

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

CIRCULATORY DEVICES PANEL MEETING

Volume II

Pages 1 thru 228

Gaithersburg, Maryland
April 24, 1998

MILLER REPORTING COMPANY, INC.

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AT

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

CIRCULATORY SYSTEM DEVICES PANEL MEETING

VOLUME II

Friday, April 24, 1998

9:10 a.m.

Ballroom
Holiday Inn
Gaithersburg, Maryland

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

PARTICIPANTS

Anne B. Curtis, M.D., Chairperson
John E. Stuhlmuller, M.D., Executive Secretary

MEMBERS

Tony W. Simmons, M.D.

CONSULTANTS

Robert M. Califf, M.D.
Samuel W. Casscells, III, M.D.
Manual D. Cerqueira, M.D.
Thomas B. Ferguson, M.D.
Alfred F. Parisi, M.D.
David J. Skorton, M.D.
George W. Vetrovec, M.D.
Ronald W. Weintraub, M.D.
Janet Wittes, Ph.D.

GUEST

Lawrence Friedman, M.D.

INDUSTRY REPRESENTATIVE

Mr. Gary Jarvis

CONSUMER REPRESENTATIVE

Donald Altman, D.D.S.

FDA

Lillian Yin, Ph.D.
Daniel Spyker, M.D., Ph.D.

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1 P R O C E E D I N G S

2 Call to Order

3 DR. CURTIS: The first order of business will be
4 the conflict of interest statement to be read by Dr.
5 Stuhlmuller.

6 Conflict of Interest Statement

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

11 The conflict of interest statutes prohibit special
12 government employees from participating in matters that
13 could affect their or their employers' financial interests.
14 To determine if any conflict existed, the agency reviewed
15 the submitted agenda and all financial interests reported by
16 the committee participants. It was determined that no
17 conflicts exists.

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

23 With respect to all other participants, we ask in
24 the interest of fairness that all participants making
25 statements or presentations disclose any current or previous

1 financial involvement with any firm whose products they may
2 wish to comment upon.

3 Appointment to temporary voting status pursuant to
4 the authority granted under the Medical Devices Advisory
5 Committee charter dated October 27, 1990, as amended April
6 20, 1995, I appoint the following people as voting members
7 of the Circulatory System Devices Panel for this meeting on
8 April 24, 1998: Drs. Casscells, Cerqueira, Ferguson,
9 Parisi, Skorton, Vetovec, Weintraub, and Wittes.

10 For the record, these people are special
11 government employees and are consultants to this panel under
12 the Medical Devices Advisory Committee. They have undergone
13 the customary conflict of interest review, and have reviewed
14 the materials to be considered at this meeting.

15 Signed, Elizabeth D. Jacobson for D. Bruce
16 Burlington, M.D., Director of Center for Devices and
17 Radiological Health, dated 4-21-98.

18 Appointment to temporary voting status pursuant to
19 the authority granted under the Medical Devices Committee
20 charter of the Centers for Devices and Radiological Health,
21 dated October 27, 1990, and as amended April 20, 1995, I
22 appoint Robert M. Califf, M.D., as a voting member of the
23 Circulatory System Devices Panel for the April 24, 1998
24 session of the meeting.

25 For the record, Dr. Califf is a voting member of

1 the Cardiovascular Drug Advisory Committee of the Center for
2 Drug Evaluation and Research. He is a special government
3 employee who has undergone the customary conflict of
4 interest review and has reviewed the materials to be
5 considered for this meeting.

6 Signed, Michael A. Friedman, M.D., Lead Deputy
7 Commissioner, dated 4-23-98.

8 DR. CURTIS: Thank you.

9 The next thing I would like to do is have all the
10 members of the panel introduce themselves.

11 MR. JARVIS: Gary Jarvis, the Industry
12 Representative to the panel.

13 DR. SKORTON: David Skorton from the University of
14 Iowa.

15 DR. VETROVEC: George Vetrovec, Medical College of
16 Virginia, Virginia Commonwealth University.

17 DR. SIMMONS: Tony Simmons, cardiologist, Wake
18 Forest University.

19 DR. CERQUEIRA: Manuel Cerqueira, Georgetown
20 University Hospital.

21 DR. WEINTRAUB: Ronald Weintraub, cardiac surgeon,
22 Beth Israel Deaconess Medical Center, Boston.

23 DR. CASSCELLS: I am Ward Casscells. I am Chief
24 of Cardiology at the University of Texas in Houston and
25 Associate Director of Research at the Texas Heart Institute

1 in Houston.

2 DR. CURTIS: I am Anne Curtis, cardiac
3 electrophysiologist at the University of Florida.

4 DR. STUHMULLER: I am John Stuhlmuller. I am a
5 medical officer with FDA and executive secretary for the
6 panel.

7 DR. FERGUSON: Tom Ferguson, Washington University
8 in St. Louis.

9 DR. WITTES: Janet Wittes, a statistician with
10 Statistics Collaborative.

11 DR. PARISI: Alfred Parisi from Brown University,
12 Cardiology.

13 DR. FRIEDMAN: Larry Friedman, National Heart,
14 Lung, and Blood Institute.

15 DR. ALTMAN: Don Altman, Dental Director, Arizona
16 Department of Health, Consumer Rep.

17 DR. SPYKER: Dan Spyker, Medical Officer and
18 Deputy Director at DCRND.

19 DR. YIN: Lillian Yin, Acting Division Director
20 for Division of Cardiovascular, Respiratory, and
21 Neurological Devices. FDA.

22 DR. CURTIS: Thank you.

23 **Open Public Hearing**

24 The next order of business is the open public
25 hearing. As occurred at the meeting yesterday, the open

1 public hearing will be held in two portions. This initial
2 portion is for any member of the audience who has any
3 general concerns that they want to bring before the FDA.
4 There will be a separate section to the public hearing after
5 the discussion this morning related to the product that is
6 being talked about.

7 Is there anybody who would like to speak before
8 the panel now?

9 [No response.]

10 DR. CURTIS: If not, then, we will move directly
11 to the Premarket Approval Application P950015 from PLC
12 Medical Systems, Inc., the Heart Laser CO₂ Laser System.

13 We will start with the company presentation. As
14 each representative of the company steps to the microphone,
15 please identify yourself and what your financial interest is
16 in the company.

17 **Premarket Approval Application P950015**

18 **PLC Medical Systems, Inc.**

19 **The Heart Laser CO₂ Laser System**

20 **Company Presentation**

21 MR. DOW: Good morning. I am Bill Dow, the
22 President and CEO of PLC Medical Systems.

23 [Slide.]

24 As this slide depicts, I will open the
25 presentation with a brief introduction. I will be followed

1 by Dr. Steven Boyce, Director of Cardiac Surgical Research
2 at the Washington Hospital Medical Center, who will present
3 the characteristics and results of our one-year randomized
4 study of TMR with the Heart Laser.

5 Following Dr. Boyce will be Dr. Xavier Lefebvre,
6 who will present the clinical limitations to the study and
7 address those issues.

8 As you are no doubt aware, July 28th, the company
9 appeared before the panel. The panel at that time
10 recommended non-approval.

11 Following that meeting, in September, we received
12 a letter from the FDA outlining the 12 items that would
13 place the PMA in approvable form.

14 [Slide.]

15 This slide summarizes those 12 requests for
16 information. The one-year randomized study on TMR was
17 completed in September of last year. The data and
18 information from that study, along with the requested
19 information, was submitted to the FDA in December of 1997.
20 We further had the advantage of having the transcript and
21 videotapes from the previous panel meeting and to make sure
22 that we were addressing all the concerns and questions from
23 the last panel meeting and the information that was
24 submitted in December.

25 That information has been summarized in the panel

1 package that each one of you should have. The company
2 firmly believes that the information and data contained in
3 that packet supports the reasonable assurance and safety and
4 efficacy of the Heart Laser and its intended use.

5 In closing my comments, we would just like to
6 acknowledge our appreciation to the panel for putting
7 together the requirements in the September 11 letter in the
8 areas that would place us in an approvable form. We also
9 would like to acknowledge the help of the FDA in
10 understanding those requirements.

11 Dr. Steven Boyce will now present the results and
12 characteristics of the randomized study.

13 DR. BOYCE: Good morning. I am Steven Boyce,
14 heart surgeon here in Washington, D.C., at the Washington
15 Hospital Center, and Director of Cardiac Surgical Research
16 at that institution here in town.

17 [Slide.]

18 Our experience with the Heart Laser CO₂ system
19 dates back to 1995. Since that time, we have treated 72
20 patients to date with this system. This morning I would
21 like to take the opportunity to summarize the Phase III
22 randomized trial of TMR versus Medical Management.

23 [Slide.]

24 Our clinical experience with the Heart Laser goes
25 back to 1990. At that time, a pilot study at one site,

1 looking at 15 patients, all of whom had class 3 or 4 angina,
2 but were not candidates for coronary artery bypass surgery
3 or PTCA underwent treatment with the TMR laser as a
4 feasibility study to see whether this was a technically
5 possible study in the operating room.

6 Once this was found to be successful, we moved on
7 a Phase II study, which began in 1992. This was a much
8 larger study. It encompassed 201 patients, was non-
9 randomized, involved eight different sites throughout the
10 United States, but importantly, all the patients met the
11 same basic characteristics. They all had class 3 or 4
12 angina, yet they were not amenable to any other type of
13 medical therapy.

14 At that time, issues with safety were addressed by
15 looking by looking at morbidity and mortality issues, and
16 efficacy was examined by looking at angina and perfusion.

17 After successful completion of this trial, we then
18 moved on in 1995 to a Phase III randomized trial of 192
19 patients, which will be the topic of this morning's
20 discussion.

21 [Slide.]

22 This was a prospective, multi-center 1 to 1
23 randomized study of patients with class 3 to 4 angina
24 despite maximal medical therapy, that had no other surgical
25 or cardiologic options meaning they were not amenable to

1 bypass surgery or PTCA.

2 The purpose of the study was to look at the safety
3 and efficacy of TMR as a treatment modality for this very
4 difficult subgroup of individuals. The study was not
5 randomized since it would be impossible for the medical
6 personnel or the patient not to realize which arm they were
7 randomized into.

8 In terms of crossover, crossover was permitted
9 upon failure of medical management. This was defined as a
10 patient after enrollment into the study and placed in the
11 medical management arm that required rehospitalization in an
12 intensive care unit setting for a minimum of 48 hours with
13 treatment with both IV nitroglycerine and heparin.
14 Following this, they were allowed to cross over.

15 The ability to cross over was a very strong
16 determinant for patients to stay in the study and complete
17 the study if they were in the medical management arm,
18 however, every time a patient crossed over, we lost a
19 patient, so to speak, in the medical management arm to
20 follow long term at three, six, and 12 months.

21 The purpose of this study was to look at issues
22 regarding efficacy. We did that with perfusion SPECT data,
23 angina classification improvements, and quality of life
24 issues. We also looked at mortality and morbidity in terms
25 of the safety of this procedure.

1 The study was statistically set up so as to have a
2 power of significance of p equals 0.5 with an 80 percent
3 power. In establishing the statistical requirements, we
4 only needed a sample size of 12 patients per treatment
5 group. The original enrollment was for 100 patients, but
6 due to the number of patients that were crossing over, this
7 was increased to 200 patients.

8 [Slide.]

9 As mentioned, this was a multi-institutional trial
10 at 12 sites throughout the United States, basically from
11 coast to coast and north to south. Ninety-one patients were
12 originally placed in the TMR Group and 101 in the Medical
13 Management Group.

14 Today, in the audience, we have representatives
15 from the Brigham & Women's Hospital, Rush-Presbyterian, and
16 the Washington Hospital Center.

17 [Slide.]

18 In terms of follow-up accountability, if we define
19 this as the number of patients with follow-up information
20 divided by the number of patients that are eligible for
21 follow-up, we see across the board, in the TMR Group, the
22 Medical Management Group, and the Crossover Group, whether
23 it's 3, 6, or 12 months, all the numbers are relatively the
24 same, meaning anywhere from 90 percent to 97 percent, the
25 important point being that there was no difference in terms

1 of accountability between any of the three groups or any of
2 the follow-up periods of time.

3 [Slide.]

4 So, let's take a moment and look at the population
5 characteristics of the patients that entered the study at
6 time of enrollment. Ninety-one patients went in the TMR
7 Group, 101 in the Medical Management Group, and if you look
8 at demographics and cardiac status, there was no significant
9 difference here at all, and in fact there wasn't any
10 difference with any of these characteristics in terms of p-
11 value between the two groups, although a few points need to
12 be highlighted.

13 Nine out of 10 patients that came for this therapy
14 had already had at least one, if not two or three, bypass
15 procedures. Fifty percent had had a previous PTCA, 1 out of
16 3 had a previous hospitalization for congestive heart
17 failure, and 80 percent had sustained an acute myocardial
18 infarction. The risk factors are what we would anticipate.

19 Now, we used the Cleveland Clinic CABG Surgery
20 Risk Stratification Model to look at these patients and come
21 up with their scores for undergoing cardiac surgery, and we
22 see the average scores the same between the groups, 6.1 and
23 5.8, but I want you to remember the 6.1 because we will come
24 back to this when we look at the Crossover Group.

25 Since using the stratification model, any number

1 greater than 5 is considered high risk, approximately 60
2 percent of the patients were in the high risk group.

3 [Slide.]

4 In terms of TMR treatment, once patients are
5 enrolled, if they go into the TMR Group, they are brought to
6 the operating room, and after administration of a general
7 anesthetic, a small, left anterior thoracotomy is performed.
8 As mentioned, 9 out of 10 of these patients had had a
9 previous bypass operation, so once adhesions were taken
10 down, in that area of the myocardium that was found to be
11 ischemic on preoperative, that is, nuclear scanning at time
12 of enrollment, once that area was isolated, the articulated
13 arm of the laser machine was brought to the field, the laser
14 synchronized to the patient's electrocardiogram, looking at
15 the 91 patients in the TMR arm, 35 laser pulses were fired.
16 The purpose was to create a single, 1 millimeter channel
17 about every one square centimeter of ischemic myocardium. A
18 median of 30 channels were confirmed by transesophageal
19 echo, meaning that the laser penetrated from the outside of
20 the myocardium into the intraventricular cavity using a
21 laser pulse energy of 40 joules.

22 Postoperatively, the time in the intensive care
23 unit, the median was two days with a hospital median of
24 seven days. This compares quite favorably to a redo
25 population group.

1 [Slide.]

2 In terms of results, let's first look at
3 myocardial perfusion results.

4 [Slide.]

5 Each patient at time of enrollment, at 3, 6, and
6 12 months follow-up, underwent a thallium-201 SPECT
7 tomography study under both rest and dipyridamole stress
8 conditions. All of these studies were read at a blinded
9 core lab.

10 The blinded core lab developed a 24-segment model
11 for the left heart, the left heart comprising both a septum
12 in the left ventricular free wall. They accomplished this
13 by dividing the left heart into 3 slices, and each slice
14 into 8 segments to create a 24-segment model.

15 For each individual patient in the study, a paired
16 analysis was done between the follow-up at 3, 6, and 12
17 months and the enrollment nuclear scan. Following this, a
18 comparison was then made of the TMR Group compared to the
19 Medical Management Group.

20 [Slide.]

21 In terms of SPECT accountability, being a cardiac
22 surgeon I always feel a little uncomfortable when I get in
23 this arena, but nonetheless, this is a real world
24 environment, and roughly 80 percent of the SPECT studies
25 were done per protocol.

1 The important thing here is the group between the
2 TMR Group and the Medical Management Group, there was no
3 difference in these percentages in terms of the number done
4 per protocol or the number that were usable. The patients
5 with usable studies at the end of the day, so to speak, were
6 71 in the TMR Group and 61 in the Medical Management Group.

7 In this list, the usable studies per follow-up
8 period at baseline, 3, 6, and 12 months. Of note, if you
9 look at the Medical Management Group, between 6 months and
10 12 months, there is a pretty big drop-off here, and the
11 reason there is a big drop-off here is 20 of the 40 patients
12 at 6 months required readmission to the hospital for
13 unstable angina, were on intravenous heparin and
14 nitroglycerine, and ended up crossing over to TMR, leaving
15 just 15 in the Medical Management Group.

16 Fortunately, the study was statistically powered
17 in a way that we needed just 12 at the end of the day.

18 [Slide.]

19 Now, let's first look at fixed perfusion defects.
20 Certainly, this is something that we want to try to avoid
21 with any type of therapy, so if we start at baseline at
22 zero, and follow this out at 3, 6, and 12 months, we see
23 that there is a slight increase in both patients initially
24 randomized to TMR and those randomized to the Medical
25 Management Group. Both groups of patients had a slight

1 increase in the number of fixed defects, but it certainly
2 shows that there was not an increase out of proportion in
3 the TMR Group compared to the Medical Management Group.

4 [Slide.]

5 Now, if we look at reversible perfusion defects,
6 on the other hand, we see a dramatic change between the two
7 groups, so that there was not essentially any difference
8 between the number of fixed defects between the two groups,
9 but if we look at the number of reversible perfusion defects
10 in terms of change from baseline -- for the TMR Group and
11 throughout all these slides, the TMR Group is in yellow and
12 the Medical Management Group is in red -- we see that the
13 Medical Management Group over time actually had an increase
14 in the number of reversible perfusion defects, however, the
15 TMR Group had a decline, and this came with a large
16 significance in terms of p-value.

17 [Slide.]

18 Moving from the nuclear studies for a moment to
19 two other endpoints that from a clinician's standpoint are
20 equally important and certainly from a patient's standpoint,
21 that being angina pectoris classification and quality of
22 life issues.

23 [Slide.]

24 Well, certainly all patients had to be class 3 to
25 4 angina in order to enroll in the study, and this is at

1 baseline, 91 in TMR and 101 in Medical Management, all being
2 class 3 to 4.

3 If we follow these patients out at 3, 6, and 12
4 months, though, we see again a dramatic difference in the
5 anginal classifications between these two groups. Three out
6 of 4 individuals that underwent TMR treatment at 3, 6, and
7 12 months no longer had class 3 or 4 angina.

8 However, if we look at the people continued in
9 Medical Management at 3 and 6 months, we still 90 percent of
10 these individuals suffering from class 3 or 4 angina. In
11 each case, there is a significant p-value between the
12 Medical Management Group, in red, and the TMR Group, in
13 yellow.

14 Now, at 6 and 12 months, there is a decline in the
15 percentage of patients in the Medical Management Group
16 suffering from class 3 to 4 angina. Why? Once again,
17 because of crossover. There was a significant number of
18 patients that were allowed to cross over after 6 months, an
19 those patients that had the most unstable clinical syndromes
20 tended to cross over, leaving the "best" subgroup in the
21 Medical Management Group.

22 [Slide.]

23 Now, as clinicians, a change of one anginal class
24 up and down really doesn't mean that much. It certainly
25 doesn't mean that much to me as a clinician, because a

1 patient can come back at a different time period, week to
2 week, month to month, and you can look at them and give them
3 a different classification.

4 So, really to have a clinical impact, we need to
5 see at least two anginal classification changes in order to
6 make a clinical impact from both the perspective of the
7 physician and the perspective of the patient.

8 So, if we define therapy success as having a
9 decrease of at two anginal classifications, and look at this
10 group again, we see that roughly two-thirds of patients that
11 underwent TMR dropped at least two anginal classifications
12 at 3, 6, and 12 months with a persistence across the board,
13 whereas, this was certainly not in the case in the Medical
14 Management Group.

15 Now, if we take this to an extreme and from a
16 statistical standpoint look at what we call worst-worst case
17 scenario and count every single patient lost to follow-up as
18 a failure in the TMR Group and a success in the Medical
19 Management Group, and consider every additional procedure
20 and every mortality as a failure in the TMR Group, we end up
21 with this rather complicated slide.

22 [Slide.]

23 What this is going to do is look at the TMR Group
24 in the yellow, the Medical Management Group in the red, and
25 the Medical Management-Intent to Treat -- very important --

1 the Intent to Treat, these are the people that at day one.
2 enrollment were randomized to go into medicine.

3 If we follow these patients out at 3, 6, and 12
4 months, we find some interesting things. Once again, we see
5 that all missing follow-up here is counted as a failure for
6 TMR and a success for Medical Management at the same time
7 and all deaths and additional procedures are counted as
8 failures.

9 If we see that, we see that about 50 percent of
10 patients that had TMR in this worst case analysis, which is
11 a statistical analysis, we see that certainly this was not
12 the case in the Medical Management Group, 12, 7, and 5, but
13 the Intent to Treat Group, in green here, about 1 out of 4
14 up to 1 out of 3 methods criteria, because a number of these
15 in the Medical Management-Intent to Treat Group, in fact, 60
16 of the 101 crossed over to TMR.

17 Despite this, however, if we look at p-value
18 differences between the TMR Group and the Medical
19 Management-Intent to Treat Group, across the board, there is
20 a big significance between the two groups in terms of
21 improvement.

22 [Slide.]

23 Moving from anginal classification to quality of
24 life, there are at least two validated longitudinal studies
25 that look at quality of life, one being SF-36 and one being

1 the Seattle Anginal Questionnaire.

2 [Slide.]

3 If we first look at this SF-36, which is a
4 validated self-administered questionnaire, and we look at
5 baseline for both the standardized physical component and
6 the standardized mental component, we see that there is very
7 little change in the patients that were randomized to the
8 Medical Management arm at 3, 6, and 12 months, however,
9 there is a statistical change in their quality of life in
10 both the standardized physical component, as well as the
11 mental component, in those patients that were treated with
12 TMR.

13 [Slide.]

14 If we now look at the Seattle Anginal
15 Questionnaire, which is quite detailed and looks at things
16 like exertional capacity, anginal stability, anginal
17 frequency, treatment satisfaction, and disease perception,
18 and we look at this over a course of time, at 3, 6, and 12
19 months for patients randomized to the yellow bar, the TMR,
20 or red, Medical Management, we again see that there is very
21 little change in the patients that were randomized to
22 medicine, meaning they did not have an improvement in any of
23 these five characteristics, whereas, there was a statistical
24 improvement with the p-value less than 0.5 at 3, 6, and 12
25 months for all five of these criteria.

1 [Slide.]

2 Now, we have seen that there is some improvement
3 in thalliums, there is improvement in angina, there is some
4 improvement in quality of life, well, what is the cost up-
5 front? In other words, if you take a patient and you offer
6 him this therapy, what is the risk to him, what is the
7 morbidity and the mortality associated with this procedure?
8 A very important question.

9 [Slide.]

10 Well, there was a Data Safety Monitoring Board, of
11 course, in existence from the beginning of the study, and it
12 was run or chaired by Michael Gibson, who is an
13 interventional cardiology and in the room today, as well as
14 cardiac pathologist and a cardiac surgeon.

15 [Slide.]

16 They listed eight different complications as
17 primary and serious during the course of the events, and if
18 we look at these eight complications one at a time, we see
19 some interesting things.

20 First of all, perioperative, just to redefine, we
21 are looking at the period of time from the time of the
22 surgery to the first 30 days. Late is month 1 through month
23 12. We see the incidence of unstable angina in the 91
24 patients in the TMR Group 2 percent, in the control group,
25 close to 70 percent.

1 Acute myocardial infarctions, 8 percent in the TMR
2 Group, 12 percent in the control group. Congestive heart
3 failure, 11 percent in the TMR Group, 10 percent in the
4 control group.

5 Pulmonary complications are pretty much what we
6 would expect to see from a surgeon's perspective for someone
7 who meets these demographic characteristics, comes to the
8 operating room, has a general anesthetic and a small left
9 anterior thoracotomy.

10 Of note, there was only a 2 percent of atrial
11 arrhythmias, whereas, we would expect at least a 10-fold
12 greater difference from that for standard coronary artery
13 bypass surgery. There was a 10 percent incidence of
14 ventricular arrhythmias, with the vast majority of these
15 occurring in the perioperative period.

16 Of the patients that experienced ventricular
17 arrhythmias, if you follow their courses down the road,
18 there were two mortalities. Neither mortality, however, was
19 associated with their ventricular arrhythmia. One patient
20 had a CVA, and there was one laser hit-induced mitral
21 regurg.

22 Of importance, though 68 percent or 62 of the 91
23 patients treated with TMR were discharged from the hospital,
24 a median hospital stay of 7 days, median time in the ICU, 2
25 days, without any complications, 68 percent.

1 [Slide.]

2 If we look at a couple of these in particular, the
3 freedom from acute myocardial infarction, starting at
4 baseline and following these patients out at 3, 6, 9, and 12
5 months, we see about a 89 percent freedom from MI or 11
6 percent myocardial infarction rate in the patients treated
7 with TMR, and if we look at the Medical Management without
8 Crossover Group, it's about 78 percent.

9 There is no statistical significance between the
10 two groups, but certainly those patients treated with TMR
11 did not have a higher incidence of an acute MI.

12 [Slide.]

13 Now, if we look at the freedom from unstable
14 angina, we see a dramatic difference between the two groups.
15 Only 11 percent of patients treated with TMR required
16 rehospitalization for unstable angina followed out to 12
17 months. However, 3 out of 4 patients in the Medical
18 Management Group had this event and required
19 hospitalization. Obviously, there is a significant p-value
20 here.

21 [Slide.]

22 Now, in terms of mortality, if we look at this in
23 terms of a 12-month mortality, and we are going to look at
24 12-month mortality, and we are going to look at 30-day
25 mortality, and come up with some interesting findings here.

1 [Slide.]

2 We see that if we look at the TMR Group and the
3 Medical Management Group without Crossover, essentially,
4 once again, there is no difference in one-year mortality,
5 and, in fact, if you do a multivariate logistic regression
6 analysis of all the variables, there is only one variable
7 that drops out, and that is a reduced ejection fraction at
8 the time of study enrollment. That is the only variable
9 that drops out for mortality out one year. Certainly, TMR
10 is not associated with an increased mortality.

11 [Slide.]

12 Now, though, if we look at the mortality in TMR,
13 and we say when does this mortality occur, we find something
14 very interesting, and that is, it seems to occur in this
15 perioperative period. Now, how we sort this out?

16 [Slide.]

17 Let's look at the TMR Group versus the Crossover
18 Group. Sixty patients crossed over at some point after
19 initially being placed in the Medical Management arm, and 91
20 patients were initially placed in the TMR Group.

21 We see the 30-day mortality, this perioperative
22 mortality, 3 percent in patients initially randomized to
23 TMR, 15 percent in patients that crossed over. Once we get
24 past 30 days, a look at month 1 through month 12, we see
25 that the two curves pretty much parallel each other, but

1 what is causing this increased mortality in the Crossover
2 Group?

3 [Slide.]

4 Let's look at the population characteristics
5 between the 91 in the TMR and the 60 in the Crossover. We
6 have looked at these characteristics before, but if we
7 concentrate those items highlighted in green, we see that
8 only one issue drops out, and that is the incidence of
9 unstable angina, only 8 percent of the patients undergoing
10 TMR as an initial treatment option versus 70 percent in the
11 Crossover arm.

12 If we look down at the Cleveland Clinic Risk
13 Stratification Model, we see that there is now a 50 percent
14 increase in the score, from 6 to 9, when we compare the TMR
15 Group with the Crossover Group, so now we are up to almost a
16 90 percent, what we would call a high risk group for
17 patients in the Crossover Group.

18 Well, if unstable angina is the only major factor
19 that drops out in the multivariate logistic regression
20 analysis for perioperative mortality, let's look at this
21 further.

22 [Slide.]

23 There certainly seems to be an important issue
24 between the time that the patient requires hospitalization
25 and placement on intravenous anti-anginal medications,

1 heparin and nitroglycerine, and the time that the TMR is
2 undertaken, and this holds through for TMR's primary cross-
3 over and TMR crossover.

4 So, if we see if the patient has been hospitalized
5 on intravenous medication secondary to unstable angina, and
6 receives TMR within the first seven days, there is 27
7 percent mortality rate. If the TMR is done after the first
8 week, but before two weeks have passed, it drops to 16
9 percent. But if we can get the individual, stabilize that
10 patient medically, and get them out two weeks before the TMR
11 is done, the mortality drops down to 1 percent.

12 So, certainly there is a very significant
13 association between the time of the unstable anginal event
14 and the time of the TMR surgery.

15 [Slide.]

16 Now, moving from the perioperative mortality
17 issues, let's look at things long term. Certainly we have
18 data at 12 months, and we now have some data at 24 months.
19 To get data past 24 months, we need to go back to the Phase
20 II study, which I mentioned at the beginning of the
21 presentation. That was the non-randomized 201 patients that
22 went into the study.

23 Interesting, if we look at Phase II and Phase III,
24 the two curves are almost superimposed upon each other in
25 terms of the patient's mortality at one year and two years.

1 If you remember back to the mortality of the patients in the
2 Medical Management Group at one year, the survival was 79
3 percent.

4 So, if we follow this out past one year to two
5 years, certainly, it seems to plateau, because here we see
6 about an 81 percent survival rate or a 19 percent mortality
7 in those patients treated with TMR out to 2 months, 24
8 months, or 2 years, which compares very favorably with the
9 group treated with Medical Management in Phase III followed
10 out to 12 months.

11 [Slide.]

12 So, what can we conclude from all this data being
13 presented today? Certainly, in this very difficult subset
14 of patients, who have class 3 to 4 angina, despite maximum
15 medications on oral agents, that have no other treatment
16 that we can offer today in terms of bypass surgery or
17 percutaneous cardiologic interventions, if we compare
18 treating this with TMR to continuing to treat them with
19 Medical Management, this study shows that TMR is highly
20 efficacious in improving angina classification, quality of
21 life, and myocardial ischemia with an acceptable safety
22 profile.

23 There is a significant reduction in the incidence
24 of unstable angina, and there is not an increased risk of
25 acute myocardial infarction, congestive heart failure, or

1 increased one-year mortality.

2 Thank you.

3 DR. LEFEBVRE: I am Xavier Lefebvre from PLC
4 Medical Systems. I am the Director of Clinical Affairs, and
5 I will conclude this presentation by talking about the study
6 limitations.

7 [Slide.]

8 A few limitations were identified in the final
9 package, and I would like to take a few minutes to address
10 them.

11 There is nine limitations were independently
12 examined to determine their impact on the study results.
13 Following the completion of the review process, it was
14 determined that these limitations, these issues, did not
15 significantly impact the study. Most of these issues are
16 addressed in the panel package, and in the interest of time,
17 I will not discuss each of them here today.

18 I do want to make a few comments about three of
19 these issues which may not be fully covered in the package,
20 and I will be very happy to answer any questions you may
21 have regarding the other issues in the question and
22 responses that will follow the presentations.

23 [Slide.]

24 The first issue which I would like to discuss
25 involves the multivariate analysis methodology. As part of

1 the December '97 and February '98 submissions, we conducted
2 some multivariate logistic regression analysis to assess the
3 presence of predictors of outcome, such as mortality or
4 treatment success.

5 To answer these concerns, we repeated each and
6 every of these multivariate analyses using the suggest
7 stepwise analysis process. The result of the new analysis
8 matched the results of the old analysis.

9 The second issue that I would like to discuss
10 today involved the availability of SPECT data. As you may
11 recall, SPECT data availability was around 40 percent at the
12 time of the July '97 advisory panel.

13 Since then, we have completed the study and SPECT
14 usability rate is now 70 percent. The question that must be
15 answered is whether or not those 70 percent fully describe
16 the study patient population.

17 [Slide.]

18 To answer this question, demographics, medical
19 history, risk factors, and clinical status at baseline were
20 used to determine if the SPECT population was an accurate
21 representation of the entire study population.

22 We did this analysis in two steps. First, we
23 looked at the patients who had SPECT versus the patients who
24 did not have SPECT, and the research indicate that except
25 for the history of cerebrovascular accidents, the baseline

1 characteristics were not statistically different between the
2 132 patients with SPECT data and the 60 patients without
3 SPECT data.

4 Since this study is a randomized study, it was not
5 blinded, but it was a randomized study, it is important to
6 look at the distribution of the TMR patients and of the
7 Medical Management patients within the SPECT population.
8 So, we repeated the same analysis, and among the 132
9 patients with SPECT data, baseline characteristics were not
10 statistically different between the 71 TMR patients and the
11 61 Medical Management patients.

12 The SPECT population therefore appears to be an
13 accurate representation of the entire study population.

14 [Slide.]

15 The last issue which I would like to discuss here
16 today involves the crossover, and more specifically, the
17 concern raised pertaining to the attrition observed in the
18 Medical Management Group due to the crossover process.

19 As Dr. Boyce has already shown you, the number of
20 follow-up information available at 12 months was sufficient
21 to demonstrate or to determine the angina and perfusion
22 benefits of TMR as compared to Medical Management.

23 Again, the question that needs to be answered is
24 whether or not these patients, despite the attrition due to
25 crossover, whether or not these patients with 12-month

1 follow-up information, these patients fully describe the
2 entire study population.

3 [Slide.]

4 To answer this question, we again looked at the
5 demographics, medical history, risk factors, and clinical
6 status of the patients. We did the analysis for both the
7 SPECT population subgroup and the angina subgroup, and we
8 found that the baseline characteristics were not
9 statistically different between the TMR patients with 12-
10 month follow-up and the TMR patients without 12-month
11 follow-up, and maybe even more importantly, we found that
12 the baseline characteristics were not statistically
13 different between the Medical Management patients with 12-
14 month follow-up data and the Medical Management Group
15 patients without 12-month follow-up data.

16 So, this analysis indicated that despite the
17 attrition due to crossover, the patients with 12-month data
18 were an accurate representation of the entire study
19 population.

20 [Slide.]

21 This concludes the presentation. We have
22 thoroughly addressed the points and the issues discussed by
23 the July '97 advisory panel. We have completed the
24 randomized Phase III study. We believe that we have
25 demonstrated reasonable assurance of the safety and efficacy

1 of TMR using the Heart Laser, and no identified limitation
2 undermines these conclusions, and we would be happy to
3 discuss anything at the upcoming presentation.

4 Thank you.

5 DR. CURTIS: We will now have the FDA
6 presentation. Judy Danielson is the lead reviewer.

7 **FDA Presentation**

8 MS. DANIELSON: Good morning. My name is Judy
9 Danielson. I am the lead reviewer for the PMA application
10 under consideration today.

11 [Slide.]

12 I would like to begin by acknowledging the other
13 FDA staff who participated in the review of this
14 application, namely, Kim Peters, Charles Ho, Richard Felton,
15 and Think Nguyn, who conducted the reviews of the
16 engineering data. Paul Chandeyssan and Steve Kurtzman
17 reviewed the clinical data, and John Dawson, who reviewed
18 the statistical analysis conducted to support this
19 application. I would also like to thank Tara Ryan and Dan
20 Spyker who assisted in putting together the panel packs and
21 provided support in preparing for this meeting.

22 [Slide.]

23 The sponsor has provided a comprehensive summary
24 of the data in their just concluded presentation to the
25 panel. FDA's presentation will focus on three items:

1 first, PLC Medical's response to the panel recommendations
2 from July 1997 regarding the information needed to consider
3 this PMA application approvable. second, the conclusions of
4 the FDA review team; and lastly, questions which the FDA
5 would like the panel to address following discussion of the
6 application.

7 [Slide.]

8 On July 28th of last year, the Circulatory System
9 Devices Panel recommended non-approval for the PLC Heart
10 Laser System. At the same time, the panel outlined its
11 concerns, as well as the type of information needed to put
12 the application in an approvable state.

13 What I would like to do now is to go through these
14 concerns and highlight for the panel the sponsor's response
15 to each of them.

16 First, the company was asked to complete patient
17 follow-up after 12 months and also provide any additional 3-
18 and 6-month data that was not previously reported. PLC has
19 completed patient follow-up out to 12 months and provided
20 additional data at the 3- and 6-month follow-up interval.

21 [Slide.]

22 We asked the sponsor to conduct an independent
23 standardized assessment of angina class on all surviving
24 patients enrolled in Phase III.

25 [Slide.]

1 In response, an angina assessment survey was
2 conducted by an independent research organization on 108 or
3 83 percent of the eligible patients. This assessment was
4 conducted by a trained interviewer using the same script for
5 each interview. The patient was instructed not to identify
6 the treatment they were assigned. It should be noted that
7 the survey followed the clinical site assessment by an
8 average of five months.

9 [Slide.]

10 The result of this independent assessment showed
11 that 80 percent of the independent survey scores were within
12 a one angina class agreement with the clinical site
13 assessments, and the agreement between the independent
14 survey and the clinical site assessments were similar among
15 all study sites and between all treatment groups.

16 [Slide.]

17 At the panel meeting last summer, there was much
18 discussion regarding the mortality data and the difficulty
19 in assessing the true death rate given the high rate of
20 crossover in the study. The sponsor was asked to further
21 evaluate this data to determine if there was a correlation
22 between the death and other factors, such as medical history
23 or risk factors.

24 [Slide.]

25 Unstable angina was found to be a predictor of TMR

1 peri-op mortality. Overall, perioperative mortality for the
2 TMR Group was 3 percent, and 15 percent for the Crossover
3 Group, however, when these patients are analyzed as to the
4 time from their last unstable angina event prior to TMR, the
5 mortality rates become similar. Patients with an unstable
6 angina event in the two-week period prior to TMR had a
7 mortality rate of 29 percent in the TMR Group and a 21
8 percent mortality rate in the Crossover Group.

9 When the unstable angina event occurred more than
10 14 days prior to TMR, the mortality dropped down to 1
11 percent in the TMR Group and zero percent in the Crossover
12 Group.

13 [Slide.]

14 Looking at long-term mortality, which excludes the
15 30-day perioperative period, mortality rates between the two
16 groups were also similar, 11 percent in the TMR group, 10
17 percent in the Crossover Group. Compromised ejection
18 fraction was found to be a predictor of overall TMR
19 mortality.

20 [Slide.]

21 The adverse event data reviewed last summer showed
22 a higher rate of life-threatening arrhythmia and congestive
23 heart failure in the TMR Group as compared to the control
24 group. We asked the sponsor to provide a line listing for
25 each patient experiencing these events and further analyze

1 the data to determine if a correlation exists between their
2 occurrence and the patient's medical history, risk factors,
3 and ejection fraction.

4 In response to concerns voiced by the panel, we
5 also asked the sponsor to further analyze the data to see if
6 TMR increased the risk of death following a myocardial
7 infarction.

8 [Slide.]

9 In response, the company provided the requested
10 line listing and conducted a further analysis of this data.
11 On this slide, the second column refers to patients who
12 received only medical therapy throughout the study.

13 Based on the Kaplan-Meier analysis, there was a 16
14 percent incidence of congestive heart failure in the TMR
15 Group and a 23 percent incidence in patients receiving only
16 medical therapy.

17 Predictors of congestive heart failure were a
18 history of congestive heart failure at baseline and a
19 compromised ejection fraction at baseline. The Kaplan-Meier
20 analysis estimated an 11 percent incidence of acute
21 myocardial infarction in the TMR Group and a 22 incidence of
22 acute myocardial infarction in patients receiving on medical
23 therapy. Acute myocardial infarction was a predictor or
24 mortality for both the TMR and the Medical Management
25 patients.

1 [Slide.]

2 TMR surgery was associated with a 10 percent
3 incident of life-threatening arrhythmias. All but one of
4 these arrhythmias occurred during the perioperative period.
5 Two perioperative deaths were associated with a life-
6 threatening arrhythmia. Treatment assignment and age were
7 found to be predictors of life-threatening arrhythmia.

8 [Slide.]

9 In response to concerns voiced by the panel, we
10 asked the sponsor to further analyze the data to see if the
11 thoracotomy itself may have led to lifestyle changes which
12 could be a factor in the TMR patients angina class and
13 quality of life improvement.

14 The kinds of lifestyle changes the panel mentioned
15 included weight loss, cholesterol lowering, cessation of
16 cigarette smoking, and enrollment in a cardiac rehab
17 program.

18 Retrospective data was gathered on lifestyle
19 changes of the TMR-treated patients since the protocol did
20 not specifically require that this information be tracked.
21 Following the TMR surgery, despite a small, transient
22 increase at three months in cardiac rehab, no significant
23 changes were observed in the patient weight, cholesterol
24 level, smoking habits, or participation in the cardiac rehab
25 program between pre-TMR and post-TMR lifestyle.

1 [Slide.]

2 In the PMA data reviewed last summer, the
3 demographic, medical history, and risk factors, the patients
4 with analyzable SPECT data were compared to the patients
5 with unanalyzable data.

6 After the panel meeting, the sponsor was asked to
7 separate the patients with and without analyzable SPECT data
8 into their respective randomized treatment groups, and
9 perform a similar analysis.

10 This analysis showed that baseline characteristics
11 do not appear significantly different between the 71 TMR
12 patients with SPECT data and the 61 Medical Management
13 patients with SPECT data.

14 [Slide.]

15 We also asked the sponsor to perform a worst case
16 analysis on the angina data, that is, assume all patients
17 who died underwent an additional intervention or who are
18 missing an angina assessment at a particular follow-up
19 interval be considered a treatment failure.

20 [Slide.]

21 The worst case analysis was provided by the Intent
22 to Treat Group. In this analysis, all deaths, additional
23 interventions, which did not include crossover, and
24 withdrawals were assigned to angina class 4. Crossovers
25 were left in the pre-crossover angina assessment.

1 Treatment success on this slide refers to the
2 require two-class improvement in angina. Within the groups,
3 treatment success was similar for all three follow-up
4 periods. The TMR Group had a 57 percent success rate at
5 three months, which decreased to 50 percent and 48 percent
6 at 6 and 12 months respectively.

7 For the Medical Management-Intent to Treat Group,
8 the success rate was 15 percent at 3 months, and increased
9 to 18 percent at the 6- and 12-month follow-up.

10 [Slide.]

11 To further evaluate the clinical outcome of the
12 patients undergoing the TMR procedure, the sponsor was asked
13 to provide the results of any exercise testing that was
14 performed on patients enrolled in Phase I, Phase II, or
15 Phase III of the study.

16 Although not required by the study protocol due to
17 its potential subjectivity, some Phase II sites conducted
18 treadmill stress exercise tests on TMR patients. The most
19 frequently used protocol was the Bruce protocol, which is
20 represented in this graph.

21 The number of patients varied depending on the
22 follow-up interval. Data was available on 45 patients at
23 baseline and 41 patients at the 12-month follow-up, and
24 there was data on another 8 patients at 24 months post-TMR.

25 An average of 327 seconds at baseline rose to 402

1 seconds at 3 months, and in the patients tested, this was
2 maintained out to 24 months. This increase was significant
3 at all follow-up periods.

4 [Slide.]

5 At last summer's meeting, the accuracy of the
6 SPECT thallium perfusion data was discussed. The sponsor
7 was asked to clarify if the equipment used to obtain the
8 perfusion data was subjected to any quality control
9 procedures to verify the accuracy of the measurements.

10 The sponsor asked all investigational sites to
11 submit copies of their quality control programs, what
12 specific camera was used in obtaining perfusion study test
13 results.

14 A review of the quality control programs
15 demonstrated that the nuclear medicine departments at all
16 sites had regularly scheduled quality control procedures in
17 place.

18 [Slide.]

19 The sponsor was also asked to provide any
20 available long-term data, and by "long-term data," I am
21 referring to follow-up past one year. Although not
22 specifically required by the study protocol, the sponsor
23 went back and retrospectively collected all available data.
24 Long-term survival estimates were calculated using a Kaplan-
25 Meier estimator to correct for missing follow-up and

1 dropouts.

2 This graph represents an analysis of 245 of the
3 306 eligible patients or 80 percent of the patients from all
4 three phases of the study. The upper survival curve
5 represents the 14 patients in Phase I feasibility study,
6 which had an 85 percent survival out to five years.

7 Transposed on the lower curves are the survival
8 curves of Phase II, Phase III, as well as the combined
9 survival curve of all three phases. The combined survival
10 curve of all three phases was 73 percent at three years.
11 Phase III survival of patients receiving medical therapy
12 alone was estimated at 79 percent for one year.

13 [Slide.]

14 Since the study protocol did not require follow-up
15 past 12 months, long-term angina classification is not
16 available on many patients. Of the sites that did record
17 this data, it was usually done on a yearly basis, however,
18 there was data on 70 patients, or 66 percent of 106 eligible
19 Phase II patients.

20 [Slide.]

21 This graph represents the angina classification of
22 those patients from baseline out to an average follow-up of
23 34 months. At baseline, the average angina classification
24 was 3.8. Twelve months post-TMR, the average angina
25 classification was 1.4. As you can see, there is only

1 slight increase at 34 months, with an average angina class
2 of 1.5.

3 [Slide.]

4 What I would like to do next is outline the
5 conclusions from the review team regarding this PMA
6 application. The review of the reliability and shipping
7 test data is ongoing. The FDA engineers continue to work
8 with the sponsor to ensure closure in this area.

9 TMR using the Heart Laser has been shown to result
10 in a clinically and statistically significant improvement in
11 angina in patients with ischemic coronary artery disease who
12 are not candidates for conventional revascularization using
13 CABG surgery or PTCA.

14 The greater angina treatment success in the
15 patients randomized to TMR was confirmed by an independent
16 assessment.

17 [Slide.]

18 TMR patients who underwent treadmill testing
19 experienced significant increases in exercise time during
20 follow-up. There was no significant difference in overall
21 mortality and morbidity among the Phase II TMR and Phase III
22 TMR and Medical Management patients.

23 A higher incidence of life-threatening arrhythmias
24 in the Phase III TMR patients as compared to the Phase III
25 Medical Management patients can be reasonably attributed to

1 the increased risk of complications following major cardiac
2 surgery.

3 [Slide.]

4 The results of the thallium myocardial perfusion
5 imaging studies in both Phase II and Phase III are
6 consistent with improvement in myocardial perfusion in TMR-
7 treated patients. The results are in contrast to the
8 control patient studies which suggest no change or slight
9 worsening of myocardial perfusion. There is no convincing
10 evidence that the relief of angina by TMR is due to
11 infarction of the myocardium.

12 [Slide.]

13 Angina relief appears to persist over time, making
14 it less likely to be the result of placebo effect.
15 Mortality of TMR patients did not appreciably increase after
16 three years. The mechanism of TMR is uncertain and actively
17 debated. This uncertainty of mechanism does not preclude a
18 determination of safety and effectiveness.

19 [Slide.]

20 The FDA review team recognized there is
21 limitations of the clinical study that need to be considered
22 when evaluating the data provided. One unavoidable
23 limitation of the clinical investigation is the fact that
24 the study design do not permit treatment masking, thus, the
25 investigation cannot definitively rule out the possibility

1 that TMR works partly by the placebo effect.

2 A second limitation of the study is the high
3 percentage of crossovers from Medical Management to TMR in
4 the Phase III study. This naturally confounds the study
5 analysis. Another limitation is the fact that Phase III
6 thallium perfusion data was only available on 69 percent of
7 the Phase III patients.

8 One could argue that the patients who underwent
9 additional cardiac interventional procedures after study
10 enrollment should have been excluded since the protocol
11 indicated that patients should not be candidates for other
12 treatment methods, such as CABG or PTCA, however, the
13 sponsor did censor these patients from the analysis after
14 the additional interventions.

15 [Slide.]

16 Additional study limitations include subjectivity
17 of angina classification, lack of predetermined definitions
18 of adverse events, the method of scoring the perfusion
19 defects was not previously validated in a clinical study, a
20 lack of strong correlation between angina and perfusion
21 data, and finally, the multivariate statistical analysis had
22 methodological and sample size limitation.

23 [Slide.]

24 In the last part of this presentation, I will
25 outline the questions that FDA would like the panel to

1 address.

2 [Slide.]

3 First, is the clinical data presented adequate for
4 evaluation of safety and effectiveness?

5 [Slide.]

6 The following questions relate to the labeling of
7 the Laser System.

8 Do the indications for use in the labeling
9 adequately define the patient population that was studied?

10 [Slide.]

11 Question 3. Which, if any, of the alternatives in
12 bracketed phrases should be included in the indications for
13 use?

14 [Slide.]

15 Question 4. Is the proposed contraindication
16 section appropriate? Are any other contraindications for
17 the use of this device?

18 [Slide.]

19 Does the outline of the possible mechanisms of
20 action listed below and in Section 11.2 of the labeling
21 adequately summarize the current state of knowledge of TMR?

22 [Slide.]

23 Phase II perioperative mortality related to the
24 device or procedure was 11 percent in the early part of the
25 study and 4 percent in the latter part of the study. This 7

1 percent difference may be the result of a learning curve.
2 Is the proposed labeling section which describes the user
3 training and experience adequate? If not how should it be
4 modified?

5 [Slide.]

6 Question 7. Should transesophageal echo to verify
7 successful creation of channels be recommended for the
8 clinical use of TMR?

9 [Slide.]

10 Does the warnings and precautions section
11 adequately describe the higher morbidity and mortality in
12 the crossover patients?

13 [Slide.]

14 Are there any other suggestions for the labeling?

15 [Slide.]

16 In addition, FDA has two questions regarding
17 patient follow-up. What type of long-term follow-up, in
18 addition to CCS and mortality data, would be appropriate for
19 the TMR-treated patients? How long should they be followed?

20 [Slide.]

21 Are there any other issues of safety or
22 effectiveness not adequately covered in the labeling which
23 need to be addressed in further investigations before or
24 after device approval?

25 [Slide.]

1 Time permitting, FDA would also like the panel to
2 comment on a few questions regarding appropriate trial
3 design for TMR studies. We will wait until your discussion
4 of this PMA is complete before posing these questions.

5 This concludes FDA's presentation. Thank you for
6 your attention.

7 At this time, does the panel have any questions
8 related to our presentation?

9 **Panel Discussion**

10 DR. CURTIS: Why don't we go ahead and move on to
11 the panel discussion.

12 Dr. Califf, why don't you introduce yourself and
13 lead things off.

14 DR. CALIFF: I am Rob Califf from Duke University.
15 Do you want to go one question at a time or do you
16 want to have a general discussion?

17 DR. CURTIS: I guess it depends. Just go ahead.
18 If it becomes really prolonged, then, we will give some
19 other people a chance to go.

20 DR. CALIFF: Let me ask just a couple of questions
21 maybe about the presentation. The thing that still troubles
22 me the most is the follow-up. There has been a heroic
23 effort here I think to salvage a lot of methodologic
24 problems, but I am still trying to understand how it is that
25 you can't find 17 percent of patients who underwent the

1 surgical procedure and are living in communities close to
2 the places where the procedures were done. It just seems
3 like an extraordinarily high rate of inability to find
4 patients. I mean we see studies of 10,000 patients now
5 where there are fewer than 17 who can't be contacted to find
6 out how they are feeling.

7 What happened? Do you have any idea why these
8 people are so hard to find?

9 DR. LEFEBVRE: First of all, are you say 17?

10 DR. CALIFF: Seventeen percent. You said you got
11 angina status now in 83 percent of the eligible patients.
12 That means there are 17 percent of the eligible patients in
13 whom you don't even have the angina status even at this
14 point.

15 DR. LEFEBVRE: We followed 92 percent of the
16 potential follow-up studies, however, some of the patients
17 were followed up, but an angina assessment was not feasible
18 because, for example, the follow-up visit may have been done
19 by an outside cardiologist. In those instances, we decided
20 not to use the angina assessment because it would not have
21 been done by the investigational site, and could have
22 therefore introduced some bias or some additional noise in
23 the data. That is the reason, but we followed 92 percent of
24 the patients.

25 DR. CALIFF: The number I heard several times was

1 83 percent. Maybe this is the independent assessment?

2 DR. LEFEBVRE: Correct. This is the independent.
3 It is going back after the fact, which respectively we got
4 the list of all the patients who were eligible for an
5 independent assessment. That is all the patients who were
6 alive and who had not undergone an additional
7 vascularization. However, this was after the fact, so we
8 had to try to get those patients, to get back in touch with
9 these patients, and that is why we are only able to contact
10 -- when I say "we" -- it was the independent contractor that
11 was contracted for the study, that was only able to contact
12 83 percent of the patients.

13 DR. CALIFF: Do you think that that is adequate in
14 typical follow-up studies to only -- particularly small
15 studies like this -- to only find 83 percent?

16 DR. LEFEBVRE: The purpose of the independent
17 angina study was to validate the angina results conducted by
18 the sites. Therefore, this 83 percent should be adequate to
19 validate. Now, you should go back to the site assessments
20 for the angina study, and the number for that is 90 percent.
21 We have 90 percent of the angina results.

22 DR. LAVIN: I am Phil Lavin, Boston Biostatistics.
23 We are a paid consultant. Our group did the independent
24 assessment, and we conducted the survey over a two-week span
25 in the end of August and early September, so I presume we

1 were competing with the Labor Day holiday, but we did make
2 every effort to reach every possible patient on that list of
3 130, and 108 out of that 130 is pretty good for the end of
4 August and early September.

5 DR. CALIFF: But is it pretty good for something
6 so important? I mean would it be reasonable to conduct a
7 little bit longer duration of trying to find people?

8 DR. LAVIN: We did make every attempt to reach all
9 of the subjects.

10 DR. CALIFF: The only other question I have about
11 the adequacy of the data was just again a question about the
12 philosophy of how you look at data. You did the analysis of
13 the patients who did and didn't have the SPECT.

14 Do you think that the failure to find a
15 statistically significant difference between baseline
16 characteristics in such a small sample size is really
17 evidence that the groups are the same?

18 DR. LAVIN: We did look very closely, not only at
19 the baseline characteristics to see even any evidence of a
20 drift in favor of one group or another, but we also looked
21 at the subgroups who had angina outcomes, looking to see
22 whether or not there were biases there, as well, and I feel
23 very confident that there is no conscious bias going on of
24 any kind that is, at this point, favoring one group over the
25 other. The groups appear to be quite comparable from our

1 statistical perspective.

2 DR. CALIFF: Could we actually see the SPECT
3 baseline characteristics, and those who did and did not have
4 SPECT? Do you have a slide? You said they weren't
5 significantly different.

6 DR. LEFEBVRE: Yes, we have a slide.

7 Could you please put overhead No. 75.

8 [Slide.]

9 This slide shows the baseline characteristics for
10 the patients with 12-month follow-up data in both TMR and
11 Medical Management Group. The data shown is the first
12 column represent the number of patients with follow-up
13 information for the TMR Group, the next column is the
14 patients without follow-up information, the TMR Group with
15 the corresponding p-value, and then the same analyses were
16 done for the Medical Management patients, between the 23
17 patients with follow-up information and the 78 percent
18 result, 12-month follow-up information.

19 You can see as you go down, the categories that
20 the p-values are not such a statistical difference. There
21 was a statistical difference in terms of patient gender in
22 the Medical Management, but that was the only parameters
23 which deferred. It seems that overall the two groups were
24 pretty matched.

25 DR. CALIFF: I was asking about the SPECT data.

1 We had a table in the panel pack on this, and it really
2 looks to me like the patients without SPECT, the tables are
3 quite eloquent labels, T4F3F.1.

4 MR. DOW: Is that page 151, Dr. Califf?

5 DR. CALIFF: 150.

6 MR. DOW: 150.

7 DR. CALIFF: I don't know if you have a slide to
8 put up, and it is just a point, but if you go down the
9 column, you know, with such a small sample size, it is a
10 real question as whether, you know, when you have multiple
11 p-values that are trending in a direction, where they are
12 saying they are not statistically significantly different,
13 really, is the same as saying that the two groups are not
14 different. You really have power, when you combine multiple
15 small differences in two populations, you can get quite a
16 bias.

17 DR. WITTES: Can I say something? If you go down
18 the column of the patients without SPECT -- this is on page
19 150 -- versus the patient with SPECT, and you look at the
20 medical history, just the percents, arrhythmias is 27 to 17,
21 CHF 37 to 33, CVA/TIA 25 to 12, cardiac arrests 7 to 4, COPD
22 -- there are all percents -- 13 to 6, and renal disease 17
23 to 8. So, it seems to me that what you are seeing is a
24 sicker group. Whether it is a statistically significant
25 difference, I don't think it's a relevant question when you

1 are looking at trying to ask whether a group is at different
2 risk.

3 DR. LEFEBVRE: That is why we repeated the
4 analysis, looking within that group of data, for those
5 patients who were in the TMR Group and who were in Medical
6 Management Group, because the study was randomized,
7 therefore, within the SPECT population, if you look at the
8 table on page 151, then, you can really see that the
9 characteristics are pretty much balanced, pretty well
10 balanced between the two groups, which since the studies end
11 up comparing TMR to Medical Management answers the question.

12 DR. CALIFF: Well, I guess we have a difference of
13 opinion about how you interpret what randomization does,
14 because taking patients away from something that happens
15 post-randomization, at least as far as I know, you are never
16 able to really be sure. This is about the best you can do.
17 That is why I say it was a good effort with some difficult
18 data, but I think there is still some uncertainty.

19 DR. LAVIN: I want to draw your attention to the
20 companion table on page 151, that does show the balance
21 between those in the Medical Management Group versus those
22 in the TMR Group, and I would submit that that would be the
23 more critical table to look at from the perception of trying
24 to test the overall comparability.

25 DR. CALIFF: Of course, the best of all would be

1 to have a higher rate of ascertainment of the data, because
2 you never really can be sure, as I say.

3 The third point -- and it is really the last point
4 -- yes?

5 DR. CERQUEIRA: If I could make a comment. I have
6 been involved in doing trials like this using nuclear
7 endpoints for quite a long time out in western Washington,
8 and I am also familiar with what is in the literature, and I
9 agree with you that there are some limitations in terms of
10 you would like to get 100 percent studies on the patients,
11 but realistically, given the time course for acquiring these
12 studies plus some of the technical limitations, which made
13 some of these studies unusable, this is not a bad number in
14 terms of percentage of studies that were acquired.

15 I thin the early TIMI-1 and TIMI-2 trials, due to
16 lack of acquiring studies and studies rejected because of
17 poor quality, they averaged about 75 to 80 percent at best,
18 so 70 percent is not unrealistic in this patient population.

19 DR. CALIFF: Maybe it validates my main objection,
20 using this as the key endpoint. If you are going to be
21 missing an endpoint in 30 percent of people, it sort of
22 leaves you wondering. But anyway, that's a topic for later
23 discussion.

24 The last point on the adequacy of the data, it's
25 again a relatively minor issue, I think, in the overall

1 picture, but the treadmill data that was cited by the FDA in
2 particular, did you do a baseline paired treadmill studies,
3 or did you just do one baseline treadmill and then a 3-month
4 follow-up?

5 The reason I am asking that is it is well
6 documented in any study looking at follow-up treadmill
7 testing that would require, because of the learning
8 improvement that occurs in patients on no treatment, that
9 you have a stable baseline before you draw a conclusion that
10 the treatment has improved outcome.

11 If you just do two treadmills in patients who are
12 treated with no difference in the treatment between the two
13 treadmills, the second treadmill in populations is always
14 better than the first.

15 DR. LEFEBVRE: Keep in mind the treadmill data was
16 not a required test for the protocol, so we had to
17 retrospectively ask the Phase II sites to go back and get
18 the data, so we submitted you every data that we were able
19 to collect, but the data, it was not analyzed in a paired
20 fashion.

21 DR. CALIFF: I think there has been a real serious
22 effort to respond to the questions that we asked last time.
23 Those were the only questions I had.

24 DR. CURTIS: Dr. Casscells.

25 DR. CASSCELLS: I appreciate the responses to my

1 concerns last time, and I agree with the FDA advice that you
2 don't have to know the mechanism of something to approve it.
3 We used nitroglycerine for a long time successfully without
4 knowing the mechanism, for example.

5 They have answered an important concern that I
6 had, which is that after bypass surgery, it is typical to
7 have almost all the patients quit smoking and more patients
8 typically lose weight, and it is true under medical therapy.

9 At the extreme, my concern was that surgery like
10 this might be a very expensive and somewhat dangerous wake-
11 up call for the patient to get them to get their lifestyle
12 in order. The other extreme, there is a possibility that
13 the patients who had the TMR, in fact, used fewer lifesaving
14 medications.

15 If that were true -- I can't understand, I am
16 going to ask you to interpret some of these tables for me
17 like on page 41 -- it is possible that the benefits are
18 understated. The same could be true for the crossovers, of
19 course, if the crossovers from Medical Management were
20 indeed very sick people who were saved by TMR, TMR could be
21 very effective. As you know, that is only one possible
22 interpretation of crossovers.

23 So, maybe for starters, could you tell me, after
24 TMR, what medications are the patients? I can't really
25 understand page 41.

1 DR. LEFEBVRE: I think you should refer to the
2 tables on page 119 and 120. These actually look at the
3 change in medications between baseline and follow-up. Dr.
4 Boyce can answer that.

5 DR. CASSCELLS: You don't have the Medical
6 Management patients here.

7 DR. LEFEBVRE: It's on the next page.

8 DR. CASSCELLS: All right. If I could just start
9 with the upper left of this page, the patients, the first
10 group are considered an angina success, and 31 percent of
11 them got off the beta blockers, 37 percent used less of the
12 calcium channel antagonists and the nitrates.

13 Of the angina failure patients, surprisingly, 22
14 percent used fewer beta blockers and 30 percent used fewer
15 calcium antagonists, and so forth. That is interesting,
16 despite having as much or more angina, there was a
17 significant number of them decreased their medicines.

18 On the next page, page 120, I see that the angina
19 success patients, fewer patients decreased their medication
20 usage, and of the angina failure patients, very few did.

21 So, if I understand this correctly, could you give
22 me the statistics on this, are the TMR patients more likely
23 to discontinue beta blockers than medical patients or TMR
24 patients in general using more milligrams per day of beta
25 blockers than medical patients?

1 DR. LEFEBVRE: Actually, what we did is we looked
2 at the medication in a slightly different way. We look on
3 the medication in a slightly different perspective. The
4 primary concern that led us to look at the medication was
5 whether or not any improvement that could be observed in TMR
6 patients could be related to an increase in cardioactive
7 medications.

8 So, what we looked more is what is what is the
9 percentage of patients who had either no change or a
10 decrease in cardioactive medications following TMR, and if
11 you look in the table on page 119, you realize that across
12 all three categories, that number is approximately 85
13 percent.

14 So, you have 85 percent of the patients undergoing
15 TMR who had either a decrease or no change in their cardio-
16 active medications, and that is really the conclusion that
17 we are drawing about it. But as far as exact details of the
18 medication, I think Dr. Boyce can answer that.

19 DR. BOYCE: I will answer the second half; if you
20 would, are the medical patients taking more --

21 DR. LEFEBVRE: On the Medical Management, you can
22 look at the question in the opposite way. Can you say that
23 is the lack of improvement that you see in the Medical
24 Management patient due to a decrease in cardioactive
25 medication, and if you look at the table, you find that 85

1 percent of the Medical Management patients, who were not
2 successful, had either no change or an increase in
3 cardioactive medication.

4 DR. CASSCELLS: I can read that. That is a good
5 point. You are doing a very refined, within-group analysis.
6 Can you just give me sometime today the two groups, TMR
7 patients, medical patients, how much drug were they taking?
8 If you happen to have it, I know you have got some back-up
9 slides, I would be interested in some of the other
10 medications.

11 I will tell you the thing about it is that you
12 have got some pretty sick patients here. They are sicker it
13 looks like with the numbers you describe. It troubles me a
14 little bit, I mean 61-year-old patient with an ejection
15 fraction of 50 percent with class 3 or 4 angina, only 8
16 percent of whom smoke cigarettes, ought to live a long time.

17 In our group practice, we recently analyzed
18 patients with classes 2, 3, and 4 angina, almost 1,100 of
19 them, just under 1,100, and the mortality is under 1 percent
20 a year now. This is a group of patients who are getting
21 lots of statins, they are getting aspirin, many are getting
22 ticlopidine or warfarin. Almost all are getting a beta
23 blocker. A lot of them are getting ACE inhibitors, most of
24 the women are on premarin, different populations perhaps,
25 intensively treated medically, but the mortality is 0.7

1 percent. I don't know what it is in the Duke database now,
2 I would be interested in hearing that, but we are talking
3 here about a group which from a distance, with just a few
4 parameters, looks like our group or our group looks like
5 your group, but your patients have a high mortality in the
6 surgical group and in the non-surgical group, so it is
7 helpful -- one is always interested in the generalizability
8 of a study, not just is it a fair comparison of two
9 approaches, but if it is, and one is superior, to whom do
10 the patients apply. This gets to the indication.

11 So, I would like to know a little bit more about
12 the medications they got.

13 Finally, you didn't know any data on the dose
14 response. One gathers that some of the patients had 15
15 laser shots and others had 45. What is the dose response,
16 angina relief, SPECT data, do the patients with 45 holes
17 drilled do better than the patients with 15?

18 It is not a critical -- I don't think it is a
19 vote-determining factor, but it is of interest.

20 DR. BOYCE: There are, I think, a couple of issues
21 there. There is quite a range. If you look at the median
22 values, that gives you the big picture, but there is a big
23 range, and the range is related to a couple things.

24 One, this is a CO₂ laser, and the laser is
25 absorbed by the water and fat, and every once in a while one

1 will encounter an epicardium that is really encased in
2 adipose tissue, and one could discharge the laser 60 times
3 before they ended up with a sufficient number in the
4 clinician's mind of channels, trying to place one channel
5 per square centimeter confirmed by TEE that goes through and
6 through.

7 Also, not all these patients had the same regions
8 in the myocardium treated. The treatment was based on the
9 thallium scan at enrollment, so some individuals, it would
10 not be uncommon to have a patent LIMA to an LAD and
11 basically ghost vessels elsewhere, and you may have a fixed
12 defect in the RCA distribution, and basically, you are
13 treating the posterior wall.

14 In other situations, it may be a juvenile diabetic
15 with all GRASS closed, and you just basically see nothing on
16 angiogram, and you are treating the entire heart. So, yes,
17 you know, the number of channels created is dependent upon
18 the area that one is interested in addressing, and that may
19 change.

20 Finally, left ventricular size. Some of these
21 folks actually had normal LV sizes, although I think they
22 were done at the other 11 centers, not at mine, but many of
23 these people had very large hearts, and so the size of the
24 ventricular cavity that one is treating also influences
25 that.

1 On the other hand, in terms of a dose response, to
2 my knowledge, there was not a relationship between the
3 number of channels in a given patient and the success rate,
4 nor was it related to the energy of the laser. Some
5 individuals required a higher energy on the laser once again
6 due to thickness of the left ventricular wall or the adipose
7 tissue covering it, whereas, others would require a smaller
8 energy, so the success rate was not dependent upon the
9 energy of the laser nor the absolute number of channels
10 created in a dose response manner.

11 DR. CASSCELLS: One last point. In July, I asked
12 you if you could re-present the data on the septum. What
13 you have given us here is the free wall versus the whole
14 left ventricle. I have tried to mentally subtract, but
15 looking at the PET data and the SPECT data, it really
16 doesn't look bad. My concern, in case you have forgotten,
17 was that if patients underwent major lifestyle changes in
18 medications after this life-changing experience of TMR
19 hypothetically, that the septum would improve, and not just
20 the areas that had been drilled.

21 In fact, in the PET data, there is some tendency
22 toward improvement in the septum or less deterioration in
23 the septum in the TMR Group, which would be consistent with
24 an indirect effect of surgery, perhaps medications or
25 lifestyle, but the SPECT data is not really given for the

1 septum.

2 You have got two analyses, one where you go from
3 12 o'clock to 6 o'clock, and the other way, you go from 11
4 o'clock to 7 o'clock, but perhaps before the day is over,
5 you could give us a graph of some kind of the septum data
6 and how that followed up.

7 DR. LEFEBVRE: Yes, we can.

8 DR. CURTIS: I think it's time to take a break.
9 We will reconvene in 15 minutes.

10 [Recess.]

11 DR. CURTIS: We will start going around the room
12 now and ask the members of the panel if they have any
13 questions or concerns or comments about what we have heard
14 so far.

15 MR. DOW: Excuse me, Madam Chairman. Would you
16 like us to respond? We have one response to Dr. Casscells'
17 request, or should we wait?

18 DR. CURTIS: No, go ahead.

19 MR. DOW: Okay. Sorry.

20 DR. LEFEBVRE: The response is actually is in
21 respect to the contribution of the septum in the SPECT
22 perfusion changes, and the response is actually in the
23 addendum that you received later on. It is on page 154D.
24 That chart shows -- the addendum, that was sent after the
25 main package. You should look at page 154D. What you see

1 is you see two graphs, one graph that shows the left
2 ventricular free wall, and the other graph that shows the
3 left heart perfusion results.

4 So, what I am afraid I have to ask you is to do a
5 little subtraction in your mind, and basically, what you see
6 the difference between the top graph and the bottom graph is
7 the contribution due to the septum.

8 So, if you look at the dash line, which is the
9 Medical Management patient, you see that there is a slight
10 contribution coming from the septum, but if you look in
11 terms of the TMR patient, you see that the two curves
12 basically overlap pretty much, which indicates --

13 DR. CASSCELLS: I am sorry, we are on the wrong
14 page. 154B is a table, which does contain that information,
15 but I don't see the graph.

16 DR. LEFEBVRE: D as in David.

17 DR. CASSCELLS: 154D? I have just got a table for
18 that.

19 DR. CURTIS: It is E in our packet.

20 DR. LEFEBVRE: These two graphs show the perfusion
21 for the free wall and for the septum for both the Medical
22 Management and the TMR patients, so by doing the subtraction
23 of the ventricular free wall on the left, you can see the
24 contribution of the septum, and you can see if you look at
25 solid line, which is the one that shows the improvement of

1 the TMR patients, that the two curves pretty much overlap,
2 indicating that the septum does not explain the significant
3 change.

4 DR. CASSCELLS: The total, the whole heart graph
5 at the bottom half of the page, there is greater divergence
6 between the TMR Group and the Medical Management Group
7 perhaps in that graph than in the other. It's small and
8 it's consistent with the numbers on page 154B, so I think
9 the septal improvement or the slowdown in septal
10 deterioration is quite modest, and I would agree that the
11 benefit is predominantly in the areas that received laser
12 treatment.

13 DR. BOYCE: There is one other issue I would like
14 to address, sir, and that is the population demographics of
15 this particular patient population.

16 [Slide.]

17 If we look at the patients both in the TMR and the
18 Medical Group, just to highlight issues, for example, with
19 medical history, not only do these individuals happen to
20 have classes 3 to 4 angina, but they are a unique subgroup
21 within all patients that suffer from angina.

22 Over 9 out of 10 have had at least one previous
23 bypass operation, 50 percent had already been treated with
24 PTCA, 80 percent had already had a myocardial infarction, 1
25 out of 3 had already been hospitalized for CHF, and this I

1 just think is a little different subgroup of the total
2 spectrum of patients currently being treated for class 3 to
3 4 angina.

4 DR. CASSCELLS: That is true. I think patients
5 who have chronic angina, but never seem to have had an
6 infarction, do better than patients who have had an
7 infarction. I think that you make a good point there.

8 I think it is absolutely true that medical
9 management is underutilized, and the benefits are
10 unrealized, and simply looking at the 4-S results with the
11 Zocor, the mortality savings, the mortality differential
12 between Zocor and no-Zocor in that group is greater than
13 that between bypass and medical treatment in the VA
14 cooperative study or the European study or the CAST study.

15 So, we have to remember that -- and then those
16 benefits, those curves continue to diverge over years, but
17 the question is under current inadequate medical management,
18 compared to that, you offer a benefit compared to current
19 medical management.

20 The fact that medical management isn't adequate is
21 not your fault. It poses a difficulty for the panel, but I
22 accept the data.

23 DR. CURTIS: Dr. Skorton.

24 DR. SKORTON: Thank you. I have just a couple of
25 questions because a couple of the points I was going to

1 raise were already raised by Drs. Califf and Casscells. I
2 also want to thank the company for responding to the early
3 concerns in a positive fashion.

4 I do share one particular comment having to do
5 with the Phase II patients who underwent treadmill testing.
6 I understand that you just presented those data to be
7 cooperative and to help show data.

8 I do think for the record, we should state that
9 without a control for the training effect of treadmills, it
10 is very hard to interpret these data, and so it's great that
11 you presented them. I don't know what to make of them at
12 all.

13 I have a question -- maybe sort of a funny
14 question -- for Dr. Boyce. Once these products are
15 approved, their uses broader sometimes than originally
16 intended, and I am assuming that when you get to the OR in a
17 very sick patient who has difficult coronaries, that this
18 procedure must look a lot easier to do than doing
19 complicated four-vessel bypass, do you think that this will
20 get to be an alternative as opposed to a last-ditch
21 procedure when you can't do bypass, do you think that will
22 get to be an alternative to bypass?

23 DR. BOYCE: Absolutely not.

24 DR. SKORTON: Can you enlarge on that, at all?

25 DR. BOYCE: This is my own personal view as a

1 clinician. I found this procedure in my own personal
2 clinical experience to be incredibly valuable, but it is
3 valuable for those patients who have viable but ischemic
4 myocardium that cannot be treated with any other modality.
5 In my mind, and seriously, this is something that should not
6 be used when direct coronary bypass surgery or direct
7 coronary revascularization is achievable.

8 That still, however, leaves a dire medical need
9 for this particular procedure, and certainly if you were to
10 ask other physicians with experience with the technique,
11 they may give you different answers.

12 DR. SKORTON: I appreciate it. And the last
13 question is not a specific question of any of the data, it's
14 a sort of a mechanistic question, and I do agree with Dr.
15 Casscells that even though I don't understand at all exactly
16 how this works, that doesn't mean that it is unapprovable
17 because I don't understand it, but I do have to ask you
18 about the thallium data.

19 Dipyridamole thallium -- I don't mean to lecture
20 you -- but dipyridamole thallium works by increasing
21 coronary caliber by causing coronary dilation and
22 differential flow down a conduit artery that doesn't have a
23 stenosis versus one that does have a stenosis, and after you
24 do angioplasty or bypass, the reason that dipyridamole
25 thalliums get better is that there is more flow down the

1 conduit artery.

2 Why in the world does dipyridamole thallium get
3 better after this? Since this has nothing to do with the
4 stenosis in the conduit artery, I just don't understand why
5 it gets better, why it works on the thallium.

6 DR. HORVATH: I think it's a good question.

7 DR. CURTIS: Excuse me. Identify yourself and
8 your financial interest.

9 DR. HORVATH: Keith Horvath, cardiac surgeon at
10 Northwestern University. No financial interest.

11 DR. CURTIS: Were your expenses paid to come here?

12 DR. HORVATH: Yes. The question you raise is an
13 important one, but I think it points out a limitation of the
14 imaging that we have for this technique. The dipyridamole
15 thallium, as you have pointed out, is perfect for
16 revascularization of the native coronaries, and we don't
17 really have a good imaging technique, however, it is
18 probably the best and certainly the best on a wide-range
19 basis. PET scanning, you could argue is better, but is not
20 available as readily.

21 I think that basically what the dipyridamole
22 thallium is showing us is if there is any perfusion -- and
23 you can argue as how that perfusion gets there -- if there
24 is any improvement in that, particularly if there is a
25 decrease in the reversible ischemia, and I think it is

1 capable of assessing that in this application.

2 DR. SKORTON: I think it is a very reasonable
3 answer. Just also for the record, I would stop using the
4 word ischemia, and just say perfusion, because this is not a
5 measure of ischemia by any stretch of the imagination, it's
6 a measure of perfusion, and I don't understand exactly why
7 it gets better, but I agree that the data are compelling.
8 It does look as if there is many more reversible defects
9 after this procedure compared to Medical Management, I just
10 don't get it, but there is a lot of stuff I don't get, so
11 that is just one of them.

12 Those are the only questions I have.

13 DR. CURTIS: Dr. Vetovec.

14 DR. VETROVEC: Well, I will certainly second what
15 everyone else has said. I think that the data recovery here
16 been an incredible turnaround from the previous
17 presentation, and I really congratulate you.

18 I want to ask something about the deaths in the
19 crossover group, which if I understand it right, occurred in
20 patients not adversely selected because of LV function, and
21 LV function itself wasn't a risk factor, but unstable angina
22 was, and I don't quite understand why unstable angina as
23 opposed to presumably similar ischemia that is not unstable
24 changes it, but it looks like it's a terrible risk factor.

25 Can you give me some insight?

1 DR. BOYCE: When we look at the one-year
2 mortality, certainly that is when we see the influence of
3 preoperative ejection fraction at time of enrollment. When
4 we bring patients to the operating room that are acutely
5 ischemic, and we have actually had the occurrence of having
6 patients with EKG changes, this technique, by whatever
7 mechanism it works, may not supply enough blood flow to the
8 heart muscle acutely to change an impending event, which is
9 very different than changing someone who has chronic angina
10 and their clinical symptomatology with time.

11 That was the point that I was making before, about
12 why I don't feel that this is a -- although this is a
13 procedure that has, from my standpoint, a very important
14 clinical application, it is not a replacement for direct
15 coronary revascularization. It is not a treatment for
16 someone with an acute myocardial infarction.

17 DR. VETROVEC: I guess that leads me to -- and I
18 guess this extends what Dr. Skorton said -- I guess one of
19 the fears, and I recognize this improves patients who are
20 sick, but I have a fear that once out on the street, I hate
21 to suggest this, but there probably are some variations in
22 surgical quality, and I fear that some surgeons with less
23 good technique may take this as a quick out at the risk of
24 perhaps not giving patients as good a result as they might
25 get if they got good bypass grafts put in, and that is a

1 nagging concern to me.

2 Do you have any comments about that?

3 DR. BOYCE: Well, I suspect the company will
4 address issues with training, but as with any new treatment
5 modality, training will have a very critical influence here.

6 MR. DOW: We can, if you would like, go through
7 what the company is doing to make sure that surgeons
8 understand the technique and the application of the
9 procedure at this time, if you would like.

10 DR. VETROVEC: If you can do it briefly, I think
11 that would be helpful.

12 DR. CURTIS: Actually, one of the things I should
13 point out, because we discussed this yesterday, too, is the
14 fact that under the FDA Modernization Act, what we are
15 supposed to be considering are the data that have been
16 presented for the indication that has been present, and that
17 concerns about other uses for whatever this is or not really
18 should not be our concern.

19 Even if it could be used for something else, that
20 is not something that we are supposed to base our judgments
21 today on.

22 MR. DOW: We are willing to defer and come back to
23 the training later when it is appropriate, whichever way you
24 would like to go. You would like to go?

25 DR. CURTIS: Go ahead.

1 MR. DOW: All right.

2 DR. LEFEBVRE: Could we have overhead No. 100,
3 please.

4 DR. MARCH: Robert March, cardiac surgeon at Rush-
5 Presbyterian St. Luke's Medical Center in Chicago. I have
6 no financial interests in the company. I had my travel paid
7 for to this meeting.

8 [Slide.]

9 This is an important concern, and it always has
10 been for me and the company, and this is the proposed
11 training, Center of Excellence training course which would
12 educate the user in the background and, most importantly,
13 patient selection, which I think is critical, and knowing
14 when to apply this, it is probably more important to know
15 when to apply this than the actual operative procedure
16 itself, which is reasonably straightforward as far as
17 cardiac surgical procedures are performed, but you can see
18 that it is a comprehensive program at a Center of
19 Excellence.

20 Next slide, please, 102.

21 [Slide.]

22 The proposed training path would be this post-PMA
23 approval where once it is agreed upon that a site has been
24 accepted as a user of the device, there will be surgical
25 training at the Center of Excellence, including surgical

1 training at a Center of Excellence, seeing live cases, as
2 well as lectures.

3 In addition, the hospital will be in-service where
4 all the staff that will be involved will go over the safety
5 issues, and then the first case -- and we would try to
6 encourage them to cluster a couple of cases together -- will
7 be proctored by an experienced investigator followed up with
8 clinical support and service support for their subsequent
9 cases, and a one-month review of that experience and repeat
10 in-service at that time. Certainly, additional follow-up
11 will be provided depending upon the results of the one-month
12 review.

13 So, I agree that patient selection and education
14 are our best bet at ensuring that this device is used
15 properly and that the timing is appropriate.

16 DR. CURTIS: Dr. Cerqueira.

17 DR. CERQUEIRA: I don't have any real questions,
18 just some comments, that I was probably the most critical of
19 the thallium data during the July '97 presentation, and I
20 think you have done very commendable job of trying to look
21 at the quality control of the centers, as well as gathering
22 the missing data points.

23 In terms of the question about why it should be
24 improved if you are not improving the large-vessel blood
25 flow, thallium is both a marker of blood flow, but it is

1 also a marker of myocardial cellular integrity, and if you
2 have got some severely ischemic hibernating areas, and you
3 can improve blood flow through your small-vessel increase or
4 some other mechanism, I think the thallium uptake will be
5 improved.

6 I think the data is convincing in a relatively
7 small number of patients, that you do get improvement in
8 perfusion with the treatment, and I think the data fully
9 supports that.

10 I share the concerns about the sample size and the
11 loss of patients, but I don't think this is the type of
12 protocol where we are ever going to enroll 42,000 patients
13 the way you can with Gusto or some other large trials, but I
14 think the beauty of using thallium or perfusion as a marker
15 is the fact that with a smaller number of patients, you can
16 show that there is a direct benefit.

17 Ray Gibbons from the Mayo Clinic has shown that in
18 several different trials looking at this effect, so from a
19 nuclear cardiology perspective, I think the data does
20 support the fact that there is improvement in blood flow to
21 these areas, and it would have been ideal to get 100
22 percent, but I think with 62 percent that were analyzed and
23 70 percent that were obtained, I think it is supportive data
24 for the efficacy of the technique.

25 Those are my only comments.

1 DR. CURTIS: Dr. Weintraub.

2 DR. WEINTRAUB: Just a couple of personal
3 observations, confessions of a panel member. In the last
4 meeting last July, I was one of the few that voted in favor
5 of approving the PMA.

6 I am somewhat chastened by that because I think
7 that the delay has really strengthened the application
8 considerably. I think it has shown me two things. You
9 know, as surgeons, we are often approached and asked to do
10 something because there is nothing else available, and, in
11 fact, one of the things that is very obvious is that medical
12 therapy is available, and if you look at the overall
13 mortality, it's about the same.

14 So, in fact, not having the therapy performed or
15 being randomized to non-TMR did not assign the patients to a
16 death warrant, nor really to major problems. It did assign
17 them as a group to less clinically favorable results.

18 The second thing is that obviously, the PMA has
19 been strengthened and it's a lesson for the sponsors in
20 general that a good PMA with good data acquisition not only
21 will get through the panel more quickly, but it also will
22 convince the users, who are, after all, the customers that
23 you are trying to sell, that it is a product that has merit
24 rather than being left in a gray zone.

25 I have just a small number of questions. It is

1 not surprising to me that patients with unstable angina have
2 a higher mortality. We have known that in cardiac surgery
3 for many years, taking a patient who is acutely ischemic
4 down to the operating room often results in a less than
5 favorable result.

6 I would ask Dr. Boyce have you had any experience
7 or are there any data relative to the use of the intra-
8 aortic balloon pump in those unstable patients. We used to
9 use intra-aortic balloon pumps fairly routinely in patients
10 with unstable angina, and nowadays we don't use it quite as
11 much because anesthetic techniques are so much better, but
12 were such patients treated with intra-aortic balloon pump,
13 and did it make any difference in outcomes?

14 DR. BOYCE: The protocol that the investigators
15 had did not dictate to them one way or the other in terms of
16 their decisionmaking. Certainly, from my personal
17 experience, we have become more aggressive about using an
18 intra-aortic balloon pump in this patient population, and
19 this is one of the several important factors that will need
20 to be stressed in terms of the surgical technique and
21 patient selection.

22 DR. MARCH: I would like to make one comment about
23 that regarding the Rush series. We used intra-balloon pump
24 in 40 percent of our patients in order to achieve the
25 stability we felt was very important for the procedure.

1 Our 30-day mortality was 1.6 percent in about 75
2 patients, and that will be part of the emphasis of the
3 Center of Excellence, avoid inotropes, use mechanical
4 support to decrease myocardial oxygen consumption, as well
5 as improve output in coronary blood flow, and achieve the
6 stability that you need for the perioperative period.

7 The last thing is the stress of the incisional
8 pain is extremely important, so abundant use of epidurals
9 toward all things like that are also going to be
10 incorporated into the teachings.

11 DR. WEINTRAUB: I wonder if also it shouldn't be
12 part of the labeling under caution, that the therapy should
13 be used with caution or with ancillary measures in patients
14 with acutely unstable angina, because mortality rate, after
15 all, was in excess of 10 percent in those patients.

16 I was also troubled by the SPECT versus non-SPECT,
17 but I think that has been answered to the best of your
18 ability.

19 Again, to the surgeons, is there any role for the
20 device in adjunctive use? For instance, we are beginning to
21 use VGEF in patients who are undergoing coronary bypass, but
22 who may have, let's say a right coronary artery in a
23 territory, an obliterated right coronary artery with no
24 bypassable vessels in the inferior wall, and there is no way
25 to revascularize that, is there any role or could there be

1 any role using TMR in an adjunctive role?

2 I realize it has to be used with the heart full
3 and issues of anticoagulation obviously play a role, but I
4 wonder if there has been any experience in this area.

5 MR. DOW: Just a comment before Dr. Boyce
6 responds, I think this kind of clinical discussion is
7 healthy in this environment. I just want it to be clear
8 that the intended use right now is not as an adjunct.

9 DR. WEINTRAUB: I understand that, but once the
10 device is out on the market, you have very little control
11 over who is going to use it and how. So, I would like to
12 have this out in the open, that's all.

13 DR. CURTIS: I am not sure that really requires a
14 comment. I mean I think that is true, but the same comments
15 I made before about, you know, we have got to be limited to
16 what the data are today and what we are looking at still
17 holds.

18 DR. WEINTRAUB: But if there are any cautions, for
19 instance, about using it in patients on bypass, fully
20 heparinized, if that should be a caution, then, it should be
21 a caution.

22 DR. CURTIS: We might want to discuss that in the
23 labeling, but there is no data right now on doing this in
24 patients who are having bypass at the same time, correct?

25 DR. LEFEBVRE: Ongoing clinical studies.

1 DR. CURTIS: But we are not dealing with that
2 today.

3 DR. LEFEBVRE: But not today.

4 DR. WEINTRAUB: Finally, again, sort of getting to
5 the labeling or the use, I have nightmares about this device
6 being used in hospitals that don't do cardiac surgery, and I
7 think that ought to be prohibited frankly.

8 Again, we may be getting into the area you are
9 talking about, but I think that ought to just not be done,
10 period.

11 MR. DOW: Would you like us --

12 DR. CURTIS: I would imagine you might agree with
13 that statement?

14 DR. BOYCE: Certainly, that goes without saying.

15 DR. CURTIS: Thank you.

16 Any other comments?

17 DR. WEINTRAUB: I think that's it.

18 DR. CURTIS: Thank you.

19 Dr. Ferguson.

20 DR. FERGUSON: Well, again, it was my pleasure to
21 be here at the first meeting, and I want to, like everyone
22 else, congratulate you on how well you have complied with
23 the list of concerns. I think it has been a yeoman's job in
24 that regard, and I thank you for that.

25 I have a couple of questions. The first one

1 relates -- this is an educational process for a poor,
2 ignorant cardiac surgeon -- the question relates, and it is
3 an important one because it relates to labeling on page 2.2.

4 The procedure has been devised to use in stable
5 angina. The crossover -- and we know we are dealing with a
6 large number of sick patients here, I understand that --
7 should the definition say something about stability in terms
8 of time is what my question relates to, because I don't know
9 when the selection for patients are made, and perhaps you
10 could enlarge on this, at the individual centers, they say,
11 well, we have a patient who fulfills the requirements, who
12 has stable angina, and yet that patient may be one of the
13 very many that crossed over.

14 Have you looked at the situation to see if those
15 patients that crossed over were unstable within a period of
16 time before they were called stable and admitted to the
17 study? That is my question. Does that make sense?

18 DR. LEFEBVRE: I think that those patients have
19 been looked at, and Dr. Boyce presented the slide. We
20 looked at the incidence of -- crossover patient had to have
21 been unstable to be eligible for crossover, however, not all
22 crossover surgeries took place immediately after the
23 crossover event. Some took place later on down the road,
24 and so we have a group of patients for whom they were
25 crossed over, but they were not unstable in the two weeks

1 prior to surgery and for those group of patients.

2 DR. FERGUSON: That doesn't answer my question,
3 though, Xavier. My question relates to the fact that they
4 were stable for two weeks prior, so they were admitted to
5 the study, but did you look at the situation where before
6 patients were admitted, they were stable?

7 I mean you can have, as Dr. Casscells has said,
8 you can have patients who are very, very sick on Medical
9 Management, who are stable for a long time, who would
10 fulfill the requirements to be admitted to the study, and at
11 the same time you could have a patient who has had several
12 episodes of unstable angina where he responded to
13 nitroglycerine and ICU care, and so forth prior to that.
14 Were there a large number -- I am just trying to find out
15 whether that had an impact on the number of crossovers,
16 because you wouldn't expect to find 190 patients who were
17 entered into the study, you say were stable for a long
18 period of time, and then suddenly became unstable, so they
19 had to be operated upon.

20 DR. BOYCE: In other words, were there a number of
21 patients before they entered the study, before they were
22 enrolled and assigned to a treatment arm, that had in their
23 year prior to enrollment, had been in and out of a hospital
24 for unstable angina?

25 DR. FERGUSON: Right.

1 DR. LEFEBVRE: The answer is yes.

2 DR. FERGUSON: So, all of the patients were, there
3 was no way to define the groups, right?

4 DR. LEFEBVRE: It was the same. The patients who
5 crossed over did not have a higher incidence of unstable
6 angina.

7 DR. FERGUSON: As I say, I think that is important
8 because the labeling here is for stable angina, and yet,
9 even in your study, a large number of those patients have
10 become unstable, and we have been talking about that aspect
11 of it in the morning here, but the procedure, as it is
12 defined by the application, the procedure is going to
13 include, even though the labeling says for stable angina, is
14 going to include, in fact, operations on a lot of unstable
15 patients subsequently, and you might want to comment on
16 that.

17 DR. MARCH: Dr. Ferguson, I would like to address
18 your concern in the sense that the time course of angina on
19 these patients can enter into an unstable period, but my
20 point earlier was that I think with use of aggressive, you
21 know, nitrates, heparin, and even a balloon pump, you try to
22 get that patient to a stable portion of their clinical
23 course.

24 I think if you can't get them so that they are not
25 stable, then, probably reconsider the decision to go ahead

1 with TMR and consider something else if it's available. It
2 is certainly, as we have shown with the data, it is not wise
3 to go into the operating room with an unstable clinical
4 situation, so if they are not stable for at least a day or
5 two beforehand, and we are assured that there is not ongoing
6 myocardial injury, I think we should avoid the procedure,
7 and I think that goes back to the educational aspects.

8 DR. FERGUSON: I am not taking issue with any of
9 the data at all. What I am doing is doing is looking at our
10 responsibility as the indications for usage of the procedure
11 on page 2-2. That is why I really brought the question up,
12 but I think you have answered it.

13 I didn't read this perhaps as closely as I should,
14 but the guidance for using TMR on reversible units of
15 myocardium has to be guided by the perfusion scans.

16 Is that a correct statement?

17 DR. MARCH: For this study, that was the modality
18 used, but a lot of the centers may -- I don't want to speak
19 for all of them -- but will oftentimes use a stress echo, as
20 well, to make sure that we are not missing any areas that
21 should be treated, so I think that, at least at our center,
22 we use multiple studies to show what regions are reversibly
23 ischemic.

24 DR. FERGUSON: This gets again to a question that
25 the FDA has addressed to the panel, and that is whether or

1 not or say what studies should be required of patients as a
2 part of the workup for that.

3 The two things that concern me in that situation
4 again are, number one, are you applying the drill holes to
5 salvageable myocardium in so much as you can rather than
6 just going in and putting the holes in a patient who has
7 been heart failure, and so on, and number two, the issue of
8 identifying a full wall thickness by the use of TEE, which I
9 think is a critical -- my personal view is that that is a
10 critical issue and will become ever more critical when we
11 talk about percutaneous or endocardial techniques, but that
12 again is another --

13 DR. MARCH: I would agree with you that you need
14 some study to show where the regions are, and I would also
15 agree that transesophageal echo is important for a number of
16 reasons, not only to show that you have penetrated the wall
17 thickness, but it helps identifying moving walls, the
18 thickness of the walls, what the function of the ventricle
19 is throughout the operation, so that you could intervene
20 earlier, it's an earlier sign that you are maybe getting
21 into trouble with particular patient, and institute balloon
22 pump support.

23 So, I think that a TEE is a very important
24 modality because it forces a little bit more cognizance on
25 the part of the anesthesiologist and the surgeons to make

1 sure that you are not going to get into trouble and that you
2 are going to be stable throughout the procedure and get a
3 good result.

4 DR. FERGUSON: That gets to whether that is a
5 condition for labeling. That is why I bring that up.

6 One third quick point, if I may. On page 210, the
7 last page in the book, these are device failures. These
8 admittedly look like they are minor, but they are not
9 decreasing in number, and these are in the study group, so
10 presumably there are not more devices being used to account
11 for more failures.

12 Would you comment on this page?

13 DR. LEFEBVRE: The device reliability, as
14 mentioned during the FDA presentation, is currently being
15 discussed and reviewed with the idea --

16 DR. FERGUSON: Pardon me?

17 DR. LEFEBVRE: The reliability of the device.

18 MR. DOW: Part of the application process is to
19 provide information on manufacturing and the quality of the
20 device and information about the reliability of the device.

21 Just as a general response, Dr. Ferguson, as this
22 company moves from the research into hopefully the
23 commercialization phase in the United States, but we are in
24 the commercialization phase around the world, there are more
25 and more quality systems that have been implemented to

1 identify root cause, if you will, in these kinds of failures
2 and correcting them as we go, so it's the course of the
3 company moving out of research to manufacturing facilities,
4 so these issues are known and investigated under good GMP
5 practices.

6 DR. FERGUSON: Just one last question. Are these
7 truly device failures or are some of these due to the
8 surgeon himself? Maybe you won't answer that. I am just
9 trying to get a handle on what all of this means the device
10 would not -- I would hate to get in the operating room with
11 a machine, you know, and tell the patient that we are going
12 to do this and that, and then not have the device work, and
13 if a case is delayed five minutes means nothing, but if it
14 has to be canceled or come back another day, that's all.

15 MR. DOW: I think it would be dangerous to answer
16 the question off the cuff. The information about each one
17 of these failures is available. We don't have it here.
18 Operator errors is a part of almost using any device, and
19 it's a matter of training and experience.

20 Some of these are certainly due to the equipment
21 itself and the reliability of the equipment, but sorting
22 those out will be not a prudent thing to do.

23 DR. FERGUSON: Thank you very much.

24 DR. CURTIS: Dr. Wittes.

25 DR. WITTES: Well, if my neighbor, Dr. Ferguson,

1 can say country doc, I can say country statistician.

2 I am also impressed by the way you have pulled in
3 the data and did much more follow-up, and so forth, but you
4 feed a statistician missing data, and we get hungry. So,
5 let me ask you some questions.

6 The way I read both the primary and secondary
7 endpoints, the majority of the data are missing, and I want
8 to make sure that the things that you have done to convince
9 everybody else around the table that this is an effective
10 device, in fact, would satisfy even we statisticians.

11 What I see, the primary endpoint was 12-month re-
12 perfusion, 50 percent of the treatment data are missing, and
13 85 percent of the control data are missing, so that although
14 there is an attempt to look to see whether there is a bias,
15 it seems to me that when you are talking about that much
16 data missing, it doesn't matter whether there is a bias or
17 not.

18 Even if you look at the three-month data, 40
19 percent of the treatment and 55 percent of the control are
20 missing. So, it seems to me that therefore, the focus needs
21 to be -- and it has been around the table -- on the
22 secondary endpoint, which is angina, for which 40 percent of
23 the 12-month data in the treatment group, and 50 percent of
24 the control data are missing.

25 What you have done, and I really want to

1 congratulate you, is because when I saw that the pack, the
2 data in here, that the worst case analysis was an analysis
3 that was extremely -- it made it so that the more missing
4 data you had in the control group, the better the device
5 was, and that has been rectified in the presentation today,
6 and I am really pleased to see that.

7 I did a quick analysis, and I calculated -- I
8 don't quite get the less than 0.5 at 12 months that you get,
9 it may be -- let me ask a little technical question. Was
10 that corrected for continuity or not?

11 DR. LAVIN: We used a Fisher's exact test.

12 DR. WITTES: Okay. The other issue that -- I want
13 to get back to the angina in a little bit, but let me ask a
14 couple of other technical questions. As I look at the
15 graphs, the standard errors for a lot of the temporal trends
16 stay constant over time even though the sample size goes
17 down, and I just don't understand why that is true.

18 DR. LEFEBVRE: You are correct. That actually, in
19 the graphs that you have, it's just an artifact of using
20 Power Point presentations that requires you to have the 95
21 percent confidence interval to acquire sizes, however, in
22 the presentation by Dr. Boyce, we went back, eliminated all
23 those, and we put the correct values on the slides, so if
24 you had looked at the presentation, you could see that the
25 actual error bars increase in length as time went by, as you

1 point out, because of the lower sample size.

2 DR. WITTES: But you can see that, as a reviewer,
3 it is very hard to look at data when there is that kind -- I
4 mean I appreciate that it has been corrected, although I
5 didn't notice, because I couldn't see the graphs, but it is
6 very hard to review things when you know that standard
7 errors can't possibly be correct.

8 Let me get, then, to what I think is for me the
9 crucial issue, and that is the angina data, the class data.
10 What I understand is that the endpoint is really a two
11 category change in angina class, and that the thrust of the
12 argument is that no matter even if the worst case scenario
13 is applied, and I think any of us believes it couldn't
14 possibly be as bad as that, then, you see a significant
15 difference, a significant benefit for the device.

16 But it seems to me what that does is throws the
17 question back on the -- given the amount of missing data and
18 given the fact that this is an open study -- it throws the
19 question back on the reliability of the angina measurement,
20 especially at baseline, because if you are off by a class,
21 and if there is any kind of bias in the way people are
22 assessing the class, a small amount of bias can have a huge
23 amount of effect in the outcome.

24 So, I want to ask a series of questions, but what
25 you need to understand, that the whole thrust of it is are

1 we seeing something artifactual or is this real.

2 The first question has to do with the survey that
3 looked at the agreement between the study angina results at
4 the end and the confirmatory ones, and what we know is that
5 80 percent were within one angina class, but what I didn't
6 see -- and I may have missed it in the report -- was a table
7 that showed the cross-classification of class by class,
8 because the important -- it is not only how much agreement
9 there is, but what is important to me is where the
10 disagreement occurs, and does it occur at parts of that
11 matrix that could affect the important two-class change.

12 So, that is one thing. The other part -- and I
13 want to throw it all together because it is sort of one
14 question with lots of pieces -- at baseline, which was the
15 class of record, and was that class determined -- how was
16 the process by which screening, randomization, and
17 determination of the baseline class established, and was
18 there any dropout between the point of determining class and
19 actual entry into the study?

20 DR. LEFEBVRE: The way the patients were enrolled
21 in the study, the sites would call PLC, and they would have
22 an eligibility check list, and we would have an eligibility
23 check list, and we would go down the check list.

24 So, if they did not have that check list filled
25 out prior to calling us, the patient could not be enrolled i

1 the study, and one of the requirements was for the patient
2 to be class 3 or 4 angina. In terms of how the angina was
3 being assessed, there is a table in the panel pack which
4 indicates how and whom decides the angina assessment.

5 Typically, the angina assessments were done by the
6 same people at baseline and at the follow-up visit. That
7 table is on page 101.

8 DR. WITTES: Was there anybody who was deemed
9 eligible, given an assignment, and then not entered into the
10 study?

11 DR. LEFEBVRE: There were actually a few patients,
12 six patients who were enrolled the study and randomized to
13 TMR, and who, in fact, never received TMR treatment for
14 reasons ranging from the fact that insurances would not pay
15 for the procedures, other reasons, so there were six
16 instances in which patients had been enrolled in the study,
17 and were basically dropped afterwards, because they did not
18 receive the TMR treatment.

19 DR. WITTES: Were they followed at all, are they
20 in the denominators at all?

21 DR. LEFEBVRE: Since these patients did not
22 receive TMR, they were not followed.

23 DR. WITTES: Can I get the answer to my cross-
24 classification question?

25 DR. LEFEBVRE: Correct. If you look in panel

1 package on page 103, and on page 104, you actually have the
2 answers to -- you have actually, on page 104, you have the
3 answer with respect to the agreement between the different
4 sites, which shows that the agreement between the
5 independent survey and the site was seen at all
6 investigations, institutional centers participating in the
7 study.

8 DR. WITTES: No, that is not the answer. I don't
9 think I can get from that. I tried to look at this data and
10 get the answer.

11 DR. LEFEBVRE: Wait a minute. I think you are
12 asking whether or not the agreement matched at 3 months, 6
13 months, and 12 months?

14 DR. WITTES: No.

15 DR. LAVIN: No. Let me take a shot at the
16 question. I think what Dr. Wittes is asking is what
17 proportion of the classifications could have been affected
18 in terms of 3-4, because of the misgrading possibility, and
19 I think that requires a look, for example, if you were to
20 look at all of the subjects who were classified as a zero,
21 well, they could have been off by 2, and it still would not
22 have been a 3-4, but then you have the group who was a 1,
23 who could have been a 3, which didn't happen very often, and
24 then you have a group of 2 that could have been a 3, and
25 that is the edgy situation.

1 I looked at that, and that's around 15 to 17
2 percent of the population. Of course, there also were some
3 that were 3's that could have been 2's, so it goes in both
4 directions.

5 So, my sense is that it is a wash, and my sense is
6 that the assessment by the independent survey showing a 38
7 percent advantage for TMR is a valid result that still
8 holds.

9 DR. WITTES: Let me ask you very specifically.
10 You have answered sort of the second part of the question.
11 The first part is what is the cross-classification if you
12 just took the classes 1, 2, 3, 4, by 1, 2, 3, 4, what does
13 that 16-cell matrix look like?

14 DR. LAVIN: We didn't bring that with us today,
15 but I do have a good picture of it in my mind. There are
16 about 3 percent that are off by 2 classes, and there is
17 about, let's say, 18 percent, I think it is indicated in
18 there, but we do not have the data with us today.

19 DR. LEFEBVRE: One way you can look at it is on
20 the bottom of page 103, it is a summary of that matrix that
21 you are talking about. It just gives you the distribution,
22 how far away from the diagonal those patients would be,
23 which would answer your question.

24 DR. WITTES: But only partly. That table is
25 consistent with quite a number of different matrices, and I

1 want to know what the specific matrix is.

2 Let me ask you one more question that is related
3 to something really very different, and it has to do with
4 what I understand the change in the protocol that said I
5 think it was seven months through the study, there was a
6 change in protocol that said that patients entering the
7 study could not go on -- patients entering the medical arm
8 couldn't be crossed over for six months.

9 Is that right, did I understand that right?

10 DR. LEFEBVRE: Correct.

11 DR. WITTES: Have you done any analysis -- you
12 see, one of the things I was trying to do when I was reading
13 the panel pack is sort of back up and say, okay, you can't
14 get the 12-month data because there is so much missing data,
15 let's see what there is at 6 months, let's see what there is
16 at 3 months, sort of back down and ask the question are the
17 data compelling as we move backward in time.

18 Now, it seems to me that one way to do this would
19 have been to look at the subgroup of patients who had been
20 randomized after 7 months, and there you would have had
21 clean data for the 6-month analysis, and so the question is
22 do you have an analysis -- I realize it is not going to have
23 a lot of power, but it certainly should show a trend of
24 angina, a proportion who have two-step changes in angina
25 class among those people randomized after the first 7

1 months. Is the question clear?

2 DR. LEFEBVRE: I think the question is clear, but
3 we have not done the analysis, but if you look at another
4 analysis which may be close enough to answer your question,
5 which is the one where we looked at those Medical Management
6 patients who did not cross over at any point into the study,
7 so if you look at those patients, that may be better to
8 answer, and the analysis is in the package.

9 DR. WITTES: That won't answer it, because that is
10 a mixture of two groups, one who crossed over -- one who
11 didn't cross over because they were randomized in a way that
12 said you can't cross for six months, and another who didn't
13 cross over because they didn't run into medical problems, so
14 I think we need to step -- I would like to see those two
15 groups separate. I want to see sort of the pure randomized
16 group from the post --

17 DR. BOYCE: I am sorry. From a clinician's
18 standpoint, I still don't get it. What are we looking for?

19 DR. WITTES: One of the problems we have is this
20 crossover stuff, and how does the crossover affect the
21 inference about the 6-month data. All right, we can't --
22 let's forget the 12-month for a minute.

23 Now, there is a group of patients, the patients
24 who entered in the first 7 months of the study were allowed
25 to cross over if they ran into trouble, whenever they ran

1 into trouble, so that first group of patients, it seems to
2 me, the question about -- am I wrong?

3 DR. CALIFF: No. I will add another clinician's
4 viewpoint --

5 DR. WITTES: Okay. That group of patients we
6 can't really -- we are always going to be stuck with the
7 problems of confounding of crossover -- but for the group of
8 patients that entered after 7 months, the problem of
9 confounding at least to the first 6 months, it seems to me
10 is clean, and we would a really clean analysis of what is
11 the effect on angina of patients who don't cross over, and
12 so -- what?

13 DR. BOYCE: I really don't mean to be dense here,
14 but in order to cross over, you had to have an unstable
15 event and be admitted to an intensive care unit for a
16 minimum of 48 hours, so you are stipulating that that group
17 would be less ill?

18 DR. CALIFF: I think what she is saying is that
19 you basically have an uninterpretable experiment until you
20 change the protocol. There is nothing you can compare when
21 you over half the patients have not had the assigned
22 treatment.

23 So, what she is saying is you changed the protocol
24 to make the experiment interpretable. How about if we just
25 looked at the results from that part of the study that had a

1 protocol that one could really interpret?

2 DR. WITTES: To me, that is really the strength of
3 the study, and if you show that, that could be really
4 convincing.

5 DR. BOYCE: But the patients, by definition, had
6 to fail medical management --

7 DR. CALIFF: In an unblinded study where the
8 doctors knew a lot about who the patients were and what
9 treatment they had received before, and, you know, there is
10 a long history of this in clinical trials, very hard to
11 interpret that sort of information. You are just missing
12 over half the patients as far as an interpretable endpoint.

13 MR. DOW: If I understand, the issue is if the
14 people that were in the Medical Management study from the
15 beginning, that population is different, could be different
16 in your mind from the people that entered Medical Management
17 after 7 months of this new protocol, and you want to study
18 those people that were put into Medical Management after 7
19 months?

20 DR. WITTES: No, no. I want to think of the study
21 as two different strata, where there is a fundamental change
22 in protocol at 7 months after the study began, to what I
23 believe is a better protocol. The first study, the first
24 part, so really you have two protocols, we have a protocol
25 amendment essentially that changed the protocol. In the

1 first 7 months, there is no way you can disentangle
2 crossover from not crossover. When you are trying to
3 compare the Medical Management from the Device Group, you
4 have got the problem of crossover.

5 In the second part of the study, you don't have
6 that problem anymore, because you have said you can't cross
7 over for 6 months, so you have -- if you threw away the
8 first part of the study, you have an absolutely clean 6-
9 month study in the second part when you are trying to
10 compare Medical Management to Device Management patients,
11 that is the subgroup that I would like to see.

12 DR. LAVIN: I understand here your question and I
13 think that it is something that we can take a look at. I
14 think what you are really getting at is the issue, has the
15 study outcomes changed as a result of the change in the
16 protocol.

17 I think it is a good, interesting question, and I
18 would submit that one of the groups will have a higher
19 angina response rate, and one of the groups will have a
20 lower angina response rate. The Medical Management Group
21 may well be different, and the crossover may well be
22 different, and I think it is something that is worth looking
23 at, but I would submit that the studies, the entity and the
24 combination of both, and that based on statistical
25 inference, the statistical inference would really allow us

1 to just basically look at the patients as randomized, and I
2 would submit that the final results should stand, but I do
3 think that is an interesting sidebar question that you have
4 raised.

5 DR. WITTES: That is all my questions.

6 DR. CURTIS: Dr Parisi.

7 DR. PARISI: Thank you. At least from a
8 clinician's point, I thought you had done everything
9 possible to bail out from this lack of data, and I was
10 impressed by the reasonable agreement that I thought
11 occurred when you had an independent group come and at least
12 post hoc contact all these patients after 12 months. I
13 thought probably 80 percent agreement was probably as good
14 as you are going to get, although I agree that Dr. Wittes'
15 point about the baseline was not determined by the same
16 individuals.

17 Nevertheless, I suspect these patients were
18 reasonably scrutinized to be sure that they were class 3 to
19 class 4 at the beginning, as well. I thought the worst case
20 analysis was quite reasonable. I am also impressed by if
21 you follow the patient who develops unstable angina and who
22 doesn't as you follow them, and I think unstable angina, as
23 you have defined it, where the patient is in an intensive
24 care unit, is a pretty impressive and different syndrome
25 from a clinical point of view than someone you are managing

1 in the office with a class 3 to 4 angina, which we have all
2 the time.

3 So, despite the missing data, the way you have
4 attacked it, I think is probably as good as you could have.
5 I was a little more concerned with whether the mortality
6 data and vital status and missing data -- it bothered me a
7 great deal because I think determining vital status is a lot
8 different than putting patients through questionnaires or
9 meeting and seeing them. It is much easier to determine.

10 If you go to page 56, I guess, at Tab Roman V.3,
11 at 12 months, I only see 137 patients listed if you add the
12 64 and the 73. I dug through the protocol to find who was
13 missing, and I found therefore, if you subtract out the
14 number of deaths, which was 7 in the Medical Management, 15
15 in the Crossover Group, and 13 in the TMR Group, what I
16 found was 5 missing from the original TMR Group and 15 from
17 the Medical Management Group, and then I did the same thing
18 to convince myself that this was going to be reasonable.

19 I did a worst case analysis and said all the
20 missing TMR patients were dead and all the missing medical
21 patients were alive, and I came out with equal mortalities
22 practically, then, at 20 and 22 percent, but I would like to
23 see that validated. I would like to know that the patient
24 mortality, given the missing patients, and since you don't
25 have the vital status -- which I think is something that

1 easy to ascertain, particularly in a study that is done in
2 the United States rather than a multinational study
3 involving a small number of patients -- I would like to be
4 convinced that the mortality is clearly in no case worse by
5 having this worst case analysis.

6 DR. LEFEBVRE: I think what I can answer is where
7 the missing data that you called where they are. They were
8 due to the fact that we had 6 TMR patients who underwent
9 additional vascularization procedures, therefore, these
10 patients are censored from the analysis from the time of the
11 additional interventional.

12 In the Medical Management Group, you have 7
13 patients who underwent additional vascularization
14 procedures. Additionally, you had 2 patients who withdrew
15 from the study in the TMR Group and 5 who withdrew from the
16 study in the Medical Management Group. Those patients
17 decided they did not want to be part of the study any longer
18 as they have the right when they signed the Informed
19 Consent. So, from that standpoint, we had to censor them,
20 as well. This explains these lower number of patients that
21 you have observed.

22 DR. PARISI: I guess the other issue that I am
23 still very unhappy about is the whole approach to the
24 analysis of the primary endpoint here, the SPECT data.

25 As I recall from the July meeting, I had asked I

1 guess one of the experts, the nuclear experts, about what
2 the error of the method was, in other words, if you showed
3 the same study to a nuclear expert on two different
4 occasions, did it always 100 percent of the time get read
5 the same way, and the answer to that question, as I recall,
6 no, it didn't always get 100 percent. If you had a 24-
7 segment model, a difference of 1.-something segments was the
8 error of the method, and the total average result of
9 improvement in reversible defects was within that error of
10 the method.

11 If you turn to the change in the number of
12 segments, the supplemental pages, Section -- I guess it's
13 Arabic 4-35B, and you look at these cross-classifications of
14 change in angina class versus the number of ischemic
15 segments, a lot of the patients who have TMR get better in
16 angina class, but also get worse in the segment score.

17 This is 4-35B, which would be in the Section Roman
18 IV in the supplemental information that was given out. I
19 guess I have a great deal of perplexity in trying to reach a
20 mechanism. I am not sure there is a mechanism, maybe there
21 are multiple mechanisms. In particular, I am troubled by
22 the patients who get better in angina class, and yet worse
23 with thallium score. I think you have to interpret it both
24 ways.

25 So, I am not at all convinced that the assessment

1 really does represent, for the whole population, a change.
2 I think there are individual responses that you have shown
3 here, and it may vary from patient to patient.

4 I am also concerned that the patients, 30 percent
5 who had missing SPECT data, there were twice as many
6 patients who had cerebrovascular disease by history, TIAs
7 and stroke, and that to me is a much more diffuse kind of
8 vascular disease, it implies a much more diffuse vascular
9 disease as a clinician than someone who doesn't, and
10 therefore, I don't think the SPECT data you have really
11 represents the broad population that you have.

12 I think there is a subpopulation that you have
13 characterized her. So, I am not convinced that the sole
14 mechanism for this entire population is improved perfusion.
15 I think it may be occurring. I don't think that is critical
16 to my impression that this does really improve angina, nor
17 necessary for approval, but I would hate to have the
18 misperception that you are going to have better perfusion in
19 your heart if you have this. You may have improvement in
20 angina, and you may or may not get a better thallium score,
21 whatever that means, for this procedure.

22 DR. HORVATH: A couple of responses, comments to
23 the issues you have raised. First, as far as the SPECT data
24 is concerned, you are correct in that in the meeting last
25 July, the error between reviewers of SPECT data was about

1 1.2, I believe, segments in a 24-segment model, and we are
2 looking at, if I remember correctly, about 8 or 9 segments
3 for these patients that were reversible or that were areas
4 that we treated with the laser.

5 But more importantly, you have talked about the
6 lack of correlation between the angina and the SPECT scans,
7 and I think that, as a clinician, we frequently see people
8 that have severe coronary artery disease on an angiogram
9 that does not necessarily match their symptoms. I think you
10 would find that that is the case fairly often in clinical
11 practice.

12 I think when you are looking at different types of
13 evaluation of angina, symptoms versus an anatomic source or
14 an anatomic method of analyzing their angina, you are not
15 going to see a correlation. In fact, there is a quote I
16 would like to add here to verify this. When distinctly
17 different classes of information, such as symptoms, and
18 anatomic information, such as the perfusion scan, are
19 compared, a measure of one distinct phenomenon is being
20 compared to a measure of a second distinct phenomenon.

21 In this situation, one test can't be considered
22 the gold standard for the other since findings of one test
23 can't overrule the other, and a correlation isn't to be
24 expected.

25 I think that summarizes it very well, and, in

1 fact, Dr. Califf is the co-author on this paper, and I think
2 he will agree that you are not going to be able to get an
3 exact correlation between angina and SPECT data.

4 DR. PARISI: I think you are trying to say that
5 perfusion is improved, and I am just going to take the data
6 and say using the SPECT as the standard for whether
7 perfusion is improved, and looking at the frequency
8 distribution and the change of ischemic segments, I see
9 quite a bit of scatter.

10 DR. HORVATH: I think there is scatter in the
11 data, there is no doubt about that, and if you are talking
12 about -- are you talking about those scattergrams that are
13 trying to correlate the two?

14 DR. PARISI: Yes.

15 DR. HORVATH: I think there is definitely, as you
16 can see, scatter in the data, but I think the other thing
17 that you can draw from looking at those at each of the time
18 points, 3, 6, and 12 months, the majority of the patients
19 treated with the laser were on the improved side, and the
20 majority of the patients treated with medical therapy were
21 not improved, and that's about the only conclusion I think
22 you can draw.

23 DR. PARISI: From the angina score, I agree.

24 DR. CALIFF: Having had my name used, I have to
25 make a comment. I actually very much stand by the quote,

1 but I think the issue here is to the extent that an imaging
2 study is being used as a surrogate or a stand-in for a
3 clinical benefit to the patient, then, when you see a lack
4 of high correlation -- which again is not unexpected -- it
5 seems to me to be an illogical argument to say that we can
6 use one to replace the other, but we also would a priori say
7 that they are not going to be highly correlated.

8 So, I look at the SPECT as nice, interesting, sort
9 of Phase II information that says there is a physiologic
10 rationale for this treatment, but it is really how patients
11 feel that they generally care about. Not many of my
12 patients come in and ask me how their SPECT scan looks. Now,
13 I did see in Houston that there are some highly educated
14 professional people who actually follow serial PET scans for
15 their angina, but most of us can't afford to do that.

16 DR. HORVATH: I think you are absolutely right. I
17 think the fact that the patients are better is the important
18 feature. I think it was an incorrect assumption perhaps
19 when we started this study that there would be a
20 correlation, and that is definitely proven not to be true.

21 DR. CURTIS: We will go with Dr. Friedman and then
22 we will break for lunch.

23 DR. FRIEDMAN: Thank you. Most of the comments
24 that was going to make have already been made. Let me just
25 emphasize a couple of points. One is that I guess it is

1 obvious now that a study that has some problems in design in
2 the beginning that lead to inadequate or missing data, this
3 is what we end up with, and that is struggling to try to
4 come up with an answer.

5 There is no good way, no optimal way of truly
6 answering the question unambiguously when we have as much
7 missing data as we have in this particular study. I was
8 reassured by the numerous analyses that showed the relative
9 robustness of the conclusions despite the various ways the
10 data were looked at.

11 I do think it is very important to look at the
12 data in the way that Dr. Wittes suggested, that is, those
13 particular patients who are in the cleaner part of the
14 protocol.

15 One other question on the analysis has to do with
16 the SPECT data. The analyses that I noticed -- and perhaps
17 I missed one -- had to do with particular defects. Have
18 per-patient analyses been done with the SPECT data, and if
19 so, what do they show?

20 In other words, it works better in some way,
21 because in most of these studies, since the patients are
22 randomized, and not defects, we want to analyze the data by
23 the unit of randomization, that is, the patient, the way you
24 did it with the angina data, for example, was that done in
25 some way with the SPECT data?

1 DR. LEFEBVRE: We looked at the SPECT data on a
2 defect basis. We did not look at the better or worse or no
3 change.

4 DR. FRIEDMAN: I might suggest that because there
5 can be biases. We know that they are not completely
6 independent. One wouldn't expect them to be completely
7 independent, and therefore, I would suggest an analysis on a
8 per-patient basis.

9 DR. CURTIS: We will go ahead and break now for
10 lunch. At 1:15, we will reconvene.

11 [Whereupon, at 12:15 p.m., the proceedings were
12 recessed, to be resumed at 1:15 p.m.]

13

A F T E R N O O N S E S S I O N

[1:25 p.m.]

1
2
3 DR. CURTIS: Just to give you an idea how the rest
4 of the afternoon is going to work, we are going to finish up
5 the panel discussions now. A couple of people haven't had a
6 chance to say anything yet. Once we have gotten through any
7 other panel discussion here, there will be an opportunity
8 for the sponsor to present any other data they have, a
9 chance for the FDA to make any other comments they want, and
10 our open public hearing.

11 After that point, then the rest of the discussion
12 will be only among the panel members. What we will be
13 getting into are the questions that the FDA has posed to us
14 and the voting later on.

15 I would like to start first now with Dr. Altman.
16 Do you have any comments to make?

17 DR. ALTMAN: No.

18 DR. CURTIS: Mr. Jarvis?

19 MR. JARVIS: No.

20 DR. CURTIS: I wanted to make a couple of comments
21 here before we went any further. One of the things that had
22 bothered me about looking at the original submission and I
23 think has been helped somewhat by the current one, and
24 nobody has really talked about it much, but it has always
25 been that issue of the possibility of placebo effect.

1 The fact is you can't help--there isn't any other
2 way to do it, but you can't help the fact that some of the
3 patients--the patients who got treated got a surgical
4 procedure and your control group doesn't. You can't do sham
5 surgeries on human beings.

6 So there is always that strong concern about a
7 placebo effect in patients feeling that their angina got
8 better. I think what has helped a little bit now is that
9 there is some information on the patients past one year.
10 There was some data and some discussions in the panel pack
11 about the fact that a placebo effect could possibly last out
12 that long.

13 But when you start getting information beyond that
14 point and seeing that angina still remains improved, I think
15 it makes me feel a little better about the fact that there
16 may well be a real effect.

17 But I am bothered still by the fact, and some of
18 the people have mentioned it before, things like out of the
19 phase III patients, the patients treated with TMR, that you
20 have got angina data for 78 out of 91 patients and so,
21 therefore, around 15 percent of the patients either were
22 missing baseline or three-month data or something, either or
23 both I would imagine.

24 So there is a fair bit of missing data. The way
25 that has been handled is by trying to tease out, well, out

1 of the ones we have, are the comparable and is this a real
2 result and all that. I still don't quite understand for
3 such a big surgical procedure why you would have that much
4 information missing on patients.

5 We are not talking about two years of follow up or
6 something. I am not sure why you don't know angina status
7 in 15 percent of the patients either at baseline or at three
8 months or both.

9 DR. LEFEBVRE: I think that the reason why we do
10 not have--it is not that we do not have the angina. It is
11 just that the patients were not eligible to receive the
12 angina. We had angina assessment for all patients at
13 baseline. Then, once you go down the study, you start
14 losing a few patients--you start losing patients due to
15 death, due to additional procedures and so on.

16 So those patients become ineligible to get angina
17 assessment. If you take the three-month assessment, the
18 six-month assessment and the twelve-month assessment, we
19 were able to collect 90 percent of the angina data. So,
20 granted, we missed 10 percent. But 90 percent of the
21 possible angina assessment that could be collected, we
22 collected them.

23 The reason for those decreases in numbers is just
24 due to the attrition. Some patients become uneligible to
25 receive that angina assessment.

1 DR. CURTIS: In that TMR group, between baseline
2 and three months, it was 91 possible patients. You had
3 information on 78.

4 DR. LEFEBVRE: Actually, maybe we can show you
5 backup transparency which should address this point.

6 Could I have backup No. 54, please. The slide
7 that you are going to see shows you exactly what happened to
8 the patients throughout the twelve-month study.

9 [Slide.]

10 On the left-hand side of the view-graph, you have
11 the 91 TMR patients at enrollment. Then, between enrollment
12 and three-month follow up, you had 6 patients who died and 3
13 patients who received an additional intervention. That led
14 to 82 TMR patients eligible for an actual angina assessment.

15 Of those angina assessments, we collected 79.
16 Therefore, we lost 3 patients. If you go down, all the way
17 down to twelve months, you have the numbers. This part of
18 the slide here shows you the cumulative total at baseline,
19 three months, six months and twelve months.

20 These are the actual number of follow ups
21 conducted. These are the follow ups that we missed. This
22 is what we missed. Everything else here, this is not our
23 fault. This is just due to normal attrition because the
24 patients become uneligible for additional follow up.

25 DR. CURTIS: Actually, I find that very helpful.

1 You certainly assess somebody who has died. It shows that
2 it is not just missing data, that there are reasons why it
3 is not there. I think that is fine. I am glad that you
4 showed that.

5 I don't know. Some of the discussion today was
6 about primary and secondary endpoints and about using SPECT
7 data versus the patient's anginal history. Dr. Califf had
8 mentioned that he cares more about what the patients feel
9 better than their SPECT. I think that makes sense but,
10 again, the issue of the possibility of placebo effect. It
11 would be nice if there were something that the patient had
12 no control over that you could hang your hat on as being a
13 difference in effect.

14 The SPECT data certainly looks promising. It is
15 all in the right direction. The less than perfect
16 correlation between the SPECT and angina assessment is a
17 little bit bothersome but, if and when we learn what the
18 mechanism of this thing is, it may be that the SPECT is not
19 relevant to what is going on. I'm not sure.

20 I don't really have any other comment to make
21 about than that. It is just I was curious. I don't have
22 any other comments right now. Do you have the other data
23 that you were mentioning ready?

24 DR. LEFEBVRE: We are actually working on it right
25 now. We did not bring it with us.

1 DR. CURTIS: Where is it?

2 DR. LEFEBVRE: Well, it is coming from Boston.

3 Some of the analyses that were suggested by Dr. Wittes are
4 being done right now because we did not do them, and the
5 other data is being faxed right now.

6 DR. CURTIS: Okay. Anybody else on the panel have
7 any other comments they want to make now, anything they
8 didn't get to say the first time around.

9 DR. CALIFF: Just one more technical question
10 about the measurements you made. Perioperative MI--because
11 you showed this difference in non-fatal infarction rates in
12 follow up. What was the definition of perioperative MI?
13 Did you measure enzymes in all patients?

14 DR. LEFEBVRE: There was no set requirement for
15 the definition of the MIs. All the adverse events were
16 reviewed by the Safety Committee to look at them on a global
17 basis.

18 DR. BOYCE: Electrocardiograms were used more
19 frequently than CPKMP assessment.

20 DR. CALIFF: That was true in follow up, too?

21 DR. GIBSON: Yes. Mike Gibson, Harvard Medical
22 School. My trip here was paid for today. We did review all
23 these events, as the Data Safety Monitoring Board. We used
24 criteria from the TMI studies, in fact, the case report
25 forms from the TMI studies.

1 Where we did have CK data available, it was five
2 times the upper limit or 50 percent increase over the
3 preoperative CK. And, when there was EKG data also, we
4 looked for new development of Q waves.

5 DR. CALIFF: What percentage of patients had CPK
6 data at the time of surgery?

7 DR. GIBSON: I can't tell you right off the top of
8 my head.

9 DR. CALIFF: Was it high or low, would you say?

10 DR. GIBSON: I would say it was moderate. We
11 tried to get narrative summary data wherever we could.

12 DR. CALIFF: It is just a point in consideration,
13 much like the treadmill data. I think if you don't look at
14 the time of the surgery, then you compare follow-up MI
15 rates--it definitely is not negative data that is shown, but
16 I don't think it is definitive by any means, either.

17 DR. CASSCELLS: I want to follow up, if I may, on
18 the issue of patient selection. As with any device or drug
19 or operative technique, initially there is a lot of
20 variability and a lot of confusion and, over time, we
21 understand more and more about it.

22 With bypass surgery, I remember very well when a
23 low ejection fraction was a contraindication to bypass
24 surgery. Now, of course, we know that the largest relative
25 and absolutely benefits are derived from operating on those

1 patients with an impaired left ventricle.

2 So we learn more over time. Of course, the faster
3 we can do that, the better. I am sure you would agree, we
4 don't want to leave any stone unturned and any opportunity
5 not to optimize the patient selection.

6 In the history of most operations and most
7 medications, there is an offsetting of patients who are
8 harmed and patients who are helped and it takes a long
9 postmarket surveillance period to figure that out. So I
10 would think it would be very, very helpful if, today or
11 subsequently, you could supply the following information.

12 It depends on how well computerized your database
13 is whether you can get it to us today, but I think it is
14 critical to begin to get an idea what predicts a beneficial
15 outcome whether measured by angina, survival or SPECT data.
16 I would suggest a grouping in the following clinical
17 categories: one would be the patient's preoperative
18 condition, the angina class, Canadian Cardiovascular
19 Society; the ejection fraction; any angiographic predictors;
20 the degree of congestive heart failure either measured by
21 the New York Heart Association or, perhaps, treadmill time;
22 something about right-ventricular performance; the total
23 burden of peripheral vascular disease; the creatinine and
24 urinary protein; presence of diabetes, severe lung disease,
25 ventricular tachycardia, and depression.

1 I will happily repeat them if I have spoken too
2 quickly. I think these are very helpful in culling out a
3 group that could really benefit and making sure we don't
4 harm anybody.

5 Then the medications are also critically
6 important. In all your deaths, and I have read every death
7 last night and this morning, the majority have almost
8 nothing about the medications. I want to emphasize that the
9 medications are life saving. We are not in an era anymore
10 where medications are considered palliative and surgery is
11 considered life saving.

12 The coin is almost completely flipped. It
13 behooves you, and it is your obligation, to tell us more
14 about the medical therapy. I want to give you a little list
15 here of the medications I would like to hear about. I would
16 like to know who was on aspirin, who was on heparin, who was
17 on nitroglycerin, beta blocker, diclopidine, a statin drug,
18 a calcium antagonist or a digoxin.

19 I am not saying all these drugs help. The digoxin
20 and the calcium may be harming some of these patients but
21 they may impact arrhythmogenic effects of the procedure and
22 so forth.

23 The data from Rush suggests that specific centers
24 or specific procedures at those centers can make a big
25 difference. The intraaortic balloon pump may be

1 underutilized. It may be that within your group, there are
2 some centers doing much better and maybe the balloon pump
3 would be a candidate for something that would help things.

4 I would like to see that data, who got a balloon
5 pump and how did the different centers do. You can mask
6 them. If there are some centers that are demonstrating a
7 learning effect and others that just don't seem to learn, I
8 think that is important. That would affect some of the
9 restrictions that might be put on it.

10 Some of the surgical issues are important. It
11 sounds as though there is not a good relationship between
12 the number of lesions induced and the outcome. Now, Dr.
13 Weintraub and I were talking about this. It is not a simple
14 thing in the beating heart to tell the areas that are
15 ischemic and the areas that are not.

16 Severe ischemia, of course, is dusky or cyanotic.
17 It might not be moving well, but it is a difficult visual
18 estimate. I presume that the surgeons involved are trying
19 to drill the holes in the areas that are ischemic or,
20 perhaps, some select border zones, or there may be sort of a
21 random pattern.

22 But surgical technique has got to figure in here
23 importantly. If you haven't done an analysis among your
24 surgeons about exactly how it was done, analogous to the way
25 one does this kind of thing in coronary-bypass surgery, then

1 it is a little bit too random.

2 The location, the number of holes, the use of
3 cardioplegia, and so forth, I think all of that would be
4 very helpful. The balloon pump. Oh; and I forgot some
5 medications. I would like to know if they had milrinone or
6 amrinone or dopamine or dibutamine, diuretics, converting-
7 enzyme inhibitors, angiotensin-2 receptor blockers and
8 antibiotics.

9 When you go through in this kind of detail 100
10 patients, you come up with a lot of spurious correlations.
11 It is called data dredging or post-hoc analysis. It really
12 is something, though, that would generate hypotheses with
13 which to analyze future patients.

14 I think it is very important. We have a technique
15 here that is leaving a lot of people a little bit uncertain.
16 We are talking about possibly allowing a technique that we
17 exclude unstable angina patients but would presumably be for
18 people who are miserable. So a person's got to have so much
19 angina that they are willing to go to the operating room and
20 yet they can't have unstable angina or they have a high
21 operative risk.

22 So we are already trying to define who is going to
23 benefit. We don't have enough data. I think we need to see
24 a little more systematic data on that.

25 Thank you.

1 DR. CURTIS: Any other comments or questions from
2 any members of panel? If you have any other questions you
3 want to ask the sponsor, this would be a good time to do it.
4 Any questions for the FDA?

5 DR. WEINTRAUB: Again, I don't know if, under the
6 new rules, whether this is proper, just for my own
7 edification. Can you use this procedure in heparinized
8 patients?

9 DR. BOYCE: Yes; you can.

10 DR. WITTES: Is part of our charge to--some of the
11 things that are in here are estimates of effectiveness and
12 so forth. Is that part of our charge to be comfortable with
13 the estimates of what the degree of effect is?

14 DR. SPYKER: We want you to be comfortable. But,
15 fundamentally, each of these decisions is a risk and benefit
16 decision. Sort of our comfort depends on how important we
17 think the benefit is to the patient. So it is a public-
18 health decision and we are asking you to help us, or
19 recommend a conclusion for.

20 Does that answer your question?

21 DR. WITTES: I guess the question really pertains
22 to the magnitude of effect. One of the things we are
23 hearing is that there are a lot of exclusions, post-
24 randomization exclusions. Now, I would not have taken out
25 the people who hadn't died. I would have measured their--

1 even if they had had a post-randomization procedure, I would
2 have included them as part of the analysis.

3 So when I try to look at what is the effect, my
4 estimate is different from the estimate in here. So the
5 question I am asking you is when we make a judgment, is the
6 judgment the estimate of effect that we see in the book or
7 is the estimate the estimate that we would have made if we
8 had analyzed the data differently.

9 DR. SPYKER: Your job is to see the truth. Truth
10 always has confidence intervals in my life, at least. Maybe
11 what you are reflecting is the confidence interval is a
12 little wide for you. That is a tough call.

13 DR. STUHMULLER: I would like to add a
14 clarification to that. In terms of when the panel votes,
15 you need to make a decision based on what is in the Federal
16 Food, Drug and Cosmetic Act. Within the Act, safety is
17 defined as reasonable assurance based on valid scientific
18 evidence that the probable benefits to health under the
19 conditions of use outweigh any probable risk.

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

24 So that is how you are being asked to evaluate
25 safety and effectiveness today. Does that answer your

1 question?

2 DR. WITTES: Yeah. That's great.

3 DR. FERGUSON: May I ask one question also of the
4 FDA. I am still hung up a little bit on the labeling
5 aspect. Our responsibility relates to that. Are we being
6 asked to approve this device for what it says there, stable
7 angina, and that's it?

8 DR. SPYKER: This is sort of a chicken and egg
9 problem to me. I feel like I have been burned when I try to
10 say to a panel, "Let's first figure out what it is best used
11 for and then decide whether it is okay for that."

12 DR. STUHMULLER: I would like to respond to that.
13 In terms of the Food and Drug Administration Modernization
14 Act, you have to make your decision based on the labeling
15 and does the data support the proposed indication for use.
16 That is what the law requires. Congress is very clear about
17 its intent. That is what the Agency is responsible for
18 making a decision on now.

19 DR. SPYKER: Right. But, as I was saying, really
20 what the intended use is is part of our task. We made a
21 cut. What we put in the panel pack was what the team from
22 the sponsor and the review team here thought was a
23 reasonable cut.

24 You will see, even in that, we put some things in
25 parentheses. So we, the Agency, the public-health

1 responsibility is to approve a device that is safe, has as
2 risk-benefit that you think is appropriate for a particular
3 intended use.

4 The point of the FDAMA was to say, FDA, you are
5 not supposed to sort of pretend you think things might be a
6 problem. If they are not on the table or not in the
7 intended-use statement, then don't get too worked up about
8 it. That was the intention of the FDAMA.

9 I think what we are talking about is a little more
10 fundamental. I view this as very much a team activity to
11 figure out what is the most appropriate labeling. To me,
12 labeling is a very important part of the process.

13 DR. CURTIS: And we will go through each step of
14 that, too.

15 DR. WITTES: Can I go back to the issue about
16 classification because this is clearly where I am hung up.
17 This is the agreement between the independent surveys, site
18 assessments, on page 104. One of the concerns that I have,
19 and I may not have expressed this well enough, is that if
20 the nature of the misclassification differs between the TMR
21 and the medical group, then you could have a bias in the way
22 that one counts the number of events.

23 Now, this isn't, of course, the table that I have
24 asked for but I think there is enough in here, and I think
25 you are right, there is information that is relevant. If I

1 am reading this right, the half of the MM group was
2 classified precisely correctly and only 16 percent of the
3 TMR.

4 So let's get to what that means. That means to me
5 that there is something about the process of the way in
6 which the on-site people were--presumably, the independent
7 evaluators, since they didn't know who was treated how,
8 should be assessing those two groups independently and the
9 same.

10 So any deviation, I would think--and this is what
11 I need your help for--would be a bias at the level of the
12 site which would be suggesting a different way of
13 classifying angina depending on what the treatment was.
14 Now, I realize these are tiny sample sizes. That may be
15 what the issue is.

16 DR. LAVIN: Phil Lavin. We did look at things far
17 beyond what was presented in the briefing document. We
18 looked at the variation among sites. We looked at the
19 difference in time between when they had their month-12
20 visit and when they were surveyed. There are so many
21 sources of variation there, I think it would be impossible
22 to categorically summarize and pick apart and find a problem
23 with the sample size that we have.

24 I would just like to reassure the members of the
25 panel and the audience that we did look at the 0s and the 1s

1 and we looked at that 0 to 4 against the 0 to 4 display. I
2 feel comfortable as a statistician here and someone who has
3 presented to panels a number of times before that there is
4 no conscious bias there and the data stand tall in terms of
5 not representing any noteworthy bias nor representing
6 anything that would refute the data that has been presented
7 here today.

8 DR. WITTES: The issue isn't, necessarily,
9 conscious bias. The issue is really conscious or
10 unconscious. I am thinking of unconscious bias.

11 DR. LAVIN: We have no statistical power to
12 conduct or discriminate with the number of study sites that
13 were there and the number of subjects that were there. I
14 think that it is really an exercise in trying to confirm the
15 overall general trend which, I think, is the big picture
16 here. And the big picture, from our perspective, is that
17 there is still, on the average of five months after the
18 twelve-month outcome, we still have a statistically
19 significant difference in a smaller subgroup of subjects
20 with respect to the treatment advantage that we initially
21 set out to look for.

22 DR. CALIFF: May you can stay up for just another
23 second. If you just took on page 104 in that table, the
24 62 percent of the patients in the TMR group who were off by
25 one class, can you tell us how many went up one class and

1 how many went down one class?

2 DR. LAVIN: I think, just giving you a rough
3 impression, it is around 35 versus, like, 27. So 27 down
4 and 35 up. It is pretty much a net wash.

5 DR. CALIFF: You told us you did produce a grid of
6 the four classes, X axis and Y axis, the thing that we are
7 all used to looking at for these kinds of things.

8 DR. LAVIN: Right. But we don't have that here
9 today.

10 DR. CALIFF: If you are getting other data from
11 Boston, could it be faxed down so we could look at it?

12 DR. LAVIN: It may take some time because we are
13 having trouble getting some faxes from there.

14 DR. CALIFF: The fax machine doesn't work? I have
15 one other procedural question because I think we are all
16 getting a little tired here. It relates to Janet's question
17 about what reasonable evidence is. There is no guidance--
18 whatever we think, looking at the data, there is no
19 statistical guidance as we get in other branches of the FDA?
20 So we don't need a p-value of less than 0.05 for primary
21 endpoint of some--it is just whatever we eyeball and say,
22 "It looks okay?" That is adequate?

23 DR. YIN: Are you looking for the FDA statistician
24 again? We will have our statistician respond to--

25 DR. CALIFF: I am asking whether there is guidance

1 from the Agency about statistical criteria--

2 DR. STUHLMULLER: Dr. Califf is a member of a
3 panel in CDER. I think the question he is trying to get at
4 is that, in CDER, there are statistical guidelines that are
5 used in the evaluation of products whether they are approved
6 or not. He is asking in a similar way, do we use
7 statistical guidelines in the same way in Devices. Is that
8 the question you are asking?

9 DR. YIN: May I have Dr. Greg Campbell answer that
10 question.

11 DR. CAMPBELL: This is Greg Campbell, Director of
12 the Division of Biostatistics in CDRH. The simple answer to
13 your question is that there is no statistical guidance of
14 the same nature that the Center for Drug Evaluation and
15 Research has.

16 DR. SPYKER: I, too, have worked in Drugs some and
17 my impression is that we have very much the same kind of
18 overall guidance. We tend to not consider bringing the
19 panel things that don't reach the usual 1 in 20 or p less
20 than 0.05. We try hard to do good science in terms of
21 defining the endpoints and holding ourselves and the
22 sponsors to the same standards.

23 I don't see any fundamental difference in how we
24 approach it or what the cutpoints are.

25 DR. CALIFF: I think we may disagree on that.

1 DR. PARISI: Could I make a point. In fairness, I
2 think, to this analysis, I don't think you can conclude from
3 this table, F1, B6, really, whether there is a bias in the
4 medical management group because this MM group of 9
5 patients, these patients never got off the dime. It is like
6 taking angiograms, and we will say how many are 100 percent
7 occluded.

8 When we look at 100 percent occlusions, everyone
9 agrees. If you look at 80 or 90 or 70 percent, you get
10 scatter. If you are class 4 angina, you have angina at
11 rest. If you have angina at rest, it is pretty easy to tell
12 you have angina at rest.

13 It is when you get into this 1 block, 2 block, 1
14 flight stuff that you are going to get the scatter. There
15 are very few patients in this whole group, so I don't think
16 you can use the MM group and say they were analyzed
17 differently from the TMR group. In fact, I think the XO
18 group which is really part of the MM as intention-to-treat,
19 and if you want to say intention-to-treat is the way to do
20 it, they are more comparable to the TMR group.

21 So I don't think we can use this. I think we need
22 to see the four-by-four table.

23 Janet, is that fair?

24 DR. WITTES: That is very fair. I did a chi
25 square and it goes 7.4 which is highly significant. But

1 that makes very good sense and I guess we would need to see
2 it.

3 DR. CURTIS: I guess one point of clarification,
4 though, is that we wouldn't be able to have any new data
5 presented by the sponsor today that wasn't included in the
6 panel pack; is that correct?

7 DR. SPYKER: I would judge this to be simply an
8 appropriate representation of the data which was summarized.
9 I think that is not a stretch. Do we want to see that table
10 for each of that groups? Do you want to see that four-by-
11 four grid or do you want to see one for the TMR and one for
12 MM and maybe one for XO; right? So you would really like to
13 see three four-by-fours?

14 DR. WITTES: At least two.

15 DR. SPYKER: At least two? MM and TMR.

16 DR. WITTES: Yes.

17 DR. STUHMULLER: I would like to interrupt for a
18 second and ask Nancy Pluhowski to clarify this issue,
19 please, from a procedural point of view.

20 MS. PLUHOWSKI: I'm Nancy Pluhowski, Panel
21 Coordinator, Office of Device Evaluation. We do have it as
22 a policy that we do not have data presented live that the
23 panel and the FDA staff has not had an opportunity to look
24 at in advance.

25 DR. CURTIS: Does that include--I think the intent

1 here was that it is the same data looked at in the different
2 way.

3 MS. PLUHOWSKI: Exactly. It is a reanalysis of--

4 DR. CURTIS: And that is not permitted; is that
5 what you are saying--or not usually done?

6 MS. PLUHOWSKI: I am saying, in this setting,
7 right now, I think it may be difficult to assess.

8 DR. CURTIS: Okay.

9 DR. LAVIN: I do have some of the results that
10 were faxed to us. We got the fax machines to work. I want
11 to share with you the results of the first half of the
12 subjects.

13 DR. CURTIS: They just said no.

14 DR. LAVIN: Is the answer no?

15 DR. STUHLMULLER: The answer is no.

16 DR. LAVIN: Okay.

17 DR. CURTIS: Thank you.

18 DR. SKORTON: Could I take a crack at a user's
19 view of the Modernization Act. I don't work for the FDA but
20 I have a slightly different view. Tell me if this is way
21 off. My view of the Modernization Act and the issue of the
22 indications and so on is that the point of this change was
23 to not make the approval process a moving target for
24 industry so that whatever they brought in, they would have a
25 chance to look at and you sort of go or not go, and that the

1 point of not bringing up more data is that they don't have a
2 chance to look at it, the FDA doesn't have a chance to look
3 at it.

4 So I understand that part. It is also the case,
5 isn't it, that if the panel feels unable to have an approval
6 action based on not enough data, that is an action the panel
7 can take. So it is very straightforward. The panel can
8 vote up or down approval based on what is here. If the
9 panel feels strongly enough that it needs more data, then
10 that buys another meeting for the process.

11 Is that correct?

12 DR. STUHLMULLER: Dr. Yin, do you want to comment
13 on that, please?

14 DR. YIN: I would agree that if this data is very
15 difficult to analyze--I don't know if you get four-by-four,
16 whatever--if you can make a decision. If you can make a
17 decision that fast, maybe our statistician can also. But
18 that is the kind of data that I am unwilling to make our
19 statistician--say, well, you have got to do it just because
20 our panel can't.

21 But here is our chief statistician who reviewed
22 this PMA. I am willing to say, let's go for it. If he
23 says, "Well, I'm sorry, Lillian, you go review it yourself,"
24 that is what you can--

25 DR. STUHLMULLER: We are going to take a ten-

1 minute break and sort out these procedural issues.

2 DR. YIN: Let him see if he is willing to do it.

3 DR. STUHLMULLER: We are going to take a ten-

4 minute break to sort of out procedural issues.

5 [Break.]

6 DR. CURTIS: The data, as I understand it, is to
7 answer Dr. Wittes' question from before. So it is a
8 clarification of the data that was already discussed and is
9 in the PMA. This is not new data.

10 Obviously, none of us has had a chance to see what
11 you are going to show. But we are looking at it as a
12 response to her question. Once we have seen the data,
13 though, we have no way of being absolutely sure of the
14 accuracy of the data and the FDA will need to check into
15 that later on.

16 But go ahead and show what you wanted to show.

17 DR. LAVIN: Phil Lavin. The question on the floor
18 that Dr. Wittes raised was regarding to the effect of pre-
19 rule change in protocol where patients were allowed to
20 switch before six months versus when the protocol rule had
21 been enacted which prohibited switching earlier.

22 What we did, in order to produce an analysis for
23 this meeting, is to break the subjects up into the first
24 half of the study versus the second half of the study. We
25 called the first half of the study, for the purposes of this

1 presentation, "early," versus the second half which we are
2 going to call "late."

3 What I have had the troops do back in Boston is
4 pull together the worst-case analysis which is the one that
5 the statisticians would always seem to favor. I have looked
6 at the results for three months, six months and twelve
7 months in what I am going to present.

8 The data, essentially, show no difference between
9 the early and the late phases of the study. For example, at
10 three months, there is a 56 percent success rate for the
11 angina score; in other words, an improvement by two or more
12 scores for TMR versus 0 percent for medical management
13 early. This is at three months.

14 It holds, in terms of being 0 percent and
15 46 percent at six months. It drops to 0 percent and
16 45 percent at twelve months. That is the early first half
17 of the study.

18 The second half of the study is quite similar, as
19 I just mentioned. It is 8 percent for medical management,
20 57 percent for TMR at three months. It is 6 percent and
21 56 percent for six months and it is 8 percent and 51 percent
22 at twelve months.

23 Thus, I would conclude, as I am sure you folks
24 would, also, that there is essentially no difference between
25 the performance of patients in the first half of the study

1 relative to the second half of the study. If anyone is
2 interested in looking at the output here, I do have that
3 available.

4 DR. CURTIS: That answers your question? Any
5 other panel comments or questions?

6 If the sponsors would step back from the table,
7 now, please. Does anyone from the FDA want to respond to
8 what was just presented? All right.

9 At this point, we are supposed to have a
10 discussion among the panel which is going to be in
11 preparation for a vote and for answering the questions that
12 were posed to us.

13 DR. STUHLMULLER: Just procedurally to clarify
14 again what the FDAMA--what will happen now is the panel
15 discussion will take place amongst the panel and, at the
16 completion of the panel discussion, the sponsor and the FDA
17 then have the opportunity to address any questions that were
18 raised amongst the panel.

19 Then, at that point, we will have the second open
20 public hearing and then the vote will take place after the
21 open public hearing.

22 DR. CURTIS: Dr. Califf, why don't you start.

23 DR. CALIFF: I guess the summary of my feelings at
24 this point--I feel a bit trapped, I think, by the standards
25 that I am accustomed, the study is still fatally flawed. On

1 the other hand, there appears to be a different set of
2 standards for devices than for drugs which is where I have
3 done most of my work.

4 I think it is also just as fair to say that all
5 the evidence goes in the same direction, that we have the
6 magnitude of the evidence of fuzziness, the uncertainty, the
7 very small sample size, in my opinion, to assess the safety
8 of a device for a disease which affects 8 million plus
9 people in the United States and could be widely used.

10 All these things are very, very concerning. But,
11 on the other hand, relative to where we were at the last
12 meeting, we have made a tremendous step forward, I think
13 given what I regard as fatal flaws in the study design,
14 about the best effort has been made that could be made to
15 salvage the data.

16 So I am interested in what other panel members
17 feel about the balance of the evidence at this point. I
18 doubt if any discussion is going to shed any further light
19 on anything other than trying to come to a level of comfort
20 in people's minds.

21 DR. CASSCELLS: I guess I am next. These
22 procedures are hard to evaluate. I was struck, reading a
23 paper in Circulation, a journal we put out in Houston three
24 or four months ago--I can't remember where it came from, but
25 they looked at spinal anesthesia, compared it in a

1 randomized trial against bypass surgery. The spinal
2 anesthesia came out better in terms of symptoms in left-
3 ventricular function.

4 It is something very important that the nervous
5 system does. This is a large randomized trial and I was
6 very surprised. Of course, our anesthesiologists said, "Oh;
7 we told you so." I can't see putting epidural catheters in
8 people and having them wander around, but it was the same
9 kind of patient population we are talking about today, very
10 sick patients with multi-vessel disease.

11 You all presented data suggesting that there was a
12 large denervation effect. I think that is very important.
13 The animal data are pretty conclusive that these holes close
14 off. I have been involved in angiogenesis research for
15 about twelve years and the amount of angiogenesis you get
16 from a little injury is very small. It doesn't last.

17 So I don't believe for a second that there is an
18 angiogenic effect here. It is possible that, combined with
19 vascular endothelial growth factor or fibroblast growth
20 factor, as Dr. Weintraub alluded to, that this is a platform
21 for future and hybrid therapies, but we are certainly not
22 asked to address that today.

23 Looking at the data, and assume the data is
24 exactly as it is represented, I have to conclude that this
25 procedure works for some people. I think the key thing, as

1 I mentioned a minute ago, it is important over time to
2 figure out for whom this is a life-enhancing or life-
3 prolonging procedure and for whom it may be a morbid
4 procedure.

5 I think it is critical, as we did with the York
6 Shiley valves--or, as you all did; I wasn't on the panel--
7 and Acufix J Lead and things like that, that if this is
8 approved, and I think it should be, that there be close
9 monitoring. I would think it very important that every case
10 be registered for some time, that the follow up be complete,
11 none of this 75 percent follow up, and that there be a
12 complete dataset with proper attention to the physiological
13 factors, and even the psychological factors, that may impact
14 the outcome, and certainly all the medications.

15 One other thing I think would be very important,
16 and that is to protect the patients with a standardized
17 consent form. It is very easy to talk a patient into
18 surgery. It is very easy to talk them into a medication.
19 Many times, I have seen the enormous influence the surgeons
20 have on my patients. My father is a well-know surgeon and
21 developed arthroscopy, the first person in the world to do
22 it.

23 I remember the early days of that. I remember how
24 important it is to protect the patient. I think it is
25 critical that a consent form be standard, somehow, and that

1 patients be told that there is no data of life prolongation.
2 There is a strong inference which is made to many patients
3 by surgeons that if this operation isn't done, the leg will
4 fall or, or if this operation isn't done, the patient will
5 not go back to work or will not live.

6 When you say to somebody, "We have got to
7 revascularize you," or, "If we do this operation, it will
8 bring more blood flow to the heart," if you say nothing
9 about the life-expectancy, the patient infers that. I think
10 that is something we want to talk about.

11 That is all I have to say.

12 DR. CURTIS: Dr. Weintraub, any comments?

13 DR. WEINTRAUB: Just a brief one. As a
14 practicing, humble cardiac surgeon, I am interested in
15 cautions, in particular the issue of unstable angina. That,
16 somehow, should be in the labeling. The second issue, and
17 again, we are sort of treading on grey ground here, or in
18 the grey area, is any kind of cautionary note or something
19 about adjunctive therapy; that is, the use of laser
20 revascularization with coronary bypass because people are
21 going to try it.

22 The experience of the investigators should be
23 somehow--should deal with that in some way. That's all I
24 have to say.

25 DR. CERQUEIRA: Again, I would like to make a

1 couple of comments about the incomplete data on a fair
2 number of patients. I think that there was a fairly good
3 explanation for the angina classification and, similarly, if
4 we look on page 147 and 148 on the original material that
5 was distributed, there is a fairly good breakdown of
6 eligibility for SPECT studies and why studies were either
7 not done or why they were not interpretable.

8 There were a total of 80 percent of the patients
9 got in the studies which, in the studies that I have had
10 experience with where you are trying to get these very
11 difficult endpoints, there is a fairly high enrollment rate.
12 Then you can see that it drops down to the 70s when discs
13 could not be read in 33 patients, technical patient problems
14 in another seven.

15 I agree with you, from a statistical perspective,
16 it would very important to have all those datapoints, but my
17 interpretation is that there was not an intentional bias to
18 include or exclude patients.

19 For those of us who work in this area, this is a
20 reasonable set of data. I think the angina information
21 which is there supports the fact that there is benefit and
22 the nuclear data with the selection bias does also support
23 the fact that there is some improvement in perfusion.

24 I agree with what Dr. Parisi said that it would be
25 nice to have had that reproducibility data, and there can be

1 some variability. If that variability was there, I would.
2 have expected it to have more scatter in the data and I
3 would have been more surprised if there had been an effect,
4 if it was all due to scatter, the fact that there was sort
5 of systematic trend, to me, suggests that there was
6 improvement in perfusion.

7 But I would agree that this data is minimally
8 flawed, but I think flawed in a way that those of us doing
9 clinical research could find acceptable. I would also
10 recommend that an ongoing registry to try to look at some of
11 these mechanisms be continued to try to address some of
12 these points.

13 Those are my only comment.

14 DR. CALIFF: Manuel, it is really not a
15 statistical issue, I don't think, the issue of what you do
16 with the patients who didn't have the data ascertained. It
17 is really a question of, if the purpose of a study is to
18 tell you what is going to happen to the next patient, you
19 either use the treatment or don't use it.

20 What do you do with the patients that didn't have
21 an endpoint measured? Do you pretend like they never
22 existed? How do you handle that?

23 DR. CERQUEIRA: Al Holstrum, who has been involved
24 in a lot of these trials, and we have tried several
25 different approaches in Seattle where, if a patient died

1 when you couldn't measure a value, we would give that
2 patient the worst score that was gotten by any patient in
3 the study.

4 That is one approach that can be taken and I think
5 it would be possible to perform that analysis with this
6 dataset. I think that would begin to address some of those
7 issues as well.

8 DR. VETROVEC: No major comment. I think this
9 procedure decreases septums in certain patients. I think
10 the critical issue is going to be labeling and appropriate
11 utilization.

12 DR. SKORTON: I empathize with Dr. Califf and
13 share his concern about the softness of the endpoints. I
14 think that I also empathize with him, although I wouldn't
15 want to attribute this to him--I think that I will gain a
16 little more confidence in a lot more reevaluation of data.

17 I think, with all due respect to the statistical
18 point of view, it is more an experimental design, study-
19 design, issue than a post hoc statistical-analysis issue. I
20 think there are going to be limitations on how much more we
21 can get.

22 And there are questions that remain. So I think
23 we really have three choices; either approve it as it is,
24 require a brand-new study design or approve it and insist or
25 strongly suggest to the agency that there is postmarket

1 surveillance and outline what the postmarket surveillance.
2 should be. It is the third course of action that I am going
3 to be supportive of approving it, but with some specific
4 postmarketing surveillance.

5 MR. JARVIS: No comments.

6 DR. ALTMAN: My concerns have to do with the
7 contraindications, but I can wait until we go down these
8 questions.

9 DR. PARISI: Obviously, I think the panel to this
10 point has brought up the mixed feelings that can be
11 generated by this data. It is not a double-blind study, but
12 you are never going to be able to do a double-blind study on
13 a surgical procedure. I think you have to get that out so
14 the standards that you would like to have for a study that
15 is double-blind, placebo-controlled, like a drug study,
16 aren't going to be there.

17 I think investigator bias is going to become a
18 problem. We did the ACME trial which was the first trial
19 comparing balloon angioplasty the medical management and I
20 would say that that trial, under this scrutiny, would say we
21 shouldn't be doing balloon angioplasty on patients with
22 angina.

23 So I have trouble with the rigidity that we have
24 to put on drug studies which are applied across populations
25 of millions, many millions. This is a very select

1 population. I think the labeling should reflect the
2 selectivity of the population on which the data was
3 ultimately based.

4 These patients, 92 percent of them had a previous
5 operation. They all had class 3 and 4 chronic stable
6 angina. They are very highly selected. You know if you
7 deal with that kind of patient that you have to be pretty
8 much of a tiger if you have something that you think can
9 help them, based on the previous experience you have with
10 other patients, to just refuse them a procedure.

11 So although all the elements of this can be
12 challenged, I think the totality of the data would warrant
13 an approval but with the caveats that Dr. Skorton suggested.

14 DR. WITTES: I believe that we are not talking
15 about intentional bias. We are not talking about--I think
16 that everybody knows that surgical trials cannot be blinded.
17 The issue for me is that we did ask a question about
18 classification the last time because we were concerned that
19 the endpoint that we were going to be using, which was
20 angina, had the potential for being misclassified and had
21 the potential for being misclassified differentially in the
22 two arms.

23 In the absence of seeing those data, these data
24 that I see don't tell me that the procedure is working. I
25 think that you have got data available and that you can look

1 at it and, perhaps, once you look at it and the FDA can see
2 it, maybe those concerns that I have would be allayed. But,
3 in the presence of the data that I see, my concerns are not
4 allayed.

5 The other issue is I really don't believe that we
6 should analyze experiments differently if they are in
7 devices or if they are in drugs. The interpretation may be
8 different, the way we look at, the way we understand the
9 biases. But we don't jump from one paradigm to another.

10 DR. FERGUSON: That last comment is about the
11 hardest pill in the world for me to swallow as a surgeon
12 because I have been in many studies on heart valves and
13 other devices that we use in cardiac surgery. I sit at a
14 viewpoint where I envy the pure, double-blinded studies that
15 everybody talks about and touts that are done in the medical
16 sphere.

17 So that is all I will comment on that.

18 I want to say that my feeling is that we came back
19 with our best shots from last year and listed a number of
20 concerns. The issue to me is whether those concerns were
21 answered adequately by the presentation today. I think that
22 is the way we must judge this. We can't say, "But, you
23 didn't do this and you didn't do that," and those particular
24 issues were never on the table at our last meeting.

25 So, speaking for one panel member, I would say

1 that I think that the manufacturers have done a tremendous
2 job--that is my feeling; a tremendous job--in answering the
3 concerns. I have all of the worries and concerns that Dr.
4 Wittes and the rest of them have demonstrated here, but I
5 would leave those concerns to those experts--my feeling,
6 again, goes with the individuals on the panel who said that
7 labeling will be all-important because the machine is going
8 to be used in many, many ways that it was not intended to be
9 either by the company or by this panel or the FDA.

10 So that is my feeling.

11 DR. CALIFF: I can't let the discussion stop with
12 the sort of statement that what those of us who are rigid is
13 talking about is whether studies should be double-blinded.
14 My concern has nothing to do with double-blinded. There are
15 a lot of drug studies that can't be double-blinded. The
16 issue is really how you design studies and things that you
17 do in the context of an unblinded study to try to be
18 unbiased in the assessment, intentional or unintentional.

19 Then, finally, at the end of your day, you have
20 measured your endpoint and the statistical inference that
21 you draw has nothing to do with whether the study was
22 blinded or not. The statistical assessment has to do with
23 how you deal with things that happen after randomization,
24 how many missing endpoints you are willing to accept along
25 the way.

1 I just can't accept that because it was a device
2 that was studied that, somehow, we accept the p-value that
3 could be anywhere between 0.01 and 0.45 which is probably
4 what you get if you counted the missing data one way or
5 another.

6 It seems to me that we are not really, again,
7 talking about whether the study is double-blind. We are
8 talking about when you look at the endpoints, what
9 statistical inference do you draw. I think it has to be, or
10 at least I have to say, that beginning with making sure that
11 investigators don't have a vested interest in the product,
12 doing everything you can to make sure the assessment is as
13 close to blinded as it can be.

14 Those who do the procedure don't have to do the
15 assessment. Measuring patient benefit and preventing
16 unnecessary crossover when the device, itself, or the
17 treatment is experimental are just fundamentals of how you
18 do studies. That is what makes me relatively uncomfortable,
19 not that I would want this to be a 40,000-patient blinded
20 study.

21 It is just that there are some real fundamentals
22 that are taught in many medical schools today that were not
23 taken into account by this study.

24 Having said that again, I will just reiterate all
25 the data goes the same direction which is not the same

1 degree of certainty that one would ideally like to see.

2 DR. CURTIS: Other comments from the panel? We
3 are going to be getting into the public hearing now. Does
4 anyone from the sponsor want to make any clarifications or
5 comments now? It is your last chance to speak. Remember,
6 you can't bring up any new data. It is just to clarify
7 points in the discussion that we had.

8 MR. DOW: I am sorry; I didn't hear you.

9 DR. CURTIS: At this point, you can't bring up any
10 new data but if you want to clarify or comment on any of the
11 points that were discussed here, feel free.

12 MR. DOW: I think maybe in a general sense, again,
13 watching the process as I have a few times, I respect the
14 fact that this is a continuum. Medical studies are a
15 continuum. This particular process is a continuum and there
16 are always ways to do things in a better way.

17 I think the message, and it has just been
18 interesting, again, to listen to the comments, is that a
19 year ago, we went through the process. I was with the
20 company at the time, but I was here watching the
21 proceedings, attempting to design the major points, twelve
22 major issues, that many members of this panel were part of
23 coming up with and then there are some of you that are new.

24 I applaud the consensus that the company has done
25 a major job in answering those issues. I stated at the

1 beginning, and I think it was stated by some of you more
2 eloquently, the issue is is there a reasonable assurance of
3 safety and efficacy in this device.

4 I respect the fact, as well, that the studies of
5 this procedure need to continue by us and other companies
6 that are entering the business in this procedure. The
7 question, certainly, we believe has been adequately answered
8 in the information that has been presented to the panel.

9 Thank you.

10 DR. CURTIS: Is there anyone from the FDA who
11 would like to comment or clarify anything that we have
12 discussed?

13 DR. SPYKER: Some of the review team would like to
14 make a couple of comments.

15 MS. DANIELSON: Just one comment. Judy Danielson.
16 The company has provided all the raw data from the
17 independent assessment survey. FDA can request that the
18 company perform the suggested analysis on this data.

19 DR. KURTZMAN: Steve Kurtzman, medical officer in
20 the Office of Device Evaluation. I just want to point out
21 an analysis we had done. It is in my memo. This addresses
22 Dr. Wittes' concern, and that is an independent survey for
23 each of the three treatment groups, the clinical assessments
24 were, on average, better--i.e., had a lower angina class
25 rank--than the survey assessments, and the average

1 differences in class rank and similar magnitudes.

2 These similar magnitudes and similar directions of
3 the average differences in class rank suggest that there was
4 no significant bias in the clinical assessments.

5 **Open Public Hearing**

6 DR. CURTIS: At this point, I will open the
7 hearing to the public. Is there anyone in the audience who
8 would like to comment on the issues that have been discussed
9 here?

10 If not, we will move on.

11 **Panel Discussion**

12 DR. CURTIS: I think I would look at this process
13 as the first question that we have been asked to address is,
14 is the clinical data presented adequate for evaluation of
15 safety and effectiveness which, in my own mind, and you can
16 correct me if I am wrong, what we are going to do first us
17 just make a judgment, can you judge, can you make a decision
18 about whether or not this device is safe and effective based
19 on the data you have here.

20 Not whether it is ideal, but, basically, is it
21 fatally flawed and you can't judge it or is there enough
22 information that you can say yes or no. If we decide that
23 the data just isn't there to make a decision, that is going
24 to naturally lead into a certain vote and would make that
25 vote..

1 On the other hand, if we have enough information
2 to judge safety and effectiveness, then I think we possibly
3 could hold the vote at that point realizing that if we
4 decide conditions--I mean, anything we discuss about the
5 labeling would become a condition.

6 Dr. Califf, could you comment on the first
7 question?

8 DR. CALIFF: I think this is very far from what I
9 would like to see, but from what I understand the precedents
10 to be and the guidance I have gotten in the discussion
11 today, enough of the data goes in the right direction that I
12 would say that it meets the usual criteria for safety and
13 effectiveness of devices.

14 I think I would have to go along with that within
15 the limited indication that has been asked for.

16 DR. CURTIS: So you can judge that data? It is a
17 big difference whether it is what you would like.

18 DR. CALIFF: Given the precedence and guidance I
19 have gotten, I think it is within the realm of what is
20 acceptable in this circumstance.

21 DR. CURTIS: Does anybody among the panel here--do
22 we concur with what Dr. Califf is saying or is there anyone
23 here who would like to express an opinion that the data is
24 so flawed that you can't even decide whether or not you
25 think it is safe and effective. That is what we are asking

1 right now. Do you think you can judge it?

2 I am getting a bunch of nodding heads.

3 DR. WITTES: I am having trouble for the reasons I
4 said before. I am comforted by the statement that you made
5 and I would like see those data, but, in the absence of
6 seeing that, I can't.

7 DR. CURTIS: So we have a no over there. I mean,
8 is this valid scientific evidence; that is what we are
9 trying to base it on. I doubt that there is anybody at the
10 table who wouldn't say that the data is flawed and that it
11 could certainly be improved upon.

12 But I think a lot of issues were answered from the
13 last panel meeting and I got a consensus that there was
14 enough of a comfort level to make a judgment on this today,
15 except for the dissenting opinion at the end of the table.

16 If so, then I think it might be appropriate to
17 move into a vote on the PMA, after which we could go through
18 all the additional questions and labeling issues. Do you
19 want to go ahead and read that?

20 DR. CERQUEIRA: Madame Chair, may I get some
21 clarification?

22 DR. CURTIS: Sure.

23 DR. CERQUEIRA: In addition to indications, can
24 there be a requirement for a registry? Can we express an
25 opinion--I have expressed a lot already, but can I express

1 it again about postmarketing surveillance and data
2 collection to optimize patient selection. Are we allowed to
3 do that?

4 DR. CURTIS: That would be an appropriate type of
5 postmarket study.

6 DR. CERQUEIRA: In that case, I am ready to vote.

7 DR. YIN: But not at this time. Later on; yes.

8 DR. STUHLMULLER: One point of clarification,
9 again. FDAMA changed postmarketing surveillance. One of
10 your options, when I read the list, is that you can
11 recommend post-approval requirements which can be written
12 into the approval order. So I will read, at this time, the
13 panel recommendation options for premarket approval
14 applications.

15 "The Medical Device Amendments to the Food, Drug
16 and Cosmetic Act requirement that the Food and Drug
17 Administration obtain an recommendation from an outside
18 expert advisory panel on designated medical device premarket
19 approval applications that are filed with the agency. The
20 PMA must stand on its own merits and the recommendation must
21 be supported by safety and effectiveness data in the
22 application or by applicable publicly available information.

23 "Safety is defined in the Act as reasonable
24 assurance based on valid scientific evidence that the
25 probable benefits to health under conditions of use outweigh

1 any probable risk. Effectiveness is defined as reasonable
2 assurance that, in a significant proportion of the
3 population, the use of the device for its intended uses and
4 conditions of use, when labeled, will provide clinically
5 significant results.

6 "Your recommendation options for the vote are as
7 follows. Option 1, approval. There are no conditions
8 attached. Option 2, approvable with conditions. You may
9 recommend that the PMA be found approvable subject to
10 specified conditions such as resolution of clearly
11 identified deficiencies which have been cited by you or by
12 FDA staff.

13 "Prior to voting, all the conditions are discussed
14 by the panel and listed by the panel chair. You may specify
15 what type of follow up to the applicants response are the
16 conditions of your approvable recommendation you want; for
17 example, FDA or panel. Panel follow up is usually done
18 through homework assignments to the primary reviewers of the
19 application or to other specified members of the panel.

20 "A formal discussion of the application at a
21 future panel meeting is not usually held. If you recommend
22 post-approval requirements to be imposed as a condition of
23 approval, then your recommendation should address the
24 following points. A, the purpose of the requirement. B,
25 the number of subjects to be evaluated. And C, the reports

1 that should be required to be submitted.

2 "Option No. 3, not approvable. The five reasons
3 that the Act specifies for denial of approval, the following
4 three reasons are applicable to panel deliberations. A, the
5 data do not provide reasonable assurance that the device is
6 safe under the conditions of use prescribed, recommended or
7 suggested in the proposed labeling.

8 "B, reasonable assurance has not been given that
9 the device is effective under the conditions of use
10 prescribed, recommended or suggested in the labeling. C,
11 based on a fair evaluation of all the material facts in your
12 discussions, you believe the proposed labeling to be false
13 or misleading.

14 "If you recommend that the application is not
15 approvable for any of these stated reasons, then we ask that
16 you identify the measures that you think are necessary for a
17 the application to be placed in an approvable form.

18 "Option 4, tabling. In rare circumstances, the
19 panel may decide to table an application. Tabling an
20 application does not give guidance from the panel to FDA or
21 the applicant thereby creating ambiguity and delaying the
22 process of the application. Therefore, we discourage
23 tabling of an application.

24 "The panel should consider a not-approvable or a
25 approvable-with-conditions recommendation that clearly gives

1 described corrective steps."

2 DR. CURTIS: Rob, would you like to make a motion?

3 DR. CALIFF: It is a mouthful, but the motion
4 would be to approve with conditions. I think we will have a
5 very interesting discussion on conditions because I have no
6 idea what would give you any further assurance,
7 postmarketing. But that is something that I think we need
8 to figure out.

9 DR. CURTIS: If we were to approve with
10 conditions, we do have to spell out what they would be and
11 we have to vote on those as well.

12 DR. CASSCELLS: I second that.

13 DR. CURTIS: There is a motion on the floor that
14 has been seconded. What we can do is vote on the motion as
15 it has been presented and then we will have an opportunity
16 to spell out what the conditions would be.

17 We are getting clarifications as we go along. We
18 have a motion that has been seconded. It has been
19 recommended to us that we go through the questions because
20 some of the answers to the questions could become
21 conditions. I think that would be reasonable. I think that
22 would be kind of natural. And then we could make any other
23 condition statements that we would like and then vote at the
24 end on the entire package.

25 We will go through them in order. Number 2; "Do

1 the following indications for usage adequately define that
2 patient population as listed. And it says transmymocardial
3 revascularization with the Heart Laser CO2 Laser System is
4 indicated for the treatment of patients refractory to
5 medical treatment with stable angina, Canadian
6 Cardiovascular Society class 3 or 4, secondary to a
7 myocardial ischemia or coronary disease not amenable to
8 direct coronary or other types of conventional
9 revascularization."

10 Are there any comments anybody wants to make about
11 the indications as stated?

12 DR. PARISI: Could you make it clear that is not
13 indicated, based on these data, for adjunctive use
14 concomitantly with other bypass or revascularization
15 procedures. I think it should be clear because otherwise
16 someone will bypass the right and zap the area of the LAD
17 with a laser and think that they are meeting the indication.
18 I don't think that is the indication.

19 DR. CURTIS: I think that is a good point. I
20 guess the question is where that would wind up being stated,
21 because, as you said, it is not an indication, or it would
22 be a warning or a precaution or a contraindication or
23 something like that.

24 DR. PARISI: Wherever the appropriate place is.

25 DR. FERGUSON: Isn't that excluded by saying, "not

1 amenable to direct revascularization."

2 DR. PARISI: They may split patients from vessels.

3 DR. CALIFF: Different parts of the heart.

4 DR. SPYKER: That was our intent with that, but if
5 you want to add CABG or whatever to make that more specific,
6 that would certainly--

7 DR. CURTIS: So some comment along the lines of,
8 "Patients who are not having concomitant CABG."

9 DR. PARISI: Right. "It is not intended for
10 concomitant use with other revascularization procedures."

11 DR. CURTIS: That is a good point.

12 DR. SPYKER: Why don't we write that statement and
13 then we can put it either here or whatever location is
14 appropriate.

15 DR. FERGUSON: "One of the other types of
16 conventional revascularization." What does that mean? I
17 don't know what that means?

18 DR. CURTIS: Let's take one step at a time here.

19 DR. FERGUSON: I'm sorry.

20 DR. CURTIS: Do you want to try to word that
21 statement, Dr. Parisi?

22 DR. PARISI: Yes. I would say, "It is not
23 intended for concomitant use with other revascularization
24 procedures."

25 DR. CURTIS: Okay, good. That could be up in

1 there. I think what happened, the way this indication was
2 written, was that there were choices or suggestions for
3 alternative wordings, so Dr. Ferguson, if you want to make
4 some comments on that.

5 DR. FERGUSON: I just questioned what they were,
6 that's all. It seems to me that saying, "direct coronary
7 revascularization," if that includes all of the medical
8 indications for revascularization, then that would be
9 inclusive.

10 DR. CURTIS: I think the bottom line is you are
11 talking about bypass surgery or angioplasty stents, that
12 sort of thing. So the question is how do you word that last
13 phrase. Does, "Not amendable to direct coronary
14 revascularization" cover it?

15 DR. PARISI: Yes.

16 DR. CURTIS: And just take out the entire
17 bracketed statement.

18 DR. CALIFF: I wonder about using coronary disease
19 instead of myocardial ischemia because what we really have
20 in the study is patients with class 3 or 4 angina and had
21 coronary disease. We don't necessarily know that--the
22 clinician assumes the symptoms are due to myocardial
23 ischemia. If we leave it myocardial ischemia without the
24 coronary disease in there, there are patients without fixed
25 obstructive disease who have class 3 or 4 angina.

1 It seems like it is a better description of what
2 was actually done in this study to call it coronary disease.

3 DR. CURTIS: So you would suggest saying,
4 "secondary to coronary disease?"

5 DR. CALIFF: Yes.

6 DR. CURTIS: Any comments on that?

7 DR. VETROVEC: Just to be certain that coronary
8 disease covers all types of myocardial ischemia or lack of
9 blood flow which are not ordinarily associated with
10 coronary-artery occlusions. Transplant is one. If you
11 agree that that is covered, then that is fine. Otherwise, I
12 think--

13 DR. SPYKER: One of the things that we expect from
14 the panel is we are using you as a sounding board. If it is
15 not clear to you, then I think you should assume that you
16 are not way off the mark.

17 DR. FERGUSON: One of the real uses in this device
18 as far as I am concerned in our group is in those patients
19 who have had cardiac transplants.

20 DR. CALIFF: We don't have any evidence to that
21 population in this setting.

22 DR. FERGUSON: That is my question, specifically
23 because the reason those patients get into trouble is
24 coronary occlusion, as you know. Is that included in that
25 group? Is that cohort included in this definition?

1 DR. CALIFF: If they have coronary disease.

2 DR. FERGUSON: I think they all do. That is what
3 they get in trouble from.

4 DR. CALIFF: If that is the reason it is being
5 done, it would be included.

6 DR. VETROVEC: I think Dr. Califf's, if I could
7 kind of comment for him, fear is that somebody will do this
8 on somebody with supposedly small-vessel disease without
9 major vessel coronary disease. Is that your concern?

10 DR. CALIFF: The wording would leave it open to
11 that. It seems like what we have in the study are patients
12 with severe angina and coronary disease.

13 DR. VETROVEC: The only other thing would be to
14 say--as long as they say, "secondary to coronary-artery
15 disease" to reflect that this is the cause of it. I think
16 that is the important thing because I guess the other fear
17 you always have is that--we all have had patients in the
18 unit with intractable chest pain and coronary-artery disease
19 and we were never 100 percent sure the two overlap.

20 I guess that is a concern here. If you say
21 "secondary to coronary disease," I think you are all right.

22 DR. SKORTON: Do you want to say, "secondary to
23 atherosclerotic coronary disease?" There are other kinds of
24 coronary disease, Kawasaki disease and other things. Maybe
25 that would satisfy you.

1 DR. CALIFF: Okay.

2 DR. FERGUSON: That wouldn't satisfy me for the
3 reason I just mentioned because I don't think that in
4 cardiac transplants, it is an atherosclerotic process.

5 DR. PARISI: Dr. Ferguson, there are no patients
6 with cardiac transplant in this database so how would we
7 justify using it?

8 DR. CURTIS: I don't see how you could possibly
9 say it is indicated for patients with heart transplants.

10 DR. FERGUSON: I guess I am extending it beyond
11 what I should be, then. Okay.

12 DR. CURTIS: One of the other bracketed statements
13 was Canadian Cardiovascular Society class 3 or 4. That one
14 bracketed statement, I think, would have to stay in there
15 because otherwise stable angina could apply to somebody who
16 was class 2 and we don't want to do that.

17 It seems to me that what we wind up with, then, is
18 "Transmyocardial revascularization with the Heart Laser CO2
19 Laser System is indicated for the treatment of patients
20 refractory to medical treatment with stable angina, Canadian
21 Cardiovascular Society class 3 or 4, secondary to
22 atherosclerotic coronary disease not amenable to direct
23 coronary revascularization." And then there was your final
24 statement.

25 DR. FERGUSON: "It is not intended for concurrent

1 use with other revascularizations."

2 DR. CURTIS: "It is not intended for concurrent
3 use with other revascularization procedures."

4 DR. PARISI: "With other coronary
5 revascularizations."

6 DR. CURTIS: With other coronary revascularization
7 procedures."

8 Any other comments on the indications? That
9 actually also covers No. 3 since we were supposed to see
10 which of the bracketed phrases we wanted.

11 Let's move on to No. 4; "Should there be any
12 contraindications? Is the proposed contraindication section
13 appropriate? Are there any other contraindications for the
14 use of this device." And, as listed now, it says, "The
15 Heart Laser CO2 Laser System is contraindicated where the
16 ischemia is limited to the ventricular septum and/or right
17 ventricular wall."

18 DR. SKORTON: I would like us to consider adding
19 unstable angina to the contraindications.

20 DR. WEINTRAUB: I would find that is a problem
21 because, obviously, it is being used in that and some of the
22 patients have--it has been used in some patients with
23 unstable angina after they have been stabilized. Perhaps a
24 caution should be put in, that is something to the effect
25 that, "Mortality rate has been found to be high when the

1 modalities are applied to patients having unstable angina,
2 Every effort should be made to stabilize the patient prior
3 to operation."

4 DR. VETROVEC: What if his statement were modified
5 to say, "Current unstable angina," because the mortality
6 rate is 25 percent in the first week.

7 DR. CALIFF: George, actually this is bringing up-
8 -I had to get into this, but what is the difference between
9 class 4 angina and unstable angina? It seems like we have
10 got a real murkiness here.

11 DR. WEINTRAUB: I think what it means is that
12 patients should not be brought to the operating room when
13 they are acutely ischemic. I think that is really what it
14 means.

15 DR. SKORTON: I think there is a better answer for
16 that. Class 4 stable angina is angina at rest that is
17 stable. Unstable angina is angina of any severity that is
18 not stable, at rest, changing, getting worse with time.
19 George's idea, I think what he was getting at and what you
20 are trying to get at, too, I think, is that you would feel
21 less uncomfortable treating somebody with unstable angina
22 who had been stabilized, who had been modified by medical
23 therapies.

24 So I agree it is somewhat murky, but that is a
25 dataset that we look at that is a red flag to me. It looks

1 like that is a very, very high-risk population.

2 DR. CALIFF: I would think a relative
3 contraindication.

4 DR. SKORTON: I don't think there is a such a
5 thing. I think it should be a caution or a
6 contraindication.

7 DR. CURTIS: There is a warnings and precautions
8 section that that might go into.

9 DR. SPYKER: It is already in the very first
10 warning on the top of page 23. It is line 3, unstable
11 angina. As you know, there was actually an arm in phase II
12 that you looked at back in July and it is still in your
13 summary sheet. So we do have a good deal of data on that.
14 I think your suggestion that we put in the percentage of
15 mortality, for example.

16 Our general policy has been to go toward getting
17 more evidence, getting more data and less pronouncements of
18 what thou shalt do.

19 DR. VETROVEC: I think to somehow define it so it
20 is clear because a warning has a certain relative indication
21 and a 25 percent mortality in the data that you have is a
22 little more than a warning to me.

23 DR. SKORTON: I would be happy--I looked at it
24 before but forgot about that. I would be happy with a
25 strong statement but in the warning section. That would be

1 fine with me.

2 DR. CURTIS: Because we discussed yesterday that
3 contraindications mean you should never, ever, ever do it.
4 That would just be wrong. And there could be patients in
5 whom you know darned well that you would rather not do it
6 but you have run out of options. You might accept a higher
7 mortality risk. So then it would fall into that warnings.

8 I agree that saying that the risk of perioperative
9 mortality is higher isn't quite as strong as saying, "Hey;
10 listen. It is 25 percent if you get these early patients.
11 But it is 1 percent if you get them out past a couple of
12 weeks," would be a very valuable thing to have mentioned in
13 there.

14 So the unstable angina issue has been discussed.

15 DR. ALTMAN: I have, actually, a clarification I
16 need. I am not sure why, under contraindications, this is a
17 contraindication. If you look on page 2-5, 7.2, the fifth
18 bullet down, isn't that virtually the same thing? I am
19 confused if that wasn't studied in the population, why that
20 would be a contraindication and all these other ones
21 wouldn't.

22 DR. CURTIS: That is a good point.

23 DR. ALTMAN: Was it studied or was it not or is it
24 a contraindication, or would all of these be
25 contraindications?

1 DR. CURTIS: It was not studied. No laser lesions
2 were delivered to the septum of the RV.

3 DR. ALTMAN: So why wouldn't all the rest of these
4 that weren't studied also be contraindications?

5 DR. CURTIS: That is a great point? Do you have a
6 clarification for us?

7 DR. SPYKER: There was some discussion with the
8 sponsor team and the review team about that. Our thinking,
9 initially, was, well, if you can't reach it with the device,
10 you ought not to be considering that indication, if that is
11 the only place you have the lesion.

12 You can see we were a little ambiguous about it
13 ourselves. We put it in both places. I was, honestly,
14 reluctant to have no contraindications. I guess that was
15 part of my problem.

16 DR. CURTIS: You had to find one. I think it
17 serves a purpose in highlighting the fact that it just
18 wouldn't make any sense to do it under those circumstances.
19 But I think your point is well taken.

20 Any other comments on that?

21 DR. FERGUSON: I think it belongs where it is
22 because the use of the instrument on the right ventricle, if
23 I interpret what I hear correctly, would be dangerous.

24 DR. PARISI: Why not just delete that line from
25 section 7.2. "Patients with myocardial ischemia limited to

1 the right ventricular wall or septum." You have already
2 said it is a contraindication so why would you want to bring
3 it up again? Just delete it from that.

4 DR. CURTIS: Yes. It would probably make you feel
5 more comfortable than having no contraindications at all, I
6 would imagine.

7 No. 5; "Does the outline of the possible mechanism
8 of action of the labeling adequately summarize the current
9 state of knowledge of TMR. Possibilities include increased
10 perfusion of the myocardium, collateralization via
11 angiogenesis, disruption of pain fibers or possible placebo
12 effect."

13 Any comments on that?

14 DR. PARISI: Does there have to be one mechanism
15 and should possible micromyocardial infarction also be
16 included?

17 DR. CALIFF: Do we have to have a mechanism?

18 DR. CURTIS: No.

19 DR. CALIFF: I don't see any reason to put that in
20 there. It is fun to talk about, but what does it have to do
21 with whether you use or not.

22 DR. CURTIS: We have no idea. The usual state of
23 medicine is the more answers you have, the less you know.
24 The more possibilities you have, the less you know. So we
25 have no idea. I would agree, I am not sure it is important

1 to have a mechanism in there, although when you talk about
2 drugs, you usually have a mechanism of action listed.

3 DR. CALIFF: Half the time, it is wrong. And you
4 don't know which half.

5 DR. FERGUSON: If you include it, I think you need
6 to put "current theories include," certainly.

7 DR. SPYKER: We didn't exactly put it in the
8 indications. It is back in section 11. This was more like
9 emphasizing, sort of giving the truth. The whole truth is
10 we don't know and there are a number of things that are
11 being considered. So we thought it was of some value. We
12 are not exactly featuring it in the labeling, but we thought
13 it would be better to have it in than remain mute on it.

14 We really wanted to get into the official
15 document, the labeling that we don't know how much is
16 placebo effect. We can't rule it out. And we didn't want
17 to put that in the indications section. So this was sort of
18 a compromise at the truth.

19 DR. WEINTRAUB: It sounds to me like it is a
20 pretty good thing to do because what it says is there is no
21 known mechanism. That's all.

22 DR. SPYKER: That is sort of what it says.

23 DR. CURTIS: The issue of microinfarction maybe
24 could be listed as a fifth possibility there.

25 DR. PARISI: There is data that fixed defects

1 increase.

2 DR. CURTIS: So it is a possible mechanism.

3 DR. PARISI: For whatever that is worth.

4 DR. CURTIS: Rather than say we don't know at all,
5 my own opinion would be that it is nice to have the
6 possibilities listed the way they are.

7 No. 6; "Phase II perioperative 30-day mortality
8 related to the device or procedure was 11 percent, 11 of 97,
9 in the early part of the study and 4 percent, 4 of 104, in
10 the later part of the study. This 7 percent difference
11 possibly reflecting a learning effect has a 95 percent
12 confidence interval of 0.2 percent to 15 percent. Is the
13 proposed user-training and experience section adequate? If
14 not, how should it be modified?"

15 A thought that occurred to me as I was looking at
16 this and I didn't actually go back through the data to sort
17 it out--I was wondering how many of the early patients were
18 done within that two-week window and might have been
19 unstable. I am wondering if it is a learning effect versus
20 just getting smarter and not doing the real unstable angina
21 patients and that is why the mortality went down.

22 I don't know if anybody on the panel here has any
23 information or opinion on that.

24 DR. WEINTRAUB: I actually assumed that. I didn't
25 go back and look at the numbers, but I think the numbers

1 probably work out.

2 DR. CALIFF: Regardless, I still thought it was a
3 pretty nice program that is outlined for education. Even if
4 the learning effect is not as big as it is thought to be, I
5 think we probably all agree it would be useful to train
6 people and track a few cases to make sure things were going
7 well.

8 DR. CURTIS: I think that is a good point. So I
9 think that the proposed training is something that we
10 strongly support. As an answer to that question, it might
11 be worthwhile to go back and look at the data a little more
12 closely and see if the difference between the results found
13 early and late had maybe more to do with unstable angina
14 than actually a learning effect for the operator.

15 If so, then it would kind of obviate that issue
16 and lean more toward the fact that we believe strongly that
17 patients who are actively unstable should not be operated
18 on.

19 No 7. This is something we really hadn't really
20 talked about much. "Should transesophageal echo to verify
21 successful creation of channels be recommended for the
22 clinical use of TMR?"

23 DR. CALIFF: It was done in all the cases in the
24 study?

25 DR. CURTIS: I would say yes.

1 DR. FERGUSON: I would like to comment on that. I
2 think it is critical that that be in because, as inevitably,
3 again, as the use of the instrument is extended, there may
4 be some bad results that come up if the TEE is not used
5 because you have no other way to find out whether you have a
6 transmural laser hole or not.

7 DR. CALIFF: I would add if it was part of the
8 protocol and done in the study that we are using is the
9 evidence to recommend it, that we ought to recommend that
10 the protocol be followed.

11 DR. CURTIS: I imagine that if you used the wrong
12 energy or didn't look, you could get a real placebo effect
13 there. You would just be waving a laser over the heart and
14 not necessarily doing anything.

15 DR. PARISI: You could also be lasing a thin
16 akinetic segment. It was seem to me a recommendation isn't
17 a requirement and, whether it was in the study or not, it
18 would make sense. I think most open-heart suites now are
19 using TEE anyway. But I think it is a reasonable
20 recommendation.

21 DR. SPYKER: You have hit exactly on the reasons
22 we put the question in because sometimes, in clinical
23 trials, lots more and fancier evaluations are done than are
24 appropriate clinically. I have certainly heard your clear
25 indication that this is appropriate to continue clinically,

1 not just because it was done in the clinical trial but
2 because it makes sense with patients.

3 DR. CURTIS: Okay, good. Other suggestions for
4 the labeling? Any other issues that anybody wants to bring
5 up?

6 "Do the data presented adequately demonstrate the
7 safety and effectiveness of the device as labeled." I think
8 that comes in with the vote, and we have a motion on that
9 already.

10 I would like to move on to No. 10; "Has the
11 labeling, warnings and precautions, adverse events and
12 clinical studies adequately described the higher morbidity
13 and mortality in the crossover patients?" I think most of
14 that turns out to be unstable angina. When you have an
15 acutely sick patient, that is not the time that you want to
16 take him into the operating room, so I don't think that
17 there is going to be a major problem with that as long as
18 people pay attention to that issue.

19 DR. VETROVEC: But you are going to beef up the
20 warning section; correct?

21 DR. SPYKER: Yes, sir.

22 DR. CURTIS: We need to address the two follow-up
23 questions, too, before a vote because this gets into
24 postmarketing studies. No. 11; "What type of long-term
25 follow up, in addition to CCS and mortality data, would be

1 appropriate for the TMR-treated patients? How long should
2 they be followed? What kind of postmarketing surveillance
3 is necessary?"

4 DR. WITTES: Post-approval?

5 DR. CURTIS: Post-approval; sorry.

6 DR. CALIFF: I am real interested in hearing about
7 this because I can't imagine any postmarketing surveillance
8 that is actually going to be all that useful. I know David
9 had some thoughts about this.

10 DR. SKORTON: My idea was not to try to recreate
11 the study by doing postmarket, but I still have some
12 questions about how these people do after looking at the
13 data. So my thing was sort of a no-brainer idea. I thought
14 they should just continue to follow data, formal assessment
15 of angina data, on a certain number of patients. I can't
16 say what that right number ought to be--for a certain period
17 of time.

18 I am stumbling on whether it would make any sense
19 to continue to evaluate perfusion data with thallium since
20 my bias, as you know, is that I don't understand why
21 thallium would be useful in this setting, especially given
22 that the holes close up. I don't think it is that helpful.

23 So I was going to suggest that they be followed
24 clinically and maybe with echocardiography to look at the
25 changes in wall motion since that is a sort of a final

1 common pathway.

2 DR. CALIFF: Are you talking about this population
3 that is currently being following in the study or are you
4 talking about new patients that are going to be done when it
5 is on the market?

6 DR. SKORTON: I don't know for sure, but my slight
7 experience with this panel is that this refers to new
8 patients who will be done.

9 DR. SPYKER: You can consider either, certainly.

10 DR. SKORTON: Is that right?

11 DR. SPYKER: But the study, they followed these--I
12 was most struck by the idea that was brought up about
13 following a patient, following the training and following
14 the patients or some subset of patients to keep an eye on
15 the training and the success of that.

16 DR. SKORTON: I guess it is a little ill-formed,
17 but I feel like we are heading toward voting approval of
18 something that we are not all real comfortable with. The
19 reason why we are not all real comfortable with it is we
20 feel that some of the data, some of the experimental design,
21 wasn't perfect. Some that seemed reasonable just wasn't
22 executed as rigorously as we would have liked to have seen
23 it done.

24 So I think the collective experience with the
25 device should continue to grow under some emphasis from the

1 agency.

2 DR. CURTIS: I think it would be really necessary
3 to know that the effect on the angina was sustained. We
4 have data out to twelve months now but if, at 24 months, the
5 patients are no better off than when they started, I think
6 that would be really important to know.

7 DR. CALIFF: So that would be the patients that
8 are in the study.

9 DR. CURTIS: It could be either way. We could
10 either say keep following the ones that are in it or you
11 could say, "Well, let's start over with a brand-new set of
12 patients and do 25 or--" we should specify how many, specify
13 whether it should be new patients or the ones who are
14 already in the study and specify what it is we think is
15 important to know.

16 DR. CALIFF: The problem I am having is that,
17 without a control group, a given rate of angina is hard to
18 put under--I think the interchange between Dr. Casscells and
19 the company about his experience in his population versus
20 what was seen in the study--it is obvious that you can get
21 very different outcomes depending on some pretty hard-to-
22 define selection criteria.

23 So the question would be if you got a certain rate
24 of return of angina in a new population without a control
25 group, with would be the criteria for saying it is not good

1 enough.

2 DR. WEINTRAUB: It seems to me postmarket
3 monitoring is useful, aside from the scientific issues,
4 mainly for one reason and that only and that is to uncover
5 potential problems that you don't pick up with the first
6 hundred patients that you are looking at.

7 This is certainly true in valves. I think this is
8 very similar. After all, of the randomized group, there are
9 only, what, 102 or 99 patients that have been looked at very
10 carefully. There may be new complications that we don't
11 know about that may be uncovered. That is the main reason
12 for postmarketing surveillance.

13 That may not be picked up by the Safety Act of
14 1990. Those may not be picked up but I think it is
15 important that some cohort from this group be picked up and
16 also that new patients be subjected to some kind of
17 surveillance so, again, we pick up new problems that haven't
18 arisen thus far.

19 DR. VETROVEC: I think you can quibble a lot about
20 the angina and the follow up but it seems to me you really
21 want mortality data on the follow up. Nobody has mentioned
22 that. That is a concern in at least one subgroup of
23 patients in this study. The others looked very good but I
24 think you want to make sure that that is reproducible in the
25 real world once a lot of different surgeons start doing it.

1 These were highly skilled surgeons that were doing this.

2 DR. CASSCELLS: I want to echo that. There is
3 something wrong here. A lot of these patients are dying
4 within the first month. There is something very wrong about
5 that. Over time, it can be figured out. We don't have
6 deaths like this. I don't know whether these are patients
7 with a little bit of azotemia or whether these are the
8 diabetics or whether these are the patients who are
9 malnourished.

10 I am very keen to see the follow up if the
11 benefit--if there is a mortality benefit in those patients
12 who take their medications after this. Here, 25 percent of
13 them cut back on their medicines and 15 percent went up and
14 the rest didn't change. That is a critically important
15 point.

16 This is a technique that is a two-edged sword,
17 like all surgical procedures. If we don't follow it and
18 define a large group of patients with better data
19 collection--I don't apologize about recreating a study. It
20 has to be a better study or I wouldn't vote for it.

21 I think it needs very careful follow up. I have
22 already suggested the kind of data I want. The recording
23 secretary and I have sat down and gone over it. I would
24 like to see all that data collected.

25 DR. SKORTON: Maybe the FDA staff can speak to Dr.

1 Califf's question which is a very fair question. If I could
2 restate it a different way; if we recommend--and all this is
3 a recommendation to you--that it is approvable with post-
4 approval surveillance, I assume that what you do when
5 surveilling it is you decide either to do nothing or come
6 back and reconsider the approval if there is big problem
7 that is uncovered; is that correct?

8 DR. SPYKER: Sure.

9 DR. SKORTON: So I guess the point is, even though
10 this would not be a controlled trial in any stretch of the
11 imagination, if something is uncovered in what we are asking
12 them to gather that would suggest that outcome is different
13 than was portrayed in the pre-approval study, then it is the
14 FDA's prerogative, if they want to, to ask for more studies,
15 controlled studies.

16 DR. CERQUEIRA: Without a control group, if you
17 just look at mortality alone, it is going to be difficult to
18 do that depending on how you select the patients. I think
19 we obviously need to have a registry of device malfunction
20 and then, also, of surgical complications with all of the
21 devices. That would be a reasonable thing to do.

22 We have shown that if you put holes in areas of
23 myocardium where you can show that there is ischemia, you
24 get improvement. To just do this on everybody without some
25 documented evidence of ischemia would also be a problem. So

1 I would put in some proviso that before you do this, you
2 have to have some demonstrated evidence of viable myocardium
3 in that area.

4 Again, I think the nuclear imaging was the only
5 thing we have information on. Some of these other things,
6 out of fairness to the company, we have to define a little
7 bit what it is we want. This is pretty open-ended. Words,
8 the list of categories, is quite broad. We would need to
9 define how many patients or for how long a time period and
10 what you are going to compare this to, what are going to be
11 the action points that you would take on this.

12 DR. CASSCELLS: Manuel, I think that if you have a
13 lot of patients--I think all the patients who die need to be
14 analyzed very closely and see how they differ from the
15 patients who don't die. That is very, very simple. It is
16 not the hard to do. It is not expensive. We do this with
17 the angioplasty registries. We can look at this in the
18 National Registry of Myocardial Infarction, which is not
19 mandatory.

20 We do it with the Summit Medical System for
21 Intervention of Cardiology. Data collection is not that
22 onerous. These data-collection systems are much better.
23 Every hospital of any stature is concerned with the optimal
24 outcomes and there are people collecting data. This is
25 important. I would require that data be collected.

1 DR. WEINTRAUB: Could I just suggest that,
2 perhaps, the FDA staff would work this out with maybe a
3 small subcommittee or something because we can't spin this
4 out this afternoon.

5 DR. YIN: Let me share with you, we do want some
6 exact conditions from the panel because we can come up with
7 ours. Now, you do want the conditions, this particular one.
8 So what we can do is we will work with the sponsor and you
9 guys set up a subcommittee, and we will come back, say,
10 within a week or whenever they got the study done and come
11 back to the subcommittee here and get some kind of reading,
12 and then we will go with it.

13 I don't want you to leave it to FDA open wide and
14 we may not necessarily agree.

15 DR. PARISI: I would like to support Dr. Casscells
16 requirement for a registry so that every patient who has
17 this is registered because I do think you are not going to
18 get the results of a randomized trial but you are going to
19 be able to assess baseline characteristics relative to
20 outcomes and you are going to be able to look at mortality
21 data as well as clinical-benefit data.

22 I think the first thousand patients, really, we
23 ought to know this data. We are doing this for angioplasty.
24 We have done it for several decades and SCS database is
25 really looking, still, continuously in most responsible

1 hospitals at coronary surgery. There are big databases at
2 Duke. I think this is a very important thing to have.

3 DR. WEINTRAUB: You are right about that, but I
4 don't think--tell me if I am wrong, but I don't think the
5 FDA has ever, as a condition of approval, demanded that the
6 sponsors set up a complete registry. Maybe for valves.

7 DR. PARISI: You have to realize, Ron, this
8 approval is getting through by a hair's breadth. This is
9 not exactly everyone screaming to approve this and let's
10 walk out of here. I think we all have reservations about
11 this approval.

12 DR. WEINTRAUB: I think it is going to be very
13 hard to do that on a practical basis.

14 DR. CALIFF: Why do you say that? Why would it
15 be?

16 DR. WEINTRAUB: Because there are going to be a
17 lot of hospitals out there. You talked about the PTCA
18 registry. How many hospitals are not in that? You are
19 talking about academic institutions and other institutions
20 that do a fair amount of PTCA. There are lots of hospitals
21 that don't contribute to that.

22 DR. PARISI: We are not saying this necessarily go
23 on forever, but at least it ought to go on for enough
24 reassurance because we have such a skimpy database here on
25 which we are making the decision to let us be more confident

1 that the decision was the right one.

2 DR. WEINTRAUB: I would have to accede to--I don't
3 know what conditions FDA can impose, but I suspect this is
4 getting a little far afield.

5 DR. YIN: You can specify how many patients but I
6 thought if you are going to specify whatever numbers, make
7 sure that you know why you want to do that number.

8 DR. WEINTRAUB: I think that is reasonable, but
9 you can't just say everyone that has a TMR has got to be in
10 the registry.

11 DR. YIN: Correct.

12 DR. WEINTRAUB: That is just not going to happen.
13 It is impractical. It will never happen.

14 DR. YIN: Then we would request that they provide
15 all the information that Dr. Casscells wants; right? Would
16 that make sense? What other things, because we need some--

17 DR. CALIFF: Wait. I am a little confused right
18 now.

19 DR. WEINTRAUB: In other words, what she is saying
20 is that you can demand a cohort for postmarket approval of
21 whatever number is deemed to be appropriate.

22 DR. CALIFF: But the cohort could be whichever
23 patients get put into it. So you could put in all the
24 patients that did well, for example.

25 DR. YIN: No; you cannot do that.

1 DR. WEINTRAUB: But the cohort can be derived from
2 five institutions or something like that, not all patients.

3 DR. CALIFF: Okay. So a systematic cohort.

4 DR. WEINTRAUB: Some sort of systematic cohort.

5 DR. WITTES: A systematic cohort with a fixed
6 closed time. I think the other thing we need to make sure
7 is that, if there is a registry, that people are followed
8 until some date certain rather than until they have another
9 procedure.

10 DR. YIN: You could specify what should be the
11 endpoint for this patient to follow until then and how many
12 patients you do want and what type of information on
13 medication would should collect. I think then we will work
14 out with them, would that be part of the approval process.

15 DR. CURTIS: I think we can and should give some
16 guidance here as to what it is we are talking about, not
17 just say some kind of post-approval study would be a good
18 idea. The question is exactly what it is is important to
19 know.

20 As in anything, the more things you want to ask--I
21 mean, if you want to know if the patients are diabetic and
22 if they are hypertensive and if they--well, you can get
23 yourself a very, very complicated database that would be
24 very--and then it becomes very difficult unless it is a very
25 limited number of patients you are doing.

1 The fewer questions you ask, the more patients you
2 could demand it of. It might be possible to know survival
3 of all patients who have TMR done at one or two years, say.
4 If you want to know dead or alive. That probably would be
5 pretty easy and not onerous to collect that information.

6 If we want to know medications that they are
7 taking, that is a study. Even though you say database, you
8 are going to have to define how many patients and over what
9 period of time. I think we would have to be very specific.

10 And then you have to know why you want that
11 information. I would want to know if patients were alive or
12 dead. For one reason, sure, it is not going to be a
13 randomized trial, but there are data published on outcomes
14 of CABG surgery, itself, outcomes of high-risk patients who
15 have CABG surgery.

16 It is not randomized. It is not prospective or
17 anything, but you could--it is an historical control you
18 could at least compare it to. I think what we would like to
19 see is that TMR wasn't way out of line to those sorts of
20 patients.

21 So I think, if we wanted to collect mortality data
22 on all patients who have TMR over the next year, or two
23 years, something like that, that would be very doable.
24 Something else; I think we need to spell out what it is we
25 want and why.

1 DR. PARISI: I think you have to have a base to
2 relate it to, though. It may not have to be very
3 complicated, but really you have to know the age of the
4 patient, the sex. You need to know the basics. If they had
5 six previous revascularization procedures, it is different
6 than--

7 DR. CURTIS: So age, sex, number--

8 DR. PARISI: I can't spell it all out here.

9 DR. CERQUEIRA: I think a subcommittee.

10 DR. PARISI: The setting is not right to spell
11 that out. I think that has to be thought out by a small
12 group. It isn't simple. I agree.

13 DR. CERQUEIRA: I think a subcommittee would be
14 ideal but I think it should be sequential patients. I would
15 be against just selecting a few sites where you are going to
16 gather this information. I don't see this as being like the
17 male impotence pill that has got 40,000 prescriptions a week
18 being written.

19 I would be in favor of doing every patient at a
20 set number with a limited questionnaire that would get at
21 pertinent information that could be used to decide whether
22 the device is safe and whether it is effective. But I think
23 2000 or some reasonable number.

24 I think to hash that out here would not be in
25 anybody's interest.

1 DR. CURTIS: I guess all I was getting at is are
2 you talking about five questions to stratify the patients or
3 40.

4 DR. PARISI: One piece of paper is what I am
5 talking about.

6 DR. CURTIS: One piece of paper. Are there two or
7 three members of the panel who would be willing to volunteer
8 to be on such a subcommittee to hash out what the details
9 would be of such a post-approval study? Dr. Parisi? We
10 have got several volunteers. Okay. Dr. Casscells, Dr.
11 Weintraub, Dr. Cerqueira and Dr. Vetrovec have all
12 volunteered.

13 DR. YIN: John, did you write it all down?

14 I must advise you, once we work with the sponsor,
15 we want to come back to you within a week. You better all
16 be available because we really want to close this. We can't
17 keep on dragging it out. Then I do want some good endpoints
18 that it is reasonable why you want to collect them.
19 Mortality is one.

20 DR. CURTIS: Right.

21 DR. YIN: That's all we want.

22 DR. STUHMULLER: If I can clarify, again, from a
23 procedural point under the panel recommendation options, if
24 you are going to recommend post-approval requirements, then
25 the recommendation has to address the following three

1 points: one, purpose of the requirement; two, the number of
2 subjects to be evaluated; and, three, the reports that
3 should be required to be submitted.

4 DR. YIN: Every six months, or every three months,
5 or whatever.

6 DR. STUHLMULLER: Then you also need to specify
7 what type of follow up to the applicant's response you want,
8 either to FDA or the panel. The panel follow up can be done
9 through a homework assignment to the primary reviewers or
10 other specified members of the panel. So if there are
11 several members of the panel who would like to do this as a
12 homework assignment in collaboration with FDA, then that
13 would meet that approvable condition.

14 DR. YIN: Why don't you go through each one and
15 let them decide. Start from the first one.

16 DR. CALIFF: This is what the subgroup is going to
17 have to get back--we will try to do that.

18 DR. CURTIS: I think the question is logistics
19 there. I think what we really can't have happen is we can't
20 say, "FDA, figure something out and go to the sponsor and
21 then let us know if we like it or not." I think they want a
22 little bit better guidance on that as to what we mean.

23 There were five people who volunteered. If the
24 five of you want to get together, I think you have got to
25 get your piece of paper and write it down and give it to

1 them.

2 DR. YIN: And remember the purpose.

3 DR. CURTIS: Right. You have to have a purpose
4 for it. You have to have the number of patients. You have
5 to have what reports are required over what interval of time
6 so that you are very specific about what it is you want to
7 know.

8 DR. YIN: Since there are five of you, I would
9 give you less than a week to get it done.

10 DR. CASSCELLS: Dr. Curtis, may I add one other
11 point. I would like to get some feedback from the other
12 committee members about a standard consent form. One of the
13 really difficult things in smaller hospitals is that one or
14 two people can push anything through the IRB. I have never
15 been declined an IRB on one of my research proposals.

16 I must say, they don't always ask the toughest
17 question. This has been a very detailed scrutiny. I don't
18 see any reason why the FDA can't, in the interest of the
19 patients, have a standard consent form that goes with a
20 procedure or a device. It is not something that is
21 routinely done but, my gosh, there are all kinds of nuances
22 in getting an informed consent. It is one of the most
23 difficult and important issues in medicine.

24 I would like to see a spelled-out standard consent
25 form in the first year of this registry. I would like to

1 hear what other people think about that.

2 DR. YIN: I am willing to double check that for
3 you because once a device is approved, we do not usually
4 impose the informed consent form. We don't review that.
5 Usually, your hospital surgical department would take care
6 of that. So maybe we specify for some tertiary--you know,
7 the institutions that you have good faith in rather than
8 come up with a form.

9 DR. CURTIS: I would have to say, with all due
10 respect, I don't think I agree with that idea that it is
11 necessary to have a standard consent form for this, that
12 this is some special exception of case compared to a lot of
13 other things that we do in medicine. We generally use
14 generic consent forms and then it is our job to explain
15 things to the patient.

16 So I think the way we normally do it, I don't
17 think there has to be an exception in this case but, since I
18 am disagreeing, does anybody else have a comment they want
19 to make on that?

20 DR. PARISI: I would agree with you.

21 DR. WITTES: I would, too.

22 DR. STUHLMULLER: The issue with the consent form
23 is there may be one that would be required in order to
24 access a patient's records as part of a follow-up study, but
25 to require a uniform consent for the procedure, that is

1 within the realm of practice of medicine.

2 DR. YIN: I don't think we can do that. Once it
3 is approved, we cannot do that.

4 DR. CASCCELLS: Do I have a unanimous vote in my
5 favor on this consent form?

6 DR. CERQUEIRA: Is this how you get things through
7 the IRB?

8 DR. SPYKER: On that point, there is going to be a
9 patient manual. We do, typically, and certainly would in
10 this case with this suggestion, work with the sponsor to
11 make sure that this is even-handed and appropriately warning
12 them of the risks.

13 DR. CURTIS: I would like to make a suggestion.
14 Dr. Parisi, would you be willing to spearhead this effort to
15 kind of define what the post-approval study would be rather
16 than having five people equally responsible?

17 DR. PARISI: If everyone will give me their fax
18 number before they leave.

19 DR. STUHMULLER: Actually, homework assignments
20 go from the FDA to the individual panel members and back to
21 the FDA. You can't have communications back and forth
22 between panel members because that then constitutes a panel
23 meeting and it has to be done in the open.

24 So the homework assignment will be coordinated
25 through the review team to the panel members who are willing

1 to participate and then the FDA will correlate and
2 assimilate that information and then redistribute to the
3 panel members for further review.

4 DR. YIN: And when do we expect that back to FDA?

5 DR. CURTIS: Within a week.

6 DR. STUHLMULLER: First, FDA has to send out the
7 information to the panel members.

8 DR. CURTIS: Within a week of receipt.

9 DR. YIN: Within a week from today?

10 DR. CURTIS: Within a week of their receiving it?
11 How quickly are you going to get it to them.

12 DR. YIN: You have to send it to FDA first.

13 DR. CURTIS: I think what John was saying is that
14 the homework assignment has to come from the FDA to the
15 members of the panel first.

16 DR. STUHLMULLER: The homework assignment to the
17 panel members is normally coordinated through the review
18 team to the panel members and then back to the FDA.

19 DR. YIN: Okay. The minute they receive the
20 homework assignment, they have a week.

21 DR. CURTIS: They have got one week to get it
22 back. Okay. Are there any other issues of safety or
23 effectiveness not adequately covered in the labeling which
24 need to be addressed in further investigations before or
25 after device approval. Comments on that? Okay.

1 We had a motion that was seconded for approval
2 with conditions. We have made comments about the labeling.
3 One condition would be with the changes in the labeling that
4 we have spelled out and another condition, then, would be
5 that there be post-approval studies, or study, that will be
6 worked out over the next week.

7 Anything else?

8 DR. WITTES: Can I add another condition and then
9 I can vote yes?

10 DR. CURTIS: Yes.

11 DR. WITTES: That there be an analysis of the
12 potential misclassification. I gather you have done it, but
13 just so that--

14 DR. CURTIS: Is the FDA clear what she is
15 referring to?

16 DR. SPYKER: Yes.

17 DR. CURTIS: So a third condition would be that
18 there be an analysis of the reclassification.

19 DR. WITTES: Yes.

20 DR. CURTIS: All right. Those are three
21 conditions there. Anything else that anybody else wants to
22 bring up right now?

23 DR. CERQUEIRA: The point I made before about--you
24 know, we talk about with ischemia, but without any
25 requirement to demonstrate any ischemia. Again, I would

1 worry that you could just go poking holes in people who have
2 got chest pain, but whether it is ischemic or not, some
3 demonstration of ischemia being present, I think, would be
4 essential.

5 DR. CURTIS: Where would you look for that to be?

6 DR. CERQUEIRA: The indications for usage where it
7 says secondary to myocardial ischemia. But should we
8 stipulate that the ischemia be objectively demonstrated?

9 DR. CURTIS: The way we decided to recommend that
10 it be worded is that it would be angina secondary to
11 atherosclerotic coronary disease. We took out the words
12 myocardial ischemia. That is how that indication is now
13 worded.

14 So you are suggesting that there be some
15 requirement for a demonstration of ischemia--

16 DR. CERQUEIRA: If you look at the design of this
17 trial, you had to have demonstrated ischemia in order to get
18 into it. Seven of the patients were excluded because they
19 had no demonstrated ischemia on that initial study. So I
20 think if we just say, "due to atherosclerotic coronary
21 disease," we basically are letting it open for everybody.

22 If we put in a proviso that there be some
23 objective documentation of--well, if we don't want to say
24 ischemia, we just can't say atherosclerotic heart disease.
25 What do the other panel members think?

1 DR. FERGUSON: I agree with that in the sense that
2 I am not sure what the parameters to demonstrate the
3 ischemia should be. I will let my cardiology colleagues say
4 that. But I think there ought to be some responsibility of
5 demonstration so that the instrument is not used on scar
6 tissue in a lot of hearts.

7 That was a prima facie condition in the study. I
8 don't know why we would uncover that so that the potential
9 for using the laser in non-recoverable myocardium would be
10 permitted.

11 DR. WEINTRAUB: We could change the wording and
12 just say "secondary to objectively demonstrated myocardial
13 ischemia due to coronary disease."

14 DR. SKORTON: I am very uncomfortable with the way
15 that this is going because there is also a big burden of
16 silent ischemia. The data that we are making our decision
17 on were not based on anything except people not feeling
18 well. We are saying this might all be a placebo effect as
19 far as we know. We didn't have demonstrated ischemia in
20 this study. We had perfusion abnormalities on thallium. We
21 didn't have evidence of acute wall-motion disturbances as a
22 criterion for it.

23 So I like the way it is written because it says,
24 "Patients refractory to medical treatment with stable
25 angina, class 3 and 4, from atherosclerotic coronary

1 disease." That's all the basis we have to approve this, I
2 think.

3 I understand what you are saying, I believe, and
4 that is that you want to be sure that there is something
5 being treated that really needs treatment. But I think we
6 are going tremendously on patient symptoms and the whole
7 burden of silent ischemia, we haven't talked about.

8 So I don't know, for example, whether some people
9 will use this device to treat patients who have, I don't
10 know, ambulatory monitoring evidence of ST segments going up
11 and down and no symptoms. I don't know. It opens up a
12 whole other thing to me.

13 DR. SPYKER: You may be assured that the
14 description of the clinical study will be as clear and clean
15 and complete as we can make it in a page or so in the
16 labeling. So that will certainly be a point there. There
17 also will be a section which will be new and improved from
18 the current label on individualization of treatment.

19 I have been taking notes on a number of things
20 that have been brought up to the panel that I think are
21 excellent candidates for explaining to the doc how to make a
22 decision on an individual patient. This is one of the more
23 important things we certainly will cover.

24 DR. SKORTON: Perhaps in that section, you could
25 reflect some of Manny's concerns.

1 DR. SPYKER: Yes; guaranteed.

2 DR. CURTIS: For the record, the motion on the
3 table is to approve the PMA with conditions, the conditions
4 being the alteration of the labeling as we discussed, that
5 there be a post-approval study to be worked out over the
6 next week or so. Am I forgetting anything?

7 DR. SPYKER: Analysis of potential
8 misclassification.

9 DR. CURTIS: I'm sorry; the potential
10 misclassification, have that be analyzed. There were three
11 conditions. We all discussed that transesophageal echo
12 should be used to verify successful creation of channels, if
13 you want to look at that as a condition. But we all agreed
14 on that, too.

15 DR. SPYKER: That is number one in the labeling
16 changes.

17 DR. CURTIS: So it is part of the labeling
18 changes. Am I forgetting anything?

19 We are going to go around the table now and vote.
20 Let's start over here. Dr. Skorton.

21 DR. SKORTON: Yes. Skorton, approve.

22 DR. VETROVEC: Yes. Vetovec, approve.

23 DR. CERQUEIRA: Cerqueira, approve.

24 DR. WEINTRAUB: Weintraub, approve.

25 DR. CASSCELLS: Casscells, approve.

1 DR. CALIFF: Califf, approve.

2 DR. FERGUSON: Ferguson, approve.

3 DR. WITTES: Wittes, approve.

4 DR. PARISI: Parisi, approve.

5 DR. CURTIS: The motion carries. It is approval
6 with conditions.

7 There are a few other panel questions that we have
8 been asked to address. How does the panel feel? Do you
9 want to go ahead and try to hash these out now or do you
10 want to take a break? All right. Short break.

11 [Break.]

12 DR. STUHLMULLER: Conditions and the panel follow
13 up is going to be done through a homework that follows the
14 routine procedures for homework assignments to panel members
15 and it will constitute a "subcommittee." I just need to
16 clarify that for the record.

17 DR. CURTIS: The final order of business today is
18 we had some questions posed to the panel on the future
19 development of TMR PMR. So these are going to be generic
20 issues as regards development of transmyocardial
21 revascularization and percutaneous myocardial
22 revascularization.

23 The first question; "What are the best methods for
24 assessing the effectiveness of TMR?" We are asked to
25 consider study design, primary outcome measures and

1 perfusion or metabolic imaging. We have to design the
2 perfect study, now, to do this. Make your suggestions.

3 DR. PARISI: If it is PMR, would it be legitimate
4 to do a blinded trial? I throw that right out because we
5 are not cutting open the chest. The catheter will go in and
6 you could do a sham procedure. I think that should be a
7 legitimate question, as a study design.

8 DR. CURTIS: I think that is a great suggestion.
9 Any comments on that? Good idea?

10 DR. CASSCELLS: I think that is a good idea.

11 DR. FERGUSON: I am not sure--you would have to
12 have the experts here, but I am not sure they wouldn't know
13 that something was going on unless you shot a beam of some
14 kind. If you just put the catheter in, are they not going
15 to react differently than when the laser--

16 DR. PARISI: I am not sure either. You are
17 talking about PMR, whether we could blind that.

18 DR. VETROVEC: Yes.

19 DR. PARISI: At least to the--

20 DR. FERGUSON: I understand what you are saying,
21 Al, but I think we would have to make certain of that
22 aspect.

23 DR. CURTIS: I would imagine there might be--if
24 you had one group of patients who, say, just had a left-
25 heart catheter on or something and then the other group had

1 the cath done but then somebody was stepping on a beam over
2 and over, stepping on a pedal over and over again, or
3 however you activate the thing, it probably would be pretty
4 obvious.

5 If you could have some patients who--you would
6 have to go through the same sort of process of stepping on a
7 pedal but some would actually have a laser delivered and
8 some would have nothing. That would be a way to do that.

9 DR. VETROVEC: But you are talking about taking
10 somebody from the lab and putting catheters in them which,
11 admittedly, doesn't have the risk of surgery but it has some
12 risk to it. I don't think you can justify that.

13 DR. PARISI: George, don't you think a lot of
14 people are going to use this in conjunction with a
15 revascularization of some kind, a PMR?

16 DR. VETROVEC: If it is done in conjunction with
17 balloon angioplasty, that's fine. But I would think, since
18 it is an experimental protocol, it wouldn't be something
19 that would necessarily be done on the fly.

20 DR. PARISI: I agree with that.

21 DR. CASSCELLS: But as part of a diagnostic study,
22 George, if you just had a patient who had terrible runoff in
23 all vessels and nothing--angioplasty, diabetic type patient,
24 for example--that patient could conceivably be randomized
25 during that same catheterization.

1 DR. VETROVEC: You can't get the consent if they
2 have been sedated.

3 DR. CASSCELLS: That's true.

4 DR. VETROVEC: You would have to consent everybody
5 before they went to the lab.

6 DR. SKORTON: We are not designing an experiment
7 today, but for purposes of advice to the FDA, could we all
8 agree that they should always be randomized and, when
9 possible, blinded?

10 DR. CALIFF: The other thing is that I think that
11 assessment of non-fatal endpoints can be done in a blinded
12 fashion even if the patient care is not blinded. I think
13 that is a critical issue. A lot of fields have gone through
14 this. It is not a hard thing to do. There are plenty of
15 examples of how to do it.

16 DR. WITTES: And all patients should have
17 endpoints, except the ones that are dead, of course.

18 DR. CALIFF: But that's it. I think that gets
19 into a very important philosophical issue about imaging
20 endpoints, for example. What is being done in other fields--
21 -for example, heart failure, rehospitalization, may be a key
22 endpoint--but if you are dead, that is obviously worse than
23 being rehospitalized. So you just say death or
24 rehospitalization. That way every patient counts.

25 DR. VETROVEC: One suggestion might be to consider

1 a different imaging endpoint. The issue was brought up
2 about whether this was--change in perfusion defects was
3 ischemia or not. Using wall motion would really be a better
4 endpoint for functional ischemia.

5 DR. CALIFF: George, do you think that an imaging
6 endpoint alone would be adequate for approval of the therapy
7 for--

8 DR. VETROVEC: No. I think you need to have that
9 the patients are better.

10 DR. CALIFF: Show a clinical benefit.

11 DR. VETROVEC: Show a clinical benefit. But if
12 you are looking for something of a mechanistic issue, I
13 think wall motion might be a better one.

14 DR. CERQUEIRA: I still favor some sort of
15 perfusion marker. I think you can probably combine both.
16 In some of the gated nuclear techniques, you can actually
17 get wall motion thickening as well as blood flow to those
18 areas.

19 DR. SKORTON: What did you mean, Rob, by a
20 clinical improvement, clinical benefit? What did you mean
21 by that? Symptomatic benefit?

22 DR. CALIFF: This is actually one of the easiest
23 things, from my simple-minded point of view. When a patient
24 is deciding, do I want a treatment or not, they are really
25 only three reasons that I know of why a patient would want a

1 treatment. One is to live longer. Another is to feel
2 better. And a third is to avoid an unpleasant negative
3 event.

4 All three of those things are pretty easy and
5 straightforward to measure. So a clinical benefit is
6 something that a patient can feel or relate to as opposed to
7 an imaging study which--you can imagine a lot of therapies,
8 and there have been a number, that may improve LV function
9 in the survivors but actually cause an increase in
10 mortality.

11 So clinical benefit would be something that a
12 patient could relate to or feel.

13 DR. SKORTON: But wouldn't that be mutually
14 exclusive? I guess that is my point. In the whole gamut of
15 ischemic heart disease, you asked in an ideal world what we
16 would do if we didn't have to worry about resources. I
17 would like to know the symptomatic status, some evidence
18 that there was an improvement based on imaging and, for
19 those with silent ischemia, which I think there are a lot of
20 people with silent ischemia, some way to evaluate that.

21 DR. CASSCELLS: I agree with that, David. I would
22 accept, depending on people's expertise, symptoms plus some
23 objective measure. It could be wall motion by echo or MUGA.
24 It could be perfusion by dipyridamole--

25 DR. CALIFF: So the exactive measure improved but

1 the symptoms didn't.

2 DR. CASSCELLS: That would be a problem,
3 absolutely. But ambulatory ST segment monitoring. I will
4 accept that.

5 DR. CALIFF: What if the symptoms clearly improved
6 but the objective measure didn't?

7 DR. SKORTON: My answer to that specific question
8 you are asking is that that would be great. That would be
9 peachy as far as I am concerned. But I think the state of
10 the art is still that there is discordance between these
11 methods and so I think we need more study. That is my
12 point.

13 DR. CURTIS: Is there an ideal imaging technique,
14 a way of doing this? Is there any one that we would
15 recommend or suggest over another?

16 DR. PARISI: We can find biased observers about
17 that, but I don't think if you look at totality of
18 cardiologists, that they would agree that there is one that
19 is so head and tails above the other. Maybe someone would
20 argue for PET imaging, if they really had that available.
21 But that is just not very practical.

22 DR. CURTIS: So symptomatic improvement and some
23 sort of imaging we still think is the way to go.

24 DR. CASSCELLS: We are the only center in the
25 country, we and UCLA, that could do this technique. I think

1 we would have to accept whatever people are good at.
2 Thallium is fairly sensitive and gives you viability. MIBI
3 is more sensitive but doesn't give viability. Perfusion,
4 echo is coming along very quickly.

5 It is a little bit of a moving target. I think if
6 there are some imaging data--and I agree with David that
7 imaging is not analogous exactly to ischemia but we
8 commonly--it is a pretty good proxy. Imaging plus symptoms
9 or wall motion plus symptoms. And I would accept ambulatory
10 ST segment monitoring plus symptoms without imaging, myself.

11 There are studies that are ongoing, I'm sure. I
12 don't know that all the various companies involved--we
13 probably ought not to penalize them, but we should serve
14 notice that the stuff has got to be complete. It has got to
15 be objective. It is ideally double blind. And that we want
16 symptoms plus some other objective endpoint.

17 DR. CERQUEIRA: I would also make the
18 recommendation that the endpoints be measured in a
19 centralized manner rather than just sort of clinical reports
20 and come up with a reasonable number of segments. You don't
21 want to over analyze and get so much scatter, but a highly
22 reproducible method of either perfusion or function, or
23 ideally both, in a standardized acquisition, standardized
24 process, and a standardized analysis, quantitative method
25 would be the way to do it.

1 DR. WITTES: I think one of the points that Larry
2 made should be echoed that there be a per-patient analysis
3 as well, per-segment, or whatever.

4 DR. CALIFF: I would just like to sort of try to
5 restate it see if people agree because they may not and I
6 feel strongly about this. If one accepted what--most people
7 nodded their heads about that. If symptoms clearly improve
8 but the objective parameter didn't, that would be good.
9 That would be okay. It would cause you to scratch your
10 head, but you would still say this is benefitting patients.

11 If one agreed that if the objective parameter
12 improved but the symptoms didn't that that would not be
13 enough to say this is approved for use in patients.

14 DR. CASSCELLS: Unless they lived longer.

15 DR. CALIFF: Let me get to that. Then one would
16 conclude that the primary endpoint of the study should be
17 how people feel and how long they live and that the panel
18 feels that it would be advisable and important to also
19 develop a pathophysiologic rationale and supportive data
20 through imaging. That is a recommendation.

21 One thing that I think is real important is that
22 when we say we will accept symptoms and imaging and Holter
23 monitoring, there should be--and this is one of the problems
24 we saw today--there should be a primary endpoint of a study
25 which is a testable hypothesis which is stated before the

1 study is started as a testable hypothesis.

2 We don't have a good way of combining those
3 disparate endpoints into a primary one. So, having said all
4 that, I would argue strongly that death and improvement in
5 symptoms is an easily usable primary endpoint and that an
6 imaging endpoint as a secondary, supportive data would be
7 the way to go.

8 DR. CASSCELLS: You could add the negative event
9 there, the hospitalization for unstable angina, and have all
10 three of your--

11 DR. CALIFF: Yes; those could be put into one
12 endpoint that is very testable with a single--

13 DR. CASSCELLS: Standard composite endpoint.

14 DR. SKORTON: I am 99 percent with you. The only
15 thing that sticks in my craw about that is that there is
16 nothing in the symptoms that I will be happy about in terms
17 of ventricular function unless they are in really bad heart
18 failure and you feel a little bit better because we are
19 talking about a general approach to a wide variety of
20 interventions here and not just a repeat of this thing.

21 So I think that most of the time what you said is
22 right but, for example, if you were testing a hypothesis
23 that a particular indication for a particular device was to
24 improve ventricular function, either regionally or globally,
25 I don't think symptoms are a good way to measure that.

1 Except for that, I would agree.

2 DR. CALIFF: But I think that is a great
3 scientific question but it is not a clinical question. It
4 is not a question for clinical therapeutics. I would refer
5 you to heart-failure therapies that improve left-ventricular
6 function but that kill people.

7 DR. SKORTON: That is just a restatement of the
8 state of the art, not the goal. The goal is, depending on
9 the patient and the question you are asking, to improve some
10 pathophysiological process. The current state that we are
11 at now, everybody would agree that it is nice if you feel
12 better, it is nice if you don't die as often, but there may
13 be something in between those two or different than those
14 two.

15 For example, once again, if somebody has silent
16 ischemia and you have evidence that they are doing worse and
17 worse and worse, the symptomatic endpoint will be helpful,
18 if they are diabetic or just happen to be in the subgroup
19 for those.

20 I am not arguing with the basic point of what you
21 are saying. I just think that, from my way of thinking, it
22 would be too rigid to always make it that way. There might
23 be an occasional study in which an important primary
24 endpoint would be a MUGA scan or something else with the
25 ventricular function. But, in general, I agree with you.

1 DR. CASSCELLS: Let me add that there is this
2 arrhythmia issue that has been raised. We could have
3 someone who felt better, did better on a treadmill, had
4 better ST segment performance on a Holter, had a better
5 thallium or MIBI scan and yet developed ventricular
6 tachycardia.

7 Of course, that followed long enough, presumably
8 it would be a mortality endpoint. But I would favor some
9 sort of stress test, either simple Duke stress testing or
10 ideally with some imaging modality. As long as it is
11 consistent within that study, I think we will get good
12 information.

13 DR. SKORTON: You wouldn't have to change your
14 wording, from my point of view. I would only add a phrase
15 that said, "in specific subsets, or specific studies,
16 additional primary endpoints might be useful," something
17 like that.

18 DR. CALIFF: That is quite reasonable. I think
19 Dr. Casscells raised another issue which I have really been
20 struggling with and that is the statement, "Are you
21 comfortable with safety?" When it comes to
22 revascularization procedures on the heart, or anything that
23 involves major manipulation of things in the chest, moderate
24 differences or increases in mortality require large sample
25 sizes to pick up.

1 So I would say that the data we looked at today
2 could be incompatible with a two-fold increase in mortality
3 with the experimental treatment compared with control. That
4 is not what the data showed as a point estimate, but we are
5 all familiar with studies which show that you really can't
6 tell safety, because of the confidence intervals around the
7 point estimate, unless you have a fairly large sample size.

8 I would like it if there was some guidance to
9 companies about what assessing safety really means,
10 quantitatively.

11 DR. CASSCELLS: So you would suggest, for example,
12 they should have the power to exclude a 25 percent increase
13 in mortality, for example?

14 DR. CALIFF: Something like that. I don't know
15 what the threshold ought to be but--

16 DR. CASSCELLS: 80 percent power.

17 DR. CALIFF: But study 100 patients in each group
18 and, if the numbers look about the same, then they must be
19 the same. That seems like a step backwards in scientific
20 thinking.

21 DR. WITTES: I agree fully. The problem is to
22 exclude something like 25 percent is a huge study. So it
23 may be that it has got to be excluding it doubly or
24 something like that.

25 DR. CALIFF: As long as it was something.

1 DR. WITTES: It needs to be on the table what that
2 number is.

3 DR. SPYKER: Practically what happens is we sort
4 of decide with the sponsor what is--well, I guess we
5 basically decide how many is reasonable to expect to be
6 studied and that depends on how much the device is used.
7 And then we look at what is the detectable increase in major
8 adverse events. Usually it is twofold or threefold. That
9 is the kind of typical postmarketing study objective, to
10 detect a threefold increase in some serious problem.

11 DR. CALIFF: Does that seem reasonable from the
12 point of view of the public health to approve devices that
13 may be increasing the risk of death by two-and-a-half-fold?
14 That is bothersome to me.

15 DR. CASSCELLS: Dan is referring to postmarketing
16 surveillance, Bob, where you have got hundreds of possible
17 outcomes. You have got a big Bonferoni problem.

18 DR. CALIFF: You have no earthly idea whether you
19 are increasing or decreasing. You have just got a number.

20 DR. CASSCELLS: We should do better than threefold
21 in a prospective study of PMR that is going to use important
22 clinical endpoints. But I think if you are looking for the
23 occasional agranular cytositis and Sioux City, Iowa comes up
24 with a few extra cases it has got to exceed by threefold the
25 instance in that town, that is a different statistical

1 issue, don't you think?

2 DR. CURTIS: We are talking about primary outcome
3 measures and the types of imaging. Any comments about study
4 designs? One of the things I was just thinking about is, I
5 guess it comes up in one of the other questions here about
6 adjunct to CABG. It might be nice to think about some of
7 these studies as being an adjunct to CABG or an adjunct to
8 whatever, left-heart cath or something like that, to get at
9 the issue of blinding.

10 The problem with that in following up patients is
11 that if you go ahead and do bypass surgery, you hope, even
12 without the TMR, that the patients come out in a much better
13 anginal class than they went in.

14 So it would become much harder to see what kind of
15 an effect you had from your TMR on top of doing your, say,
16 repeat bypass surgery. And you could be left with much
17 larger sample sizes or longer follow ups in order to sort
18 out and difference there.

19 I am not sure that is avoidable. Ultimately, it
20 would be kind of nice to see if there is any added benefit
21 to the TMR, but I think the study becomes more expensive,
22 more difficult, bigger. I think that is unavoidable.

23 DR. CALIFF: One approach to that, which increases
24 the screening costs, is to just take as patients, patients
25 that you know you can't revascularize all of the at-risk

1 myocardium. Those patients are more and more frequent, as
2 we all know.

3 Again, I just have to point out that we are
4 talking about 8-plus-million people in the U.S. alone. So
5 doing a study of reasonable size doesn't seem to me to be
6 too much to ask.

7 DR. CURTIS: I think that is true. I think you
8 are making a good point. The person who would not be
9 appropriate for the study, there are three discrete proximal
10 lesions that you can bypass well and you are going to put an
11 IMA in. It would be hard to know that you could do a whole
12 lot more by doing TMR on top of that. If you have bad
13 runoff, poor distal vessels, that sort of thing.

14 So if you had the proper screening criteria to get
15 the patients into the study to start with, you would
16 probably have a higher yield from that.

17 DR. CASSCELLS: I might add, Anne, that we had a
18 probably in this last company that they were looking at the
19 data the whole way along and they have to have some
20 predetermined endpoints and the Data Safety and Monitoring
21 Committee has got to publish that and it should include an
22 epidemiologist on that committee.

23 This study would not--we have got beyond these
24 kinds of studies in cardiology twenty years ago. I think
25 everybody knows that the standards are going to be much

1 higher for PMR. The cardiologists are involved and the
2 company probably ought to expect that.

3 But it is fair to just reiterate that this kind of
4 thing that got through today is probably not going to pass
5 muster next time.

6 DR. CALIFF: I think the surgeons should be
7 required to stay for the section of the panel on how to
8 design better studies.

9 DR. KURTZMAN: Steve Kurtzman, cardiologist in the
10 Office of Device Evaluation. We at the FDA have also
11 considered, as a modality for assessing success, exercise
12 time, not just stress imaging but simple exercise time on a
13 treadmill. We would like to know what you think about that.

14 DR. PARISI: I think that that is good if you can
15 blind the person who is doing the test. But if they know
16 what procedure the person got, then there is inherent bias
17 in that as well. But it is certainly one of the classic
18 ways that have been used in drug studies to assess angina
19 efficacy.

20 DR. CALIFF: I think it is a good objective
21 endpoint. Some of the problems drop out just like imaging.
22 The other trap that I believe one would fall into is you can
23 do a much smaller study that way. But, again, this issue of
24 what an adequate test of safety is, I would rather see
25 studies designed to make sure you are not missing some

1 incremental risk of clinical endpoints.

2 Then you can do a subset with exercise tests with
3 a lower sample size.

4 DR. KURTZMAN: It is also time-to-angina and time-
5 to-ST-depression, also.

6 DR. CALIFF: Nowadays, one of the classic studies-
7 -that ACME study is the classic.

8 DR. PARISI: Actually, the statistician was Pam
9 Hardigan who came up--the problem with time-to-angina is
10 that if you have got a patient who is angina-free, then you
11 lose that patient. But if you do the angina-free survival
12 time on the treadmill, make the time on the treadmill like
13 life survival, then the angina-free patient is kept in
14 there. The could be very useful.

15 DR. CALIFF: It is a very sensitive endpoint.

16 DR. CURTIS: You probably recommend paired
17 treadmills before treatment; right?

18 DR. CALIFF: I think that is ideal. But, again,
19 if you have a randomized control group, at least you have
20 the same learning in both.

21 DR. CURTIS: That's true. It depends on how the
22 study is designed.

23 DR. CASSCELLS: I would say something about the
24 crossovers, too. As I said last July, when you take a
25 number of patients and say we have got this great new

1 technology but we have to flip a coin because the darned FDA
2 requires it and we hope you get heads. Oh, shoot; you got
3 tails. You can't have TMR. That is how you get everybody
4 wanting to crossover within three months.

5 I am not sure how you control for that. But these
6 patients were stamped into TMR. I made that point in July
7 and it didn't bear repeating today. But there has got to be
8 a way to not do that. We have never, in drug or device
9 trials, with this very same type of patient, angina or
10 unstable angina, had 100 percent crossover within six
11 months.

12 That was an evangelical artifact. I am not sure
13 how to--

14 DR. WITTES: Actually, in this study, once they
15 changed the protocol, they didn't have it any more. So I
16 think maybe that is the answer.

17 DR. CASSCELLS: They crossed in six months.

18 DR. WITTES: But the point was in the first set of
19 months, they crossed in two months, in three months. In the
20 second one, they crossed in six months. If you have a clear
21 endpoint, you make sure that the protocol specifies
22 crossover only after that time. There will be some
23 noncompliance but not a whole lot.

24 DR. CALIFF: I want to point out, because I don't
25 want to sound like somebody from the FDA, but there are

1 federal regulations about selection of investigators.
2 Investigators who do not follow the protocol should be fired
3 from being investigators. I would also point out, in this
4 particular case, there would be some regulation against
5 people with an equity interest in the company in an unbonded
6 setting enrolling patients and following them in the study.
7 I don't understand how that can--

8 DR. CASSCELLS: No; I agree.

9 DR. CALIFF: There may not be a regulation on that
10 but, if there is not, there should at least be guidance.
11 That would place the results under some scrutiny or some
12 concern about whether it was objective.

13 DR. YIN: I think you are right. The company
14 should engage a monitor. Maybe if the monitor is not doing
15 their job, then that is what happens. Every study, every
16 sponsor, must have clinical monitor.

17 DR. CALIFF: But what about equity interest of
18 investigators in unblinded studies?

19 DR. YIN: That is hard to enforce. That is really
20 very difficult to enforce.

21 DR. WITTES: Why?

22 DR. YIN: But we do the--

23 DR. CASSCELLS: Disclosure. You do the
24 disclosure. But even the disclosure is not water-tight.
25 Several young surgeons got up here today and said they had

1 no financial interest except for their air fare. These
2 three, I'm sure, were very idealistic but the problem you
3 run across is that companies promise future arrangements
4 with people and your consent form does not deal with that.

5 I think Dr. Califf is absolutely right that the
6 disclosure can be stronger. People can be put on notice
7 that the question, if by some chance I am still on the
8 panel, and I am going to be looking at friends up there like
9 I have this time, but I am going to have to ask what kinds
10 of future arrangements have been discussed with the company,
11 not current equity arrangements or consultantcies, but
12 leadership of trials, authorship of articles, various things
13 like this.

14 These are not crimes. It is just that this kind
15 of disclosure is worthwhile.

16 DR. CURTIS: Getting back to the issue of the
17 crossovers, there is one great example in this study about
18 why assumptions are not always borne out. So many of the
19 crossovers were the patients with unstable angina. They
20 were the very ones who did the worst.

21 So there was a bias or a rush among investigators
22 to say, "Well, I tried my two weeks and the patient is too
23 unstable. I am going to rush him in there and do my TMR now
24 and cross him over." A lot of those patients got hurt.

25 I think the thought that we would be hurting a

1 patient by making a patient by making him wait six months is
2 not true, actually. In this case, it was exactly the
3 opposite. So I think a reasonable limit--a patient has been
4 going along the way they have been going for a while. If
5 you say, "Well, heads, you get the TMR right away. Tails,
6 you may have to wait six months but I can get it to you
7 then," is not too much to ask for somebody.

8 Saying that you are never going to get it, it just
9 runs it into the crossover area. So I think that is a good
10 way to look at it.

11 We didn't discuss No. 14, which clinical
12 classification of angina should be employed in future
13 studies; the Canadian Cardiovascular Society, New York Heart
14 Association or American Heart Association?

15 DR. CALIFF: What is the American Heart
16 Association class?

17 DR. CURTIS: I was hoping you were going to answer
18 that.

19 DR. PARISI: I thought the New York Heart
20 Association was a classification of heart failure.

21 DR. WITTES: They are very similar, aren't they?

22 DR. CALIFF: Yes; they are quite similar. I would
23 say--

24 DR. PARISI: Should be consistently applied
25 throughout the study.

1 DR. CALIFF: It probably doesn't matter as long as
2 it is done objectively by someone who is--

3 DR. CURTIS: Objectively and consistently.
4 Whatever you want.

5 DR. CASSCELLS: I think the one, and Rob may
6 correct me on this, that has been validated with a mortality
7 endpoint most extensively is the Brownwald classification.
8 Is that true?

9 DR. PARISI: That is unstable angina.

10 DR. CASSCELLS: For unstable angina. But for
11 exertional angina, they are all predictive.

12 DR. CURTIS: I mentioned something about
13 adjunctive cath studies. I am sure that will come up. I
14 was wondering if we could make--we started to and then I
15 think got away from it--how should TMR studies be done?
16 What would be the best way? We would like to blind it but
17 patients for those kinds of studies would have to be
18 identified by having had a left-heart cath already.

19 You wouldn't know somebody could benefit from a
20 procedure like that. Of course, I would think a lot of
21 times, patients have probably had more than one
22 catheterization. Is there a way to do a study like that
23 that would get the best information? I don't know that I
24 have an answer to that, but I just wanted to bring up that
25 subject.

1 DR. PARISI: I think if you know the patient is
2 having a concurrent procedure and can predict it, then I
3 think you could randomize.

4 DR. CURTIS: Concurrent procedure such as?

5 DR. PARISI: For instance, as you say, the patient
6 has had three prior PTCAs and you know from the last cath,
7 things are very iffy, then you could discuss with the
8 patient, "Look, if you don't have a really suitable lesion,
9 can I randomize you to this treatment or not?"

10 So you know you are going in there ahead. But I
11 think to go in there just to go in when you don't know what
12 you are getting into, I don't think you could do it. But if
13 you know what you are getting into, a priori, for some
14 reason, and you are going to be in there for a legitimate
15 reason, then I think you can randomize the patient.

16 DR. CURTIS: So you could randomize people to,
17 say, PTCA or stent versus PMR.

18 DR. PARISI: No; I don't think you could do that.

19 DR. CURTIS: Okay.

20 DR. PARISI: What I am saying is that if the
21 patient has a situation where you know from the previous
22 anatomy that they are going to be a very iffy situation--
23 they will be eligible for a PTCA or a stent, or they won't
24 be eligible--

25 DR. CURTIS: Plus, minus?

1 DR. PARISI: No; or they won't be. In the first
2 one, they won't be. Then you could get consent if they are
3 not eligible for the stent or the balloon treatment to do
4 the PMR. The other one, of course, is that you have several
5 areas of the heart and one area is treated with PMR and the
6 other area is treated with a stent.

7 I think that is going to come up, to some extent.
8 Those patients, I think, you could clearly randomize them.
9 But I think it is going to take a large number. It is very
10 complex because you are partially revascularizing the
11 patient and then doing this other acupuncture treatment and
12 I don't know what is going to happen.

13 DR. CURTIS: I am wondering if you couldn't take a
14 patient in whom their left heart count shows that you don't
15 think you are going to get a great result and whether you
16 couldn't randomize them to having PTCA and/or stent,
17 whatever--an attempt to open up the artery, plus/minus PMR.
18 Some of the patients would get it and some not.

19 DR. VETROVEC: The problem with that is you are
20 not going to know symptomatically whether they get better
21 because of the PMR or because of the stent you put in. I
22 think you would be much better off from a scientific
23 standpoint to isolate yourself initially only the people
24 that have no other choice.

25 DR. PARISI: That would be the best way to do it.

1 DR. CALIFF: I disagree completely with George.

2 DR. CURTIS: Oh, good.

3 DR. CALIFF: In fact, this gives me a chance to
4 get the last thing off my mind about device studies. It
5 bothers me to take idealized populations and do the studies
6 in very experienced, high-quality centers and show
7 conceptually that the treatment works and then turn it loose
8 to be done on all kinds of patients.

9 I would rather actually see more real-world
10 studies in populations like those that are really going to
11 be treated when the device is let go with the kinds of
12 operators who are going to be using the device. It is a
13 very different approach. I could be totally wrong, but I
14 think scientifically, to answer the conceptual question,
15 could the device work, George and I are in complete
16 agreement.

17 The question is whether there is a compelling need
18 societally to actually do the trials in more real-world
19 populations.

20 DR. VETROVEC: That is a good point. I was
21 looking at it purely from the science. I think that is part
22 of what we are anxious about about TMR.

23 DR. CASSCELLS: We were just looking at stent
24 versus PTCA trials and the event rates are about a fourth
25 the event rates in stents put in in clinical databases or in

1 trials that somehow involve stents but are done in the real
2 world.

3 I think the reason is because the trials were all
4 done in single idealized lesions to prove whether stenting
5 could make a difference. So you end up with sort of a funny
6 impression of what the treatment effect may be.

7 DR. VETROVEC: It is the Barry trial that only
8 applied to 12 percent of the patients being treated in the
9 cath lab.

10 DR. CURTIS: I think those were all the questions
11 we had there. Any other points anybody wants to bring up?

12 DR. STUHMULLER: Again, procedurally, I just need
13 to clarify that the TMR homework assignment regarding a
14 number of panel members that will be involved will be
15 determined in accordance with the Federal Advisory Committee
16 Act.

17 DR. SPYKER: I would surely like to thank the
18 panel. This has been, certainly, entertaining for me,
19 educational. I certainly thank you for your perseverance.

20 DR. CURTIS: Shall we move to adjourn?

21 DR. YIN: Especially for me. This is my probably
22 one and only panel with you guys. It is wonderful. Thank
23 you. A good education.

24 [Moved and seconded to adjourn.]

25 DR. CURTIS: We are adjourned.

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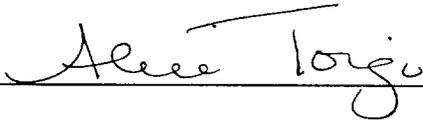
1 [Whereupon, at 4:25 p.m., the meeting was
2 adjourned.]

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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.



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