has been subjectively measured.

DR. TRACY: But there is another problem with the study. There is a group that rolled over, who were stuck in hospitals, stuck on IV for four days. They were required to be there for two attempts and the mean was 24, or whatever. But, I mean, there is a difference even between this population so we are not going to get any cleaner information out of this and I don't think that without an enormous number of patients, and Dr. Wittes can probably tell us exactly what that number would be, will we get at the mortality issue. But I do think it is very critical that that be something that is followed over time, the issue of mortality. And, I think that there is an opportunity at some point, if something is clearly demonstrated to be harmful, for it to be withdrawn.

DR. CALIFF: Well, two of you have brought this up now. If you could explain to me how in a non-randomized comparison you can tell whether a device is associated with a higher mortality, I would love to know how that can be

done.

DR. WITTES: I didn't say that. I said we need a randomized study to do it.

DR. CALIFF: I thought Tony and Cindy both brought it up. If we could do that, it would solve --

DR. SIMMONS: What if you had a trial that used entry criteria--I don't know, I guess I am asking first of all for the numbers, so then you could actually go back and try to calculate what population you would need to achieve that number. Three to four percent seems low to me. I was actually willing to accept that seven percent. But if you are willing to accept, say, five or six percent mortality and you took a group of patients with the same entry criteria and you followed them for a year and a half or two years, what number would you need to actually provide you with the confidence that it was a real number?

DR WITTES: I don't think you could do it that way. If you really wanted to know the answer, you would have to do a randomized study. You can't just follow an uncontrolled cohort. So, I don't think that is really the question. The question is are we saying that there needs to be another randomized study which is large enough to exclude the upper bound of the confidence interval of mortality, whatever it is we feel needs to be excluded? I think that is the question. I wouldn't be convinced at all by a case

series.

DR. CALIFF: I think the thing that makes this thing a little bit more difficult for us is the labeling. Actually, I do kind of agree with Mike on specifically labeling in a very up front way that patients should be informed. I mean, this is a little bit easier to do right now with drugs because you can require that the pharmacy hand the patient a sheet of paper before they take the drug that says, you know, "this drug may kill you but it also probably improves your quality of life." I think actually labeling specifically is probably the best we can do, but the question is which label do we put on it, the last 100 patients or the total experience? That is another source of confusion.

DR. DOMANSKI: We can also stipulate that they have a separate consent, just detailing the uncertainty that we are all talking about.

DR. SETHI: I think that is a good point, to have a separate consent form with, you know, what the risks are.

DR. DOMANSKI: There is also another piece when it comes to trying to figure out exactly what numbers you are looking for. In this approval process, while the different applications can't depend on each other by law, it is probably not fair for this panel to, you know, in August use one set of standards basically and then in October use a

completely different one. While I have some enthusiasm for my own standard, the fact is that out on the market is a device that is really substantially similar, and I am not sure what purpose is served by a few weeks later making a big change. So, I want to be careful about how I stake out my position. I understand the problem. I mean, I think that is significant in deciding about approval for this thing.

DR. CALIFF: I agree with you and I think the purpose of this discussion from my point of view is just to have the discussion. I would encourage the agency to think more carefully when we are dealing with situations where life and death is a key part of the issue, to at least have some standard for being able to give the patient the information the patient needs to be able to make a rational choice. I would argue that we don't have enough information from this single submission to do that, nor did we with the last similar device that was approved.

DR. DOMANSKI: We are having a lot of trouble even defining what that is. We are focusing on it now.

DR. CRITTENDEN: I think it is hard to consider even coming up with a consent that is going to be reasonable to present before a patient. We are sitting around here, and supposedly we have read all the available data about this device, and I am not sure what I would put in that

consent.

I mean, if you told someone who essentially is at a point where they have nothing else but you have something that might help, and we don't know why it works; and it may kill people--the truth is the very fact that you, as a physician, present an option to a patient carries a great deal of weight. I mean, I have had people that we have done some pretty impressive things to over the years and, you know, they just say, "well, whatever you say, doc." So, I think that a consent form may not be effective one way or the other. I think it is just an additional piece of paperwork that would find itself at the bottom of the patient's chart.

I think the real question is what we are going to do about this device. Is it safe? If we can't figure that out in a reasonable way, I guess we have to at least say is it unreasonably unsafe, and if the answer to that is no, then I guess we are pretty much constrained to go along and say, well, okay, we will wait and see what happens.

DR. GILLIAM: I am sitting here, thinking about this now in terms of what I call patients who are "unstable," have bad looking lesions and would I quote them for a redo operation, and, gee, you know, five percent doesn't look all that bad, and if you look around the country in terms of what other people are offering, I mean

some very impressive institutions have had even higher than 8 percent redo mortality. And, these are patients where you kind of wish you could do an operation because they are in pain but they have no distal targets for you to operate on. So, in terms of safety and in terms of alternative things, you know, this is really in the ball park.

DR. CALIFF: But if you look at people who didn't have anything, they were all alive at 30 days.

[Laughter]

DR. GILLIAM: There is that.

DR. CALIFF: Although it is interesting that we don't really have data about redo bypass surgery that is randomized to know where the curves come back together. In general, we believe that you take that risk and it lowers the attrition rate after the first 30 days.

Having gone through all this, is it my job to make a motion?

DR. SIMMONS: I think we can finish some of the other questions before you make a motion. I guess we have done one and two.

DR. FERGUSON: Well, what is our answer to one?

DR. SIMMONS: He will make that motion later.

DR. STUHMULLER: You can ask everybody to give their opinion.

DR. SIMMONS: Oh, do I have to? Does anybody else

want to comment on the efficacy issue? Do we want to go around the table? Question number one was whether or not efficacy has been demonstrate. Would anybody like to make a comment?

DR. SPYKER: I am sorry, it is always very difficult casting these questions. The first question is just to say is there enough data to discuss? Question 11 is really the final question. That is the way question one is being interpreted. So, it is a chicken and egg problem. We want to say is there enough to proceed to consider this application? That is question one. Then the logic is, well, in order to decide whether it is safe and efficacy as labeled, we have to label it. So the sequence is, one, can we proceed toward labeling? Then we go through the labeling specifics. Then you say is it safe and efficacy as labeled. So, that is what we are trying to get across.

DR. SIMMONS: Thanks. That helps. Dr. Tracy, are you going to comment on the first question? Dr. Sethi? Dr. Wittes?

DR. WITTES: I would say yes.

DR. SIMMONS: Dr. Crittenden?

DR. CRITTENDEN: Yes.

DR. CALIFF: By current standards, yes.

[Laughter]

DR. GILLIAM: Yes.

DR. SIMMONS: Would you like to comment, Mr. Jarvis or Mr. Dacey? No comment? So let's proceed to the second question. Do the following indications for usage adequately define that patient population? Indications for usage: transmymocardial revascularization with the Eclipse TMR Holmium laser system is indicated for the treatment of patients with angina, Canadian Cardiovascular Society class IV, refractory to medical treatment and secondary to objectively demonstrated coronary-artery atherosclerosis not amenable to direct coronary revascularization.

DR. SPYKER: The questions we passed out to you all are slightly different from the version in your panel pack. In this particular case, what is in curly brackets here is something we have added since the panel pack. It is in the hard copy we passed out earlier and it is on the screen. So, we welcome all kinds of comments but we specifically would like your discussion whether, for example, that clause which was not included in the labeling for the previous product might be included here.

DR. DOMANSKI: I am nervous about anything that implies that somehow you are addressing the underlying mechanism by which coronary disease produces ischemia. I think that in effect represents that this is a way of treating. I don't like the apparent causal link because to say this is more than a placebo goes far beyond any data

presented, and I think that is really important.

DR. SIMMONS: So you are saying you don't like --

DR. DOMANSKI: I think Holmium laser system is indicated for treatment of patients with angina--you know if I were trying to phrase that, I would say maybe it is useful in relieving angina, but "indicated for the treatment of" makes it sound as though somehow it is going to have some--I am worried about the connotation. I would like to say that it may be useful in relieving chest pain basically, but to imply that it is because it is relieving ischemia by saying that, think it conveys an impression clearly that it is treating a mechanism and we don't know that.

DR. SIMMONS: The only thing in its favor is that it does sort of more limit the population. Angina is kind of a vague term.

DR. DOMANSKI: But if I had that and I didn't know what I know, I would think that you were somehow, with this technique, addressing the underlying mechanism. I think you not only haven't shown it but I think you may not be.

DR. CALIFF: But, Mike, if you look at the entry criteria for the trial it is used as the evidence that the treatment is beneficial. The patients had to have reversible ischemic myocardium.

DR. DOMANSKI: Yes, I really understand that. That is the countervailing thing and I am uneasy about the

ambiguity, but I still think that it really pushes--it presents the appearance of something that hasn't been demonstrated. That I don't think is fair to the patients.

DR. TRACY: I agree with Mike on that because I think there isn't anything to indicate that we are even doing anything about the region of ischemia. I mean, the only reason for putting in a clause about reversible ischemia is so that people don't drill holes in people that have just completely scarred myocardium. But if they are having pain, the indication is that it is probably coming from ischemic tissue. And, you are not relieving the ischemia, you are doing something different from relieving the ischemia. So, there is a cause and effect implication there and I don't think that we have at all established a cause and effect, and I would take that phrase out. But also I don't have any problem saying it is indicated for the treatment of patients --

DR. DOMANSKI: Yes, I would say you have gone even further. This trial has conclusively demonstrated, at least to the extent that perfusion with thallium can do it, that you are not relieving ischemia.

DR. SIMMONS: So, make a proposal as to how you would like to have it worded.

DR. DOMANSKI: I think that "indicated for the treatment of" is probably okay. I would certainly get rid

of the clause. I don't know what else to do with the thing, frankly because it is indicated--you have to give an indication, for heaven's sake. It is indicated for that, but the clause is an implication that goes beyond the indication. So I think eliminating the clause probably does the trick, don't you think?

DR. FERGUSON: One question, Tony?

DR. SIMMONS: Can you speak into the mike, please?

DR. FERGUSON: Sorry. This phrase says nothing about stability and instability of the angina. I bring up the point about that because we talk about the risk/benefit ratio in certain patients in terms of having angina relief versus death, but that risk/benefit ratio goes way up if we are talking about very unstable patients. Is that not correct? Am I wrong about that?

DR. SPYKER: Right, that is the very first warning.

DR. CALIFF: How do you know you are not just looking at a table of random numbers?

DR. FERGUSON: Why don't you put the words "stable angina" in there? That is my question, I guess.

DR. CALIFF: Do you have statistical evidence that the risk is really much higher in people with unstable angina?

DR. FERGUSON: That was my question, Rob. I have

the sense that that is the case. Maybe we don't have enough data to even know that.

DR. WITTES: I am going to play the old country statistician game. If you look at the patient selection criteria, that little thing in the clause is part of what this group is. It seems to me that by getting rid of it, or by changing that language you are actually opening the indication, not closing it.

DR. SIMMONS: That is what I felt too. That was my sense also. I agree. I understand what you are saying about implications and stuff but by taking that phrase out you are actually broadening the patient population that might be candidates for this, because now people with scars and undocumented ischemia --

DR. DOMANSKI: Well, I am not sure why you wouldn't do that. I mean there is certainly no evidence that you are eliminating ischemia. So, why not?

DR. CALIFF: They didn't study people with scars; they studied people with reversible areas of ischemia.

DR. GILLIAM: They should be included.

DR. CALIFF: I agree. So, maybe we need to take a vote on that. It looks like it is going to be a close vote.

DR. DOMANSKI: I understand the problem, but I think you are implying a mechanism that doesn't exist.

DR. FERGUSON: I agree strongly with Mike on that.

I think that implies that we know all these answers that we have been struggling with.

DR. CALIFF: I don't think we are implying it; I think you are inferring it.

[Laughter]

DR. DOMANSKI: Yes, but reasonable people would reasonably infer that, and a man of ordinary sense and reason would ordinarily infer that.

[Laughter]

DR. SPYKER: We certainly can put that clause in the clinical study section where we are describing the patients that were studied. We can certainly stick it right there.

While I have interrupted, I would like to say that we just by mistake left the word "stable" out of there. I notice it is in the previous labeling. So, it should say "stable angina."

DR. FERGUSON: That was just my question, why it is not mentioned here.

DR. CALIFF: Now you are getting me riled up. I mean, there is no clinician that I know of who would describe these patients as having stable angina.

DR. SIMMONS: Class IV angina --

DR. CALIFF: Class IV stable angina? I have never heard of such a thing.

DR. DOMANSKI: You know, as a matter of consistency, a few months ago we passed one that said "stable angina." I mean, you know, the whole thing is so inconsistent that you begin to wonder what the organization is doing.

DR. SIMMONS: Let's go around the table here and elicit people's opinions. Stable or not stable? Do you want that word in?

DR. TRACY: I would leave that word out. I think just to say Canadian Cardiovascular Society class IV is enough.

DR. SIMMONS: And how about the phrase? Do you want it in or out?

DR. TRACY: Take that phrase out.

DR. SIMMONS: Dr. Sethi?

DR. SETHI: I would leave it the way it is, except take the phrase out.

DR. WITTES: I would leave the phrase in, and no "stable."

DR. SIMMONS: No "stable?" Is somebody writing these things down?

DR. STUHLMULLER: It will be in the transcript.

DR. CRITTENDEN: Leave "stable" out and leave the phrase in.

DR. FERGUSON: I would put "stable" in and take

the phrase out.

[Laughter]

DR. DOMANSKI: And I am the same on that.

DR. CALIFF: I would leave "stable" out and keep the phrase in.

DR. GILLIAM: I would like to leave "stable" out and keep the phrase in.

DR. SIMMONS: And my two cents, I would leave "stable" out and leave the phrase in. Shall we go on to number three then?

Should there be any contraindications for the use of this device? Under contraindications, there are no contraindications known.

DR. CALIFF: It seemed that from the exclusion criteria of the trial there were situations where the sponsor of the study was concerned that the device shouldn't be used, particularly, it sounds like, the mural thrombus issue is probably the most important one here. There are also criteria for COPD. You know, I think we are in a situation where the device is essentially untested in people with COPD and that they should be excluded.

DR. CRITTENDEN: Or patients with mechanical valves on coumadin.

DR. SETHI: You know, the patients with mechanical valves, you can put them on heparin and then do the

procedure.

DR. CALIFF: The sponsor said they are now doing studies in that population, so it seems like they could come in quickly with data.

DR. SETHI: But I think patients with mural thrombus and patients with a low FEV1 should be included in the contraindications.

DR. CALIFF: What about ejection fraction less than 25 percent since those patients were all excluded?

DR. SETHI: They don't have any data on that.

DR. CALIFF: Roosevelt asked an interesting question, are we talking about contraindications or warnings here?

DR. TRACY: Yes, are those really contraindications are those statements that you would make that they haven't been studied in patients with such-and-such? I mean, there is at least some apparent logic to not boring a hole through a clot. That seems to stand alone, but the issues of COPD and EF less than 25 percent I think are just untested. Usually when we have a contraindication we have a data base to make a recommendation.

DR. SIMMONS: So nobody has proposed a contraindication that there is data on. So, we are going to go on to the warnings. Under warnings, number four --

DR. GILLIAM: Well, I have a problem and I think

Dr. Califf is probably going to say the same thing. I think we need to somehow focus on what we define as unstable angina. I mean, class IV is unstable angina but what they were talking about was not unstable angina. I think we need to come up with a better descriptor for that type of patient, and I am not sure we have data even for a lot of those patients.

DR. SIMMONS: I am not sure where you are going with this. Are you talking about for the indications.

DR. GILLIAM: Well, they said unstable angina was associated with an 11 percent mortality. Well, I don't think we are seeing unstable angina, we just said patients in their study that they defined as unstable angina, not what we classically in cardiology take as unstable angina.

DR. WITTES: What if we get rid of the parentheses, "requiring IV anti-anginal medication?"

DR. TRACY: Maybe I am missing something but where is that? I don't get it because we have patients who had unstable angina who were rolled over and they had better mortality. Where are we getting this 11 percent from? We have the high mortality in the initial group before the modification. Maybe the warning should be, "don't put your patients in heart failure before you do this."

DR. SPYKER: It is study 3. That is the only place we have in the panel pack--study 3 was unstable angina

patients. That is where the 11 percent came from. We certainly appreciate your comments on numbers but we are simply trying to draw a comparison, as we did when we crafted a warning --

DR. CALIFF: I am so glad you brought up study 3 again because it is something that I kept forgetting to mention all morning. When was study 3 done temporally in relation to this investigator meeting? Was it after the investigator meeting or before the investigator meeting? After? And the definition of unstable angina in study 3 was? The answer was that it was the same definition as used in the randomized trial, that is, unweanable from intravenous medication. So, it seems to me that if we are going to have a warning, it should specifically state patients who are unweanable from intravenous medication. It is not just on intravenous medication; it is unweanable.

DR. SIMMONS: Mr. Dacey, do you want to comment?

MR. DACEY: According to the clinical practice guideline number 10, Agency for Healthcare Policy and Research, unstable angina definition throughout the guideline is defined as having three possible presentations: symptoms of angina at rest, usually prolonged more than 20 minutes; new onset less than two months; exertional angina of at least Canadian Cardiovascular Society classification class III in severity, or recent, less than two months,

acceleration of angina as reflected by an increase in severity of at least one CCS class to at least CCS class III. In most but not all of these patients symptoms will be caused by significant coronary-artery disease, on Q-wave myocardial infarction and post MI more than 24-hour angina are part of the spectrum of unstable angina.

DR. SIMMONS: So, do you want to rephrase it?

DR. CALIFF: The point is that unstable angina includes a huge population. So, the rephrasing would be, as I understand it, unstable angina--well, it would be angina unable to be weaned from intravenous anti-angina medications. Exactly how you put the words before and after that I don't know but that phrase I think is the key phrase.

DR. SIMMONS: How about angina requiring IV medications was associated with an 11 percent perioperative mortality?

DR. CALIFF: I hate to quibble over details but that is not enough, I don't think, because, you know, we put people on intravenous nitroglycerine routinely and it is really the inability to wean the patient that is the key.

DR. SIMMONS: Okay.

DR. CALIFF: I am sure you guys can work with those words.

DR. SIMMONS: So that is one warning. The next warning would be what we talked about, the mural thrombus,

the severe COPD, ejection fractions less than 25 percent, patients with mechanical valves just haven't been studied in this patient population.

DR. TRACY: In my mind there is also a question. I understand there is more information coming but anybody who requires anticoagulation--I mean, if you are going to put a warning in there about anticoagulation that is not specific to the fact that they have a mechanical valve, the problem is the anticoagulation, not the reason for it. Until they can come up with more information I don't think there is anything to say that it is not a warning.

DR. SIMMONS: Patients requiring chronic anticoagulation.

DR. CALIFF: Actually, I think the exclusion criteria from the study are pretty well worded. You can just take that phrase.

DR. SIMMONS: Okay. Shall we go on to number five then? Warning: Avoid excess fluid loading prior to the TMR procedure, unless clinically indicated --

DR. CALIFF: I have to comment on this. I have never seen clinically indicated excessive fluid loading.

[Laughter]

So, I think we would all agree we don't want to have excessive fluid loading. We can just take out "unless clinically indicated."

DR. SIMMONS: All right.

DR. SETHI: Can we hear from the sponsor what excessive means?

DR. SIMMONS: No, I don't think so. Technically, they are not here.

DR. STUHLMULLER: However, at the end of the panel discussion the sponsor will have an opportunity to comment on anything they want to.

DR. FERGUSON: I would like to ask the panel then what they mean by excessive fluid loading --

DR. SETHI: Yes, I don't know what that means.

DR. FERGUSON: -- it a very ambiguous statement.

DR. SETHI: I don't know what it means. How to you judge excessive and non-excessive?

DR. DOMANSKI: You have to know it when you see it.

DR. SETHI: By that time it is too late.

DR. CALIFF: It is funny because we are getting ready to do a randomized trial, as you know, of why they should do a Swan-Ganz catheter in patients with heart failure, and we can't get anybody to agree on why you should put a Swan-Ganz catheter in because nobody know what to do with the data once you get it. But, to me, it is not very important one way or the other. It sounds like the sponsor would like to have it in there to give them a hook for their

educational program.

DR. SIMMONS: Does anybody else want to comment on that issue?

DR. GILLIAM: I might be opening a Pandora's box. I am sort of inclined to leave it out because I don't think we have any evidence one way or the other for this, and I think it is probably good clinical sense to not put people in heart failure before you do surgery on them. I guess if you get to the point where you have to tell people to not put somebody in heart failure before you do surgery, then I don't think we need to instruct them on anything, I guess.

I just wonder, if we put so many warnings on this, then people never tend to ever look at them anyway. I don't know.

DR. SIMMONS: I guess the only thing you can make a case for is that in comparison with the other device that is on the market fluid loading is one of the things that is indicated. This is a warning that you don't need to do it; you shouldn't do it.

DR. GILLIAM: But I am sure excessive fluid loading isn't something--they don't say, well, before we do this procedure we are going to excessively fluid load you.

[Laughter]

I don't know what parameters they follow. I wasn't at that discussion.

DR. TRACY: It may not be a warning. It may just be a statement somewhere in the education that fluid loading is not necessary prior to this procedure. You know, to warn somebody not to put somebody into failure doesn't make sense.

MR. JARVIS: It could actually be a precaution versus a warning.

DR. FERGUSON: I would be much more comfortable with that statement.

DR. DOMANSKI: Does that need a motion?

DR. SIMMONS: No. Just moving it to the precaution statement rather than a warning sounds like a good consensus.

Okay, number six, the sponsor presented evidence that the frequency of ventricular arrhythmias was reduced with the introduction of a pause after the creation of every few channels in the myocardial wall. Does the proposed labeling appropriately indicate our state of knowledge? Warning: The operator should pause for so many seconds after the creation of every so many TMR channels as such pauses may reduce the likelihood of ventricular arrhythmias.

I think having it in the warnings is probably, again, not the right place for it.

DR. GILLIAM: I think I would put that as a

teaching point, how to teach the procedure because, one, I don't think we have any idea how long they are supposed to pause. I don't think there is any study done on how long they are supposed to pause, and I think this is going to be something that the surgeons are going to do because we may find that it may be five seconds or it may be thirty seconds. I don't know, I think I would put this under the auspices of letting the company teach people to do it properly, whatever that means.

DR. TRACY: It is also completely unclear whether it is the pause between the holes that is making any difference in the arrhythmia, or is it simply the fact that you are not flooding the patient, or you are not manipulating the heart as much. And, it is not as though the risk of ventricular arrhythmia was hugely less post versus pre. It was less, but these people still had a significant number or episodes of ventricular arrhythmia up to the 30-day point. I don't know how to compare that to what happened in the 30 days in the medical managed group. This is a whole area that is unexplored territory, but I don't think there is any reason to put that as a warning.

DR. SIMMONS: Does anybody want to disagree with that?

[No response]

So we are going to drop that as a warning. Number

seven, should an additional informed consent be required for the use of TMR? Patient counseling information: This device is restricted to use in patients who sign an informed consent to ensure that the risks associated with TMR have been fully explained to and understood by the patient.

Do you want to comment? Do you want a consent form?

DR. CALIFF: I guess I am a little confused. I thought you had to have a consent form for any procedure.

DR. SIMMONS: This is above and beyond a surgical hospital consent form, especially designed consent form for this procedure.

DR. CALLAHAN: This is like the white extra sheet that drugs would give out.

DR. CALIFF: I would be in favor of that. It seems like our point estimate, at least here, is that we are asking a patient to make a choice between a modest but definite improvement in quality of life and probably a higher risk of death. It seems like that choice should be made with a little bit more than just a surgeon's or the cardiologist's point of view.

DR. SIMMONS: I think that is right. I agree.

DR. GILLIAM: I am going to disagree because I think the motive is correct. I think no patient should not understand what they are going through. I mean, we are not

talking about bypass and TMR. They are signing a consent to have this procedure done. I mean, what we are saying to someone is, "okay, sign this consent. It says we are going to do the procedure. Then, sign this consent that says we really are going to do this procedure --"

[Laughter]

I mean, it is in effect two separate consents for the same thing. I think if we want to advise that the consent for the procedure have certain requirements, but when I hear an additional consent --

DR. SIMMONS: Well, most hospitals require their own consent form no matter what you do. Most hospitals for a surgical procedure have a standard consent form that has to be signed.

DR. FERGUSON: There is a long history for approving this in terms of devices that have not yet reached maturity. For that reason, that is why I would vote for it, Roosevelt, because I think until we have more background data it would be to everybody's benefit to have it, not just the FDA but the company and everybody else.

DR. GILLIAM: But when we give it our stamp of approval we are setting it loose on the public, regardless whether there are 30,000 consents or one. I understand the motive of this. I am just having a hard time reconciling that this is any different than anything else we take people

to surgery or any other procedure for.

DR. FERGUSON: If you are in a hospital and you are a surgeon, and you are going to use a device for the first time that is not recognized in the general market you would get an extra consent form. That was my point.

DR. GILLIAM: I agree. If you are doing an investigational device there is an investigational process to go through. But if I am doing a procedure that is approved, licensed and okay to be in general use, I would go to the patient, present him with the consent detailing what I intend to do, with the potential benefits and risks, and have him sign it. I wouldn't have a second consent procedure for them to sign.

DR. SETHI: I think it is slightly different than that because we do not know the safety of the device, and I think it would be probably appropriate at this point to have a consent separately, and then once they have more data --

DR. GILLIAM: But if we are giving it our approval, then we are saying that it has our approval for being safe and efficacious. That is our approval.

DR. DOMANSKI: Well, we are putting the thing on the market--the FDA is putting it on the market and representing that it is safe and effective by their process. So, I don't understand why we have another consent form.

DR. SIMMONS: I guess I disagree. I would like to

have another consent form. Shall we just go around the table?

DR. TRACY: I would not require another consent form. I think there is plenty precedent for things that we do that potentially are going to expose the patient to greater risk for which we don't have separate individual consents, and it is something that the patient should be educated about. I am all in favor of having patient education materials, but I don't think that it is reasonable to require a separate consent form, and I am not sure how we would mandate that or how it would be carried through.

DR. SETHI: I think after listening to Dr. Tracy, if we have good material for education to the patient which we can give to them, it may not be necessary. Without education material, I think a consent form should be done.

DR. WITTES: I think there should be.

DR. CRITTENDEN: I think there should be a separate consent form as well.

DR. FERGUSON: And I do too.

DR. DOMANSKI: I will vote no separate consent.

DR. CALIFF: I would have a separate consent that gives the data.

DR. GILLIAM: I would vote for no additional consent.

DR. SIMMONS: Maybe we could have our consumer

rep.

MR. DACEY: The subject of informed consent has been a source of debate for many, many and the bioethical issues alone are daunting and we could spend the rest of the week on it.

I have always been troubled by the fact that the informed consent piece of paper has been treated as a legal document, and that informed consent has not been a provider, physician, patient process. I have seen a lot of documents. They change from hospital to hospital, and I have even helped design some of them. The risks, the benefits, the alternatives, the risks of the alternatives, including the risk of doing nothing, the entire laundry list to that patient who oftentimes has already got some sedatives on board, and they have a clipboard shoved at them with a piece of paper on it to sign--I just wish there was a way that any informed consent document, from hospital, to hospital, to hospital, contained the information that is legally required, that the patient can use to make an informed decision. Regrettably, it is not. There is that much variation.

As a non-voting member, I would push the idea that since the amount of information is limited for the patient to make a decision, that at least initially they have the opportunity to see information that goes beyond what is

customarily obtained for a surgical procedure. And, I am not talking about a 12-page informed consent document. I am talking just about more information that they can use to make a decision.

MR. JARVIS: Just one comment on something you said. I would hope that nobody is consenting people under the influence of drugs. That concerns me greatly. Especially as somebody who sponsors these types of trials, I would have a big problem with that.

But as the industry as a whole, I would say that we would not like to see a separate informed consent. I would hope that we could, by giving just what Cynthia talked about, the proper training package of materials so that when people do come to consent patients they would consent them in an unbiased type fashion. They would let them know the positives and negatives of the whole procedure.

DR. GILLIAM: I have one question. Are we asking that there be two separate consents for the procedure or are we saying that we can have a consent that requires certain elements in it? Because that is not clear to me. I thought people were saying they wanted a separate consent in addition to the surgical consent signed, not just a consent form with certain parameters put in it.

DR. CALLAHAN: I think the problem comes down to one of jurisdiction. Each hospital has their own individual

form. We don't get involved with that. So, the only criteria that we have, or label, is that this patient counseling would be something the FDA would attach to someone using this particular device. We don't want to get into each surgery procedure. So, almost by definition, it has to be separate otherwise we would have to go to each hospital to make sure that they had the data in there.

DR. GILLIAM: How are you going to enforce that? You know, we have certain requirements of documents that go actually in a medical record, and if there is a loose form it goes right into file 13. If our hospital doesn't approve that form, it is not going to go in the medical record.

DR. CALLAHAN: I think the answer to that depends on how you answer question number 11. If there is yet another continuation of the study, then it will be under the study aegis of the FDA and, at least for a temporary period, it will be out there separate and we will have enforcement.

DR. TRACY: But that is a different issue. If we are going to say that there is an ongoing study that is under the FDA, under the IRB then, yes, of course there would be a separate consent, but I think Roosevelt is absolutely right, anything that is not on a Georgetown approved, IRB approved form, or that is a hospital approved form is not legally part of our document, and it will get trashed as the patients chart is finalized.

I am not aware of any precedent, maybe somebody is, of requiring such a thing to be put in a chart, and I have no idea how you would get hospitals to comply with this, and that is what you are asking them to comply with. The legality of such a document, as far as I can tell, is non-existent, and who is going to be to blame or to credit for anything that is an outcome of this thing? So, I think it is much more important to caution physicians that they must get appropriate informed consent and share with the patient important information about the potential risks and benefits of this procedure. That is what we should be doing. I don't think we can tell Georgetown Hospital to put this thing in their chart.

DR. SIMMONS: Are you aware of other protocols that have required consent forms?

DR. CALLAHAN: The PLC, which was the first transmyocardial revascularization device.

DR. GILLIAM: So we would file a separate consent form for that one?

MR. JARVIS: We didn't discuss that at all during that meeting, a separate consent.

DR. CALLAHAN: But the answer is yes.

DR. STUHMULLER: That was an agency condition of approval, not a panel recommendation the last time.

DR. SIMMONS: Well, let's go on because I think we

have all already expressed our opinions here. Does the outline of the possible mechanism of action in section 11.4 of the labeling adequately summarize the state of knowledge of TMR? The Mechanism of action: The mechanisms by which TMR relieves angina are not known. In addition to possible contribution of placebo effect, current theories include increased perfusion of myocardium via the channels created; increased collateralization via angiogenesis; symptom reduction resulting from disruption of pain fiber function; possible microinfarcts to the myocardium.

DR. DOMANSKI: I have one change that I would really like to make to that in view of the discussion we have had today. I would like to eliminate the second sentence, "in addition to possible contribution of placebo effect," that part of the sentence and make placebo effect one of the bullets, one of the possibilities, because it could be all placebo effect and this mitigates it.

So what it would read, I move or whatever, is that the mechanism whereby TMR relieves angina is not known, period. Current theories include: Then the first bullet would be placebo effect and the rest of it would be as stated.

DR. TRACY: Yes, I think that is reasonable but it could be placebo but I suspect that there is more to it than that, and we just don't know what the mechanism is.

DR. SETHI: I agree with that.

DR. WITTES: I agree.

DR. CRITTENDEN: I agree.

DR. FERGUSON: Yes.

DR. CALIFF: I agree.

DR. GILLIAM: I agree.

DR. SIMMONS: We are rolling now. Number nine, have you any other suggestions for the labeling? Is there anything else? I guess we already answered that. Number ten, do the data presented adequately demonstrate the safety and effectiveness of the device as labeled?

DR. CALIFF: I would make the motion that --

DR. STUHLMULLER: From a procedural point of view, this is not the time to make the motion. If you want to have a discussion or if you think you have adequately discussed it, then we can close the discussion but at the end of the committee discussion the sponsor is provided with time to comment on the committee discussion, and also anybody from the public that wants to get up and comment relative to the application before the panel. Then you can make a motion.

DR. CALIFF: Well, I think we have had a lot of discussion. Just to state my, maybe extreme, point of view. I am very bothered that we are turning devices loose on the country for life or death situations and have no idea what

their real safety is. But that is the way it has been done and I see no reason to hold this company hostage to a new set of rules.

DR. SIMMONS: So you are willing to close the discussion right now?

DR. CALIFF: Yes.

DR. SIMMONS: Dr. Tracy?

DR. TRACY: I don't have any other comments. I think we have discussed it enough.

DR. SIMMONS: Dr. Sethi?

DR. SETHI: No comment.

DR. SIMMONS: Dr. Wittes?

DR. WITTES: On the labeling?

DR. SIMMONS: Yes.

DR. WITTES: Patients under the age of 32, I don't like that. There is one patient aged 32 and that suggests that there have been lots of studies of patients over 32. There are three patients over 30. So, I just thought that was too definite. This is on page 26, specific patient populations. The safety and effectiveness have not been established in the following specific populations: Patients under the age of 32, suggesting that it has been established for patients over the age of 32. I looked at the data. There is one patient age 32; there is one patient age 38.

DR. SIMMONS: So, how would you like to have it

phrased?

DR. WITTES: Just drop it. I would just get rid of that sentence.

DR. DOMANSKI: I will second that.

DR. SETHI: I agree.

DR. DOMANSKI: It is obviously a motion.

DR. SIMMONS: Okay.

DR. STUHLMULLER: No, there are no motions on the table. This is just trying to get group consensus and make sure for the record that we understand what each panel member thinks on each question. That is the point of systematically going around.

DR. SIMMONS: So, we are all agreeing. Anybody object? No objections noted. Dr. Crittenden?

DR. CRITTENDEN: I just want to echo what Dr. Califf said about the inadequacy of the data. I am uncomfortable but I agree that we shouldn't hold the company hostage probably.

DR. DOMANSKI: I would encourage closing the discussion.

DR. SIMMONS: I think that is a hint. Nobody wants to make a comment? We will allow the sponsor time to come and make any comments they would like in response.

MR. CHUTORIAN: Actually, we have no further comments. I just want to thank the panel for its efforts

today. We appreciate it very much.

DR. SIMMONS: Are there any comments that the FDA would like to make? Questions we haven't answered that you would like to discuss?

DR. CALLAHAN: No, but there are follow-up questions depending on the vote.

Open Public Hearing

DR. SIMMONS: We would like to open the meeting up at this time to the public for open public discussion. Is there anybody who would like to comment? Yes?

MR. CONSUL: My name is Sam Consul, and I am a private investor.

DR. SIMMONS: You are a private investor in this company?

MR. CONSUL: No, I don't have any shares in Eclipse, nor any of my family. I just would like to make a comment. I am sitting here, and I am not a doctor; I have never been to medical school; I don't know anything about 75 percent or 90 percent of this stuff that you guys are talking about, but this is how I see it, or this is what I gathered from this meeting today:

This was a study done to show the efficacy, and the sponsor used angina to prove that and also safety, which is mortality obviously. On the efficacy issue, it seems to me that a lot of the people on the panel wanted to know how

does it occur. To me, it seems obvious from the little I know that it is a combination between angiogenesis and denervation, and the question is how much of it is each, how much of it is angiogenesis and how much of it is denervation? And, how long does angiogenesis take to work? And, if the sponsor provides that kind of information on how long angiogenesis takes to work, maybe we will find out how much of it is angiogenesis and how much of it is denervation.

On the mortality issue, it looks to me that there are more concerns about mortality among the panel and putting one consent after another, and it is just easier to not approve it, or to tell the sponsor to expand the study. Thank you.

Committee Recommendations

DR. STUHLMULLER: The panel recommendation options for premarket approval applications: The Medical Device Amendments of the Federal Food, Drug and Cosmetic Act require that the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on designated device premarket approval applications that are filed with the agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

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

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

Your recommendation options or the vote are as follows. Number one, approval, there are no conditions attached.

Option two, approval with conditions. You may recommend that the PMA may be found approvable subject to specified conditions, such as resolution of clearly identified deficiencies which have been cited by you or by FDA staff. Prior to voting, all the conditions have been discussed by the panel and listed by the panel chair. You may specify what type of follow-up to the applicant response to the conditions for your approvable recommendation you want, for example, FDA or panel. Panel follow-up is usually done through homework assignments of the primary reviewers of the application or other specified members of the panel. A formal discussion of the application at a future panel meeting is not usually held.

If you recommend that post-approval requirements

be imposed as a condition of approval, then your recommendation should address the following points: a) the purpose of the requirement; b) the number of subjects to be evaluated and, c) the reports that should be required to be submitted.

Option number three, not approvable. Of the five reasons that the Act specifies for denial of approvable, only three reasons are applicable to panel deliberation: a) the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling; b) reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended or suggested in the labeling; c) based on a fair evaluation of all the material facts and your discussions, you believe the proposed labeling to be false or misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask that you identify the measures that you think are necessary for the application to be placed in an approvable form.

Option four, tabling: In rare circumstances the panel may decide to table an application. Tabling an application does not give specific guidance from the panel to FDA or the applicant, thereby creating ambiguity and delaying the process for the application. Therefore, we

discourage tabling of an application. The panel should consider approvable or approvable with conditions or recommendations that clearly give described corrective steps. If the panel does vote to table a PMA, the panel will be asked to describe which information is missing and what prevents an alternative recommendation.

Following the vote, the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. SIMMONS: I think we are ready for our motion.

DR. CALIFF: I would move for approval, and my only stipulation would be that there be some viewing of other available data by the FDA.

DR. STUHMULLER: Can you clarify what you mean? Are you saying it is approvable with conditions? Is that what you are saying?

DR. CALIFF: Let me hear the list again.

DR. STUHMULLER: The options were approval, approvable with conditions, not approvable or tabling.

DR. CALIFF: I guess the motion I would put forward would be approvable with the condition that none of the other ongoing data indicate a problem with excess mortality.

DR. STUHMULLER: Well, the problem with that is that this data set has to stand on its own merits. So, you

can't make a motion --

DR. CALIFF: Vote for approval.

DR. SIMMONS: How about approval with some follow-up? Wouldn't you like to see 600 patients or something, 1000?

DR. CALIFF: I don't know what good that would do.

DR. SIMMONS: Well, if you had 20 percent mortality in the group?

DR. CALIFF: Well, that would be a problem. Isn't there a regulation that you have to follow patients with a device?

DR. SIMMONS: Not if you don't tell them.

DR. STUHLMULLER: Dr. Callahan, do you want to clarify that? Is the question you are asking about postmarket surveillance?

DR. CALIFF: Yes.

DR. CALLAHAN: Yes, there are a couple of aspects in which we can do it. In this particular one, if we make it a condition of approval we would do that. If we don't have conditions of approval, certainly we follow; for the extent that there are deaths we could capture that, but then you run into the problem of just collecting data on how many deaths there. So, if you are thinking that you need data of a type that is of a randomized nature, then you have to specify now, as a condition of approval, that there should

be a study and then stipulate the conditions of the study.

DR. CALIFF: I guess I agree with you that there should be a registry of patients, although we could have a long discussion about what you actually learn from that, and I don't want that to be interpreted as some kind of a real comforting issue. But if we approve it and there is required postmarketing surveillance anyway, then it is a non-issue. If there is not required postmarketing surveillance, then I think there should be.

DR. CALLAHAN: I think the difference is that if you want, for example, a continuation of a randomized study then you have to ask for that.

DR. CALIFF: No, I am not asking for a randomized study.

DR. CALLAHAN: Otherwise, there are postmarket surveillance activities that we could carry out. In that case though it might just be just a registry. It might not be anything more than that, and we would still have to discuss what kind of protocol, and so forth.

DR. CALIFF: So the motion will be approval with the condition that there should be a registry.

DR. SIMMONS: How many patients do you want in the registry?

DR. CALIFF: Oh, 500.

DR. TRACY: And don't we also have to specify the

amendments to the warnings and other things?

DR. STUHLMULLER: Yes, all those have to be listed now as conditions of approval. With the issue of a postapproval requirement of a study there were three things: The purpose of the requirement, the number of subjects to be evaluated, and the reports that should be required to be submitted. So, why don't we do that first before we do the rest of the other conditions?

DR. SIMMONS: See, otherwise what you are talking about is that if you don't stipulate it, there is some voluntary reporting of deaths that goes on, but otherwise the company isn't going to follow anybody in a prospective manner unless we tell them to or unless they just do it for their own interests. That would be my assessment. So, if you want 500 patients followed for how long, you have to say it.

DR. CALIFF: I guess what I would like to know would be a few patient characteristics and, hopefully, we don't have to go through the details of that right now, but identification of who the patients are and what the one-year mortality is.

DR. DOMANSKI: I will second that motion.

DR. SETHI: Can we discuss it at this point?

DR. STUHLMULLER: This part, yes.

DR. SETHI: The question is have we required a

similar type of requirement from the other company?

DR. STUHMULLER: Dr. Callahan, do you want to address that?

DR. CALLAHAN: Yes. Yes, we have done that.

DR. SETHI: We have asked the other company to give us follow-up on 500 patients with the details Dr. Califf is asking about?

DR. CALLAHAN: We have done lots of things. Some companies we have asked for continuation of people in the actual trial, that the trial continues and collecting data.

DR. SETHI: I am asking about this particular device, not other devices but the PLC.

DR. CALLAHAN: Yes, there is actually a postmarket study going on.

DR. STUHMULLER: I think the point you are trying to get at is it was a condition of approval as opposed to a postmarket study. From a legal point of view there is a significant difference between a condition of approval and a postmarket study.

DR. TRACY: What is it? I don't quite understand how you can approve something to be used in a randomized fashion. What is a postmarket study versus a registry?

DR. CALLAHAN: A postmarket study can be whatever you want, however you want to describe the study. A registry would just be a collection of some particular

endpoint like mortality or something like that. Sometimes we continue on in a study because there is a specific cohort of patients that you want followed up, some specific information that you want to receive from that cohort. But there is a point at which you say we are approving it and we are still going to do a study.

DR. TRACY: I suppose the biggest unanswered questions are the mortality and who are the people who really are at risk. So, I think a postmarket study, gathering information about ejection fraction, mortality, other adverse outcomes is reasonable, to include approximately 500 patients, all of whom to be followed for a year, would seem to be a reasonable amount of information to request.

DR. GILLIAM: I think that is a registry. I think it is very nice to know that but you will have no idea really of whether there is excess mortality. We would just know the mortality of the procedure that we have done because once you get it out in general use you can't control who gets it, and you can't control the operator variability. So, I think it is imperative that we do know these things perhaps, but it does not speak to the safety issues that we have here. I think we need to recognize that going into it.

DR. TRACY: But I think we have been pretty careful not to expand the indications, not to let any slide

to come in here in terms of the indications for usage, and the warning or the precautions are appropriate in terms of what has not been studied. So, if the device is approved for people in whom it was studied, then data collection will include many people of similar characteristics and I think, more than just a haphazard registry, if this was a mandated recommendation then we would have that information to compare with this very small historically controlled group of medical management. At least we would have that and that is better than just a voluntary or a haphazard registry.

DR. SIMMONS: You have to make a proposal and tell us what you want.

DR. GILLIAM: I am on very thin ice as a statistician but my take on listening to what has been going on today is that we are unsure of the safety of the device, and we would like to have at least some level of assurance that this isn't really way off the mark as far as its potentially harmful effects.

My concern is once you approve the device it is going to be used on a wide spectrum of people, some of whom are much, much sicker than the group we have.

DR. SIMMONS: So what are you proposing? What do you want?

DR. GILLIAM: I guess I would just propose a registry of patients for the first five years of use of this

device, everyone who has use of it, a registry compiling the data comparing those mortalities, just as information of the effectiveness of the procedure.

DR. SIMMONS: That is a lot --

DR. DOMANSKI: Would it make sense to say that we would like it followed in a registry format and let the FDA, in the fullness of time, figure out precisely how to organize that registry? I mean, that seems to me to make a lot more sense than trying to, off the cuff, put together a whole study at this table.

DR. WITTES: That is exactly what I was going to say. I think you understand the concerns that we have that there is a potential for excess mortality. It may just be chance. We know that a registry, by its very nature, is going to be very difficult to interpret. I am very uncomfortable about choosing either a number or a time. I think that is sort of off the cuff. What is important is that it be consecutive.

DR. FERGUSON: I would echo that by saying that the company, for its own well being, is going to follow these patients very closely, no matter what we decide here. I think the point is that we want to be concordant in terms of their data points being somewhat near our data points, and I think that is where we have control a little bit of the process, and I would agree with you.

DR. GILLIAM: If we don't instruct them I don't think they will follow them at all because they don't know who they are. Once this thing gets used in hospitals it is going to be used and no one is going to know. They may know how many units they sell but they are not going to have the names of the people.

DR. FERGUSON: I don't agree with you on that but that is something else. For their own welfare, they are going to follow these patients.

DR. SIMMONS: I don't know but, anyway, we have right now a proposal to approve with the conditions that a registry be formed to follow ejection fraction, mortality, adverse outcomes, that they be consecutive patients.

DR. STUHMULLER: I thought that Dr. Wittes' comment was that that would be worked out between the agency and the sponsor, and perhaps could be done in conjunction with a homework assignment to several of the panel members.

DR. SIMMONS: That sounds good.

DR. WITTES: Yes.

DR. STUHMULLER: So the condition of approval would be that there be a post-approval study where the structure of the study is worked out between FDA, several panel members with a homework assignment, with the sponsor.

DR. SIMMONS: Okay. So do we need to put these other conditions in there?

DR. STUHLMULLER: We need somebody to sequentially list what the other conditions of approval should be. Then we will have a motion.

DR. SIMMONS: The other conditions then, under indications, that we not put stable and we include the region of reversible ischemia. The second would be that contraindications are not known. Under warnings, we wanted to add mechanical valves, patients on chronic anticoagulation, COPD, ejection fractions less than 25 percent and mural thrombus. We wanted to drop the excessive fluid warning label.

DR. CRITTENDEN: Tony, what about unstable angina in the IV indication? You skipped over that.

DR. SIMMONS: I am sorry, and that we were going to include under the warnings angina unable to be weaned from IV medications was associated with increased mortality.

We were going to drop the warning about the operator pausing for a certain number of seconds after the TMR channels and leave that to the training session. The consensus, I believe, on the panel that we require a separate consent form, that there was a change in the mechanism of action to include placebo as one of the bullets as a trouble--possible cause of mechanism of action.

I think that was it.

DR. STUHLMULLER: So the motion, then, was

approvable with conditions and the conditions included a post-approval study, revision of the indications for use, the contraindications, the warnings and the patient-information section, the mechanism-of-action section, as discussed.

Is there a second on the motion?

DR. DOMANSKI: I second it.

DR. TRACY: Is it too late to ask a question?

DR. STUHMULLER: No; you can ask a question.

DR. TRACY: Was there a consensus on the informed consent? Was there a consensus on that on the panel?

DR. SIMMONS: You have to vote. That's what I said there was, so you have to show me. Vote yes or no.

DR. CALIFF: I don't think there was a consensus.

DR. GILLIAM: There was a majority. There wasn't a consensus.

DR. CALIFF: So you can filibuster it.

DR. STUHMULLER: Can you clarify that?

DR. SIMMONS: I will clarify that there was a majority vote of the panel to include a separate consent form.

DR. STUHMULLER: So a condition of approval will be a separate consent form. From a procedural point of view, that is what I need to make sure we understand, that the motion contained, as a condition of approval, a separate

patient consent form.

DR. SIMMONS: Do you want to vote?

DR. WITTES: Actually, let me ask you something. Can that be a recommendation but not a condition of approval? Does that make any difference?

DR. DOMANSKI: It is part of the motion.

DR. SIMMONS: At this point it is part of the motion.

DR. DOMANSKI: You can vote the motion down or--

DR. SIMMONS: Vote.

DR. TRACY: I agree for approval with the conditions, not consensus but a plurality of the panel wanting an addition consent.

DR. WITTES: Yes.

DR. CRITTENDEN: Approve with conditions.

DR. WITTES: I meant approve with conditions.

DR. FERGUSON: I approve the motion.

DR. DOMANSKI: Approve.

DR. CALIFF: Approve.

DR. GILLIAM: I don't approve the motion as is. I am concerned about safety. It is sort of a meaningless vote. The motion was carried but I have significant concerns about the safety and I think we are sort of on a slippery slope here.

DR. SIMMONS: So now do we go around and ask each

panel member to comment?

DR. STUHLMULLER: Yes.

DR. SIMMONS: Since you have to leave, do you want to make a comment?

DR. DOMANSKI: I think this is consistent with what has been done with the other similar device and I think is it probably appropriate for the FDA to be consistent.

DR. SIMMONS: Dr. Ferguson, do you want to make a final comment?

DR. FERGUSON: No comment.

DR. SIMMONS: Dr. Crittenden?

DR. CRITTENDEN: No comment.

DR. SIMMONS: Do you want to make a final comment?

DR. WITTES: No comment.

DR. SIMMONS: Final comment?

DR. TRACY: No comment. Everything has been said.

DR. SIMMONS: Do you want to make a final comment?

DR. CALIFF: I guess I would hope that the agency will work hard to come up with some criteria when devices are used in settings where death is a common occurrence for how to assess safety, that they would provide guidance so those who are designing studies can do a better job.

The other comment is this is a logarithmic advance over some of the other recent studies we have seen in similar technology.

DR. SIMMONS: Dr. Gilliam?

DR. GILLIAM: No. comment.

DR. SIMMONS: I guess I would like to make a final comment. I don't get to vote.

DR. STUHLMULLER: Under Roberts Rules of Order, the chair can vote under two circumstances; one, to break a tie and two, to cause a tie. Since neither of those conditions apply, you don't vote.

DR. SIMMONS: Do I get to make a comment?

DR. STUHLMULLER: All right.

DR. SIMMONS: I guess I would like to reiterate Dr. Califf's comment that I would like to see some sort of a panel meeting on discussion of investigators and who should be choosing investigators and qualifications of investigators because I think there are a lot of other issues that could be brought up and other ones that haven't been brought up today.

Also, again, I would like to make a plea for something to be--a comment on release of medical information on clinical investigations. Other than that, I don't have any other comments.

Why don't we take a fifteen-minute recess and then we will come back for the future concerns.

[Break.]

DR. SIMMONS: We shall reconvene. The FDA has

proposed six questions here on future developments of TMR. Because of the lateness of the hour, what we are proposing is to make this a homework assignment.

DR. GILLIAM: So moved.

DR. STUHMULLER: Do we have any volunteers from the remaining panel members who would be willing to participate in this as a homework assignment?

DR. FERGUSON: I will be happy to do No. 3.

DR. SIMMONS: That's great.

DR. STUHMULLER: I guess the issue would be would you be willing to look at the whole list in total and not pick out selected questions, but get three people who would be willing to just go down the list and potentially provide some input on it.

DR. WITTES: Oh; you mean a group project.

DR. STUHMULLER: Right.

DR. TRACY: There are five people left. I think it is reasonable to expect us all to look at these and at least come up with some--

DR. WITTES: No; I think it is reasonable for the three that have left.

DR. GILLIAM: I think we should invoke the fact that, of the group here--I am not a surgeon so I can be the first to the door, I think.

DR. WITTES: I am a statistician, so I can be the

second.

DR. GILLIAM: I am just wondering. Some of these involve actual surgical technique and, outside of Dr. Ferguson, I am not sure anybody else here--I just think that we need to involve some surgeons.

DR. SIMMONS: I think if we assign questions to people that they are not prepared to answer, you are not going to get very good results. How about if we divide them up. What are acceptable endpoints and how long should study patients be followed to demonstrate safety?

DR. STUHMULLER: I don't think we should volunteer anybody is not here. What I need to do is, from a procedural point of view, check on whether we can actually do this as a homework assignment and then figure out how many people can do a homework assignment and then sort it out that way.

DR. GILLIAM: I'll volunteer for No. 4.

DR. STUHMULLER: Dan, is that acceptable to you from a agency point of view?

DR. SPYKER: Yes.

DR. STUHMULLER: All right.

DR. SIMMONS: So you are just going to go through the list and then assign them?

DR. STUHMULLER: I will contact some people and ask them.

DR. SIMMONS: Okay. Because we are willing to divide them up if that will help you. Dr. Ferguson has already volunteered to work on one so you can look at that. Medications is something that a cardiologist would have a lot more input into than, probably, the surgeons. Quality of life is also something that cardiologists would probably have more input in. Endpoints and acceptable endpoints demonstrate effectiveness; I think you could call on either body to do that.

DR. GILLIAM: The shoe is going to drop on the other--it is, i.e., when they make this a catheter-type procedure, maybe these same parameters will go over to that if that ever comes up. Is that a fair thing to address now or--when you look at future of TMR?

DR. SPYKER: Absolutely.

DR. GILLIAM: Is that something that could be done now?

DR. SPYKER: The was the intent.

DR. GILLIAM: Okay.

DR. WITTES: It seems to me these need to be opened up. The acceptable endpoints and how long should study patients be followed really is what is the nature of the database needed for safety which is a broader issue.

DR. GILLIAM: I am sort of feeling the same way. If 30 days is the recovery from the procedure, itself, is

there any mortality outside of the operative event in this procedure. I don't know that. Maybe that is something we need to know.

My guess is, from the data that we have been presented today, outside of the 30-day event, it doesn't appear that there is any difference in mortality between the group that had the procedure and the group that did not. So maybe we don't need to follow it for that long as far as being able to characterize exactly what the mortality or morbidity associated with the procedure is.

DR. SIMMONS: More of a need to be followed just to demonstrate effectiveness so, as long as you are following one, you could just be following both. How long is it going to take to follow effectiveness for angina. We are probably talking six months or more.

DR. GILLIAM: I think that the general feeling I got from here, at least, is that the effectiveness is fairly convincing.

DR. WITTES: That was because it was one year.

DR. GILLIAM: Yes; the fact that it was. But, as far as--oh; I see--as far as future new developments, but as far as trying to prove this event any further. One year's time would be great to prove efficacy. But safety, I am not sure that we even need to look that far.

DR. CRITTENDEN: When you were talking about the

ventricular fibrillation beyond the operative interval, wasn't that a concern? Should we look at that?

DR. TRACY: Yes.

DR. GILLIAM: Yes.

DR. CRITTENDEN: So that is another safety issue, because I think that is part and parcel of the whole procedure and it seems like the operative arm had more, at least based on the data we saw this afternoon--the operative arm had more--

DR. GILLIAM: I think what we are going to find is that, in this group of patients, ventricular fibrillation, ventricular tachycardia and whatever else is a big risk, whether they have the procedure or not, maybe. But we don't know what the group who didn't have the procedure--but they had the same number of deaths if you get outside of the 30-day period.

DR. SIMMONS: Actually, the number of patients who died is pretty surprising. If you look at the MADIT data and the number of people who had low ejection fractions and coronary-artery disease in this group, you would probably have expected more patients with ventricular tachycardia or ventricular fibrillation. 50 percent of the patients had an ejection fraction of less than 35 percent, wasn't it?

DR. GILLIAM: I was surprised at how few people really did die in the year.

DR. SIMMONS: Unfortunately, I guess we don't know the long-term results. That is why I think a registry is actually a good idea. What if these people do start to turn up to have VT from all these little channels and little reentry circuits. I understand that it is not exact science but having some sort of a registry to follow these people seems like a very good idea to me.

We are not actually addressing the questions in a very coherent manner so I am undertaking a proposal. I am willing to listen to a proposal that these be assigned as a homework assignment. How does that sound? And that you will decide who is going to get which questions, John.

DR. STUHLMULLER: Yes. Tom, when you were out of the room, there was concern that, since a number of the panel members left, including the surgeons, that we didn't have enough people to address some of the issues and that I would check to see if we can do this as a homework assignment and how many people and then decide--we can solicit volunteers that way.

DR. CALLAHAN: I think that is something we could do and then we could, at another time, share it with the public.

DR. SIMMONS: Does somebody want to make a motion here?

DR. GILLIAM: I move--do you mean to assign this

at

240

as a homework assignment?

DR. SIMMONS: No; to adjourn.

DR. GILLIAM: I move to adjourn.

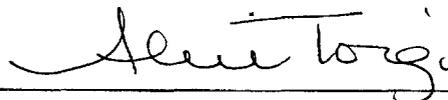
[Second.]

[Whereupon, at 4 o'clock p.m., the meeting was
adjourned.]

- - -

C E R T I F I C A T E

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

A handwritten signature in cursive script, reading "Alice Toigo", is written above a horizontal line.

ALICE TOIGO