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CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Coverage Advisory Committee

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Holiday Inn Inner Harbor
Lombard and Howard Street
Baltimore, Maryland

Panelists

Chairperson
Ronald M. Davis, M.D.

Vice-Chairperson
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Voting Members
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Steven N. Goodman, M.D., M.H.S., Ph.D.
David J. Cohen, M.D., M.Sc.
Lishan Aklog, M.D.

HCFA Liaison
Steve Phurrough, M.D., M.P.A.

Consumer Representative
Charles J. Queenan, III

Industry Representative
Michael Lacey, M.Sc.

Panelists (Continued)

Non-Voting Guest Panelists
Joel Cooper, M.D.
Eric A. Rose, M.D.

Executive Secretary
Michelle Atkinson

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PANEL PROCEEDINGS

(The meeting was called to order at 8:07 a.m., Wednesday, July 14, 2004.)

MS. ATKINSON: Welcome committee chairperson, members and guests. I am Michelle Atkinson, and I'm an executive secretary for the Medicare Coverage Advisory Committee. The committee is here today to discuss and make recommendations concerning the quality of the evidence and related issues for the use of transmyocardial revascularization and percutaneous myocardial revascularization to treat severe angina.

The following announcement addresses conflict of interest issues associated with this meeting. The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employers' financial interests. To determine if any conflict existed, the Agency reviewed all financial interests reported by the committee participants. The Agency has determined that all members may participate in the matters before the committee today.

With respect to all other participants,

we ask in the interests of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products or services they may wish to comment on. This includes direct financial investments, consulting fees, and significant institutional support. You must answer the questions to the disclosure statement at the beginning of your presentation to be recorded into the official record.

And now I would like to turn the meeting other to Dr. Steve Phurrough.

DR. PHURROUGH: Good morning. Thank you for your attendance and a special thank you to the panel members for your willingness to serve and provide us input today on this particular topic.

Just a quick explanation of the purpose of the meeting: We at CMS in the coverage group will be, over the next couple of years, having more meetings than we have in the past in addressing issues that perhaps have not reached the NCD stage yet. There are a number of issues where we have received comments, received suggestions that we address particular issues.

We're not comfortable that they're ready for that particular stage and so we are going to be asking the Medicare Coverage Advisory Committee to provide us input into what the level of evidence is and what the current technology state is of certain particular procedures, devices and technologies and so forth over the next couple of years.

This is one of our first meetings to do that and we appreciate your willingness to provide input on that. We also appreciate those who are with us today to provide expert comments from the industry and the clinicians community and look forward to your comments. With that, Ron?

DR. DAVIS: Thank you, Dr. Phurrough, and I will add my good morning to the good mornings that you have already received. I am Ron Davis, with the Henry Ford Health System, and chair of the committee. I want to draw to the attention of the members of the panel the disclosure statement that is in your packet, and the disclosure statement asks us to indicate our name, our occupation, our place of work, and our answers to four questions that are listed on this sheet, and of course if there are any other

possible conflicts of interest or any other types of disclosure that people would like to make, we would encourage them to do so.
And so we will go around the table and ask people to introduce themselves and provide the answers to the questions that are on the disclosure statement. I'm also asked to state or reiterate the charge to the panel. I think it's fairly straightforward and it includes reviewing the materials that have been distributed to us, listening carefully to the presentations that are made to us here today, as well as to the comments from members of the public, and to the best of our ability answer the questions that have been posed to us as to the strength of the evidence and the effectiveness of the interventions that are under consideration today.
So, I will start out and again introduce myself as a preventive medicine physician from the Henry Ford Health System in Detroit. I also want to disclose that I am a member of the board of trustees of the American Medical Association. However, I am not an official representative of the AMA at this particular meeting. My answers to the four

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questions on the disclosure statement are no. Barbara?

DR. MCNEIL: I'm Barbara McNeil. I work at Harvard Medical School. I do not have any financial interests. With regard to other conflicts, I serve on the Blue Cross Medical Advisory Committee and that committee has reviewed TMR plus CABG. And nobody has contacted me with regard to this particular problem.

DR. BLACK: My name is Edgar Black. I am one of the medical directors at Excellus Blue Cross Blue Shield, headquartered in Rochester, New York. My answers to the two financial interest questions are no. In terms of other conflicts, I chair our health plans medical policy committee, I serve on the Blue Cross Blue Shield Association Medical Advisory Panel and also on the association's medical policy panel, and all three of those entities have discussed these technologies. My answer is no to being contacted by other groups.

DR. GOODMAN: My name is Steve Goodman. I am an epidemiologist biostatistician from Johns Hopkins. My answer is no to all of these questions, although I also serve on the medical

advisory panel for Blue Cross Blue Shield which, as has been indicated, has discussed the TMR plus CABG issue.

DR. COHEN: I am David Cohen. I'm an interventional cardiologist from Beth Israel Deaconess Medical Center and Harvard Medical School in Boston. I have received grant support from Acordis, which is a manufacturer of a nonapproved laser device, the Biosense system. Otherwise, no other grant support to report. I have not served on any other advisory committees and have not been contacted by any parties.

DR. AKLOG: My name is Lishan Aklog. I'm a cardiothoracic surgeon at Mount Sinai Medical Center in New York and I have no financial interests or other conflicts.

MR. QUEENAN: My name is Charlie Queenan, I'm the consumer representative. I am the executive vice president and chief financial officer of an early state biotech named MRN Bio. I don't have any stock or other financial interests in either of the companies listed, nor have I received any financial support, and I haven't served on any panels that have reviewed this topic.

MR. LACEY: My name is Michael Lacey. I am the director of health economics and outcomes research at Boston Scientific, and I am the industry rep for today's panel. I have no financial interests in either of these companies and I don't have any other conflicts.

DR. COOPER: I am Joel Cooper, I'm a thoracic surgeon and chief of cardiothoracic surgery at Washington University School of Medicine. My answer is no to the questions regarding financial interests or conflict. I am the immediate past president of the American Association for Thoracic Surgery and sit on the council of that organization, but I am not here in any official capacity representing the AATS.

DR. ROSE: My name is Eric Rose, I am the chair of surgery at Columbia University in New York and my answer to the four questions is no.

DR. DAVIS: Thank you very much. I also wanted to mention for people in the room as well as for the record that Doctors Rita Redberg and Mark Slaughter, who are members of the committee, are unable to be with us here today. With that, we will proceed with the next item on the agenda, which is to receive a

presentation from CMS concerning the request and the voting questions, and we will hear from Dr. Lori Paserchia.

DR. PASERCHIA: Good morning and welcome. I want to thank you for participating in this MCAC today. The focus will be transmyocardial revascularization and percutaneous myocardial revascularization. I am Lori Paserchia, a medical officer in the Coverage and Analysis Group. My teammates are JoAnna Baldwin, the lead analyst; Michelle Atkinson, the executive secretary; Marcel Saliv, the director of the division of medical and surgical services; and Steve Phurrough, the director of the Coverage and Analysis Group.

My presentation has four goals, to present the purpose of this MCAC meeting, to provide the current FDA status, as well as Medicare coverage policy for TMR and PMR, and to introduce the questions that the panel, you will address this afternoon.

Briefly stated, the purpose is to have a group of experts come together to discuss and evaluate the evidence currently available for TMR, TMR plus CABG, and PMR.

FDA approvals currently, there is not an FDA-approved device for PMR for any indication. With regards to TMR, there are currently two FDA-approved devices, they are indicated for stable angina refractory to medical treatment, secondary to objectively demonstrated coronary atherosclerosis that is not amenable to direct coronary revascularization.

One device is approved for Canadian Cardiovascular Society class IV patients, while the other device is approved for class III or class IV patients. Lastly, the labeling for one of the devices notes that the safety and efficacy has not been established for patients undergoing CABG or percutaneous coronary intervention. The labeling for the other device is silent on this matter.

CMS currently covers TMR and TMR plus CABG as late or last resort therapy for patients with severe stable or unstable angina, in other words, CCS class III or IV, that is refractory to medical therapy, but has areas of viable myocardium not amenable to revascularization in patients with an ejection fraction greater than 25 percent. The patient must be clinically stable

and the facility must have properly trained physicians with adequate support services. In the absence of FDA approval, Medicare currently has not issued a national coverage determination for PMR. There are four identical questions for each of the three procedures that this MCAC panel will address, TMR, TMR plus CABG, and PMR. Question 1: How well does the evidence address the effectiveness of the procedure in the treatment of chronic refractory angina in study patients for whom other methods of revascularization are contraindicated? Question 2A: How confident are you in the validity of the scientific data for each of the following outcomes: Short-term mortality, long-term survival, morbidity, and quality of life? Question 2B: How likely is it that the procedure will improve the following outcomes compared to usual care: Short-term mortality, long-term survival, morbidity, quality of life? Question 3: How confident are you that the procedure will produce a clinically important net health benefit in the treatment of chronic

refractory angina in study patients for whom other methods of revascularization are contraindicated? And lastly, question 4: Based on the literature presented, how likely is it that the results of the procedure in the treatment of chronic medically refractory angina can be generalized to the Medicare population, in other words, those aged 65 and older, and providers, in other words, facilities and physicians in community practice?

Thank you.

DR. DAVIS: Thank you very much. Sorry for mispronouncing your name. It's Dr. Paserchia.

Thank you.

The next item on the agenda is a presentation of the technology assessment from AHRQ, Dr. Deborah Zarin.

DR. ZARIN: Thank you. My goal today is to review the results of the technology assessment that was done for AHRQ by the Duke evidence-based practice center. Unfortunately being summer, the Duke folks, each one of them are on vacation at this time so I am presenting their evidence report. My goal here, especially given the number of cardiologists in the room, is not to

pretend to be an expert, but to give the panel an overview of the situation basically and present this sort of as the basis for the rest of the discussion today.

As you heard, we're really talking about what you might call three different technologies in term of how the data is organized, the use of TMR alone, the use of TMR with CABG, and the use of PMR. So the task assigned to Duke was to really summarize and describe the technologies and review the peer-reviewed literature. The third task, which was to seek information on ongoing clinical trials, they did, and at least using publicly available databases of trials like clinicaltrials.gov didn't find any relevant ongoing trials.

As I think probably all of you know, this is what TMR is, it uses a laser to create channels in the myocardium. It requires a left anterior thoracotomy. The channel goes all the way through the myocardium. And the literature we read was, some of it was more specific than others of it in terms of the location and density of the channel placement, which is relevant perhaps later in your discussion of how generalizable some of

the findings are, does a TMR done by surgeons in a trial, how does that relate to TMR done in the community and how prescriptive is the procedure? It was a little bit hard for us to tell based on the literature.

The other point I'll make is as you heard, there are two laser systems that are approved by the FDA and we couldn't find any literature that would directly compare them against each other, so we really weren't able to comment on impressions of how they compared with each other. Although some of the literature refers to things about that, we didn't find any direct data.

PMR uses a catheter-based system entry via the femoral artery, and the channels do not penetrate the full wall thickness, that's one of the key points. And as you heard, there are no PMR devices FDA-approved at this time, there are two TMR devices approved.

There is a lot of discussion in the literature about possible mechanisms of action, there is no real consensus about exactly what the mechanism of action is. I think, though, there is sort of perhaps growing sense that it might be a

combination of some of the above, some of the different mechanisms. But this is also relevant when you read the data to think through how confident you feel in some of the findings. It's sometimes a little problematic when there is no consensus on the mechanism.

In terms of where we found information on current utilization of these procedures, there is a database that's organized by the Society of Thoracic Surgery which involves about two-thirds of the hospitals that do cardiothoracic surgery, and it has patient, clinical and acute outcome data on over 2 million procedures. There is a report by Peterson that I think you will be hearing some about today that reviews, that analyzes that data for the years 1998 to 2001. Briefly, though, one thing you find out by looking at the Peterson article, and that was that the use of TMR is growing over that time period. At this point 36 percent of the hospitals in their database are now performing TMR, with a median volume of 12 procedures per hospital, but a wide range, and what you can see is that the middle bar with almost 2,500 procedures is TMR plus CABG, and that seems to be where a lot of the

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growth in its use is. On the left you see TMR only and on the right is TMR with other cardiac procedures, for example a valve replacement or something like that.

So the literature search strategy is described in the technology assessment, the studies were rated on their quality, which you can find in Appendix 8.3, details of how those ratings were done, but basically a modified Jadad scale was used for the randomized controlled trials and Sackett criteria also modified were used to rate the observational studies. And evidence tables for all of the studies are found in Appendix 8.4.

This is basically what the literature was. In terms of, the left column is the number of RCTs, and the right column is the number of observational studies for each of the three technologies. In parentheses you see there were three longer-term follow-ups of originally shorter-term studies, so two on TMR alone and one on TMR plus CABG.

In thinking about the outcome measures, what you'll find when you look through this literature is that there is an array of procedures and a broad array of outcome measures, and it's

sometimes a little bit difficult to get your mind around it. One way of thinking about it is that the shorter term, especially the 30-day or sometimes it's in hospital and 30-day mortality, otherwise referred to as perioperative mortality, can be thought of as a measure of safety of the procedure. The longer-term mortality and the longer-term morbidity are certainly considered measures of effectiveness. The 30-day morbidity is perhaps, some people consider that effectiveness, some people consider that safety, but there are sort of ways of organizing your thoughts about the data.

So when you look at the data there are some issues to consider. One is the specifics of the procedure that was used in each study, the device, the intensity, meaning, for example, how many channels were placed in the heart. The control condition, and if the control condition was maximal medication therapy, different studies used different levels of precision in describing what exactly that therapy was and also the extent to which you feel confident that the medication therapy was really the same in the control and the intervention arm.

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Also in the control condition was CABG. There has been some discussion in some of the literature about whether the CABG done when it's done in combination with TMR is sort of exactly the same as the CABG done when it's done alone, and we'll come back to that later, so that's something to consider. Specifics of the patient population, for example, level of the angina class, percentage of patients who've had an MI and in particular a very recent MI, and other things. The short-term outcomes, as I mentioned, might be considered a measure of safety, and some authors worry about the placebo effect influencing short-term morbidity. For example, angina at 30 days, most of the studies are not blinded in terms of the assessor of the angina. Sometimes they are blinded for the assessor, but they're typically not blinded for the patient, so there is a concern about the placebo effect at 30 days. There's a little less concern among many authors about the placebo effect in the longer-term measures. However, when you get to the longer-term measures, you get into complications of attrition and cross-over in the different

studies, and also the additional cardiac interventions that occurred in the year or sometimes in some of these follow-up studies in the longer term after that. So these are just things you have to consider when you look at those articles.

So TMR only, basically shows when you compare TMR plus maximum medical therapy to just maximum medical therapy, and that's really what we mean by TMR only in these studies, they showed no -- well, this is the 30-day mortality in terms of perioperative risks. 30-day morbidity was harder, it was hard to find reports that documented morbidity in both the control and the intervention groups. Apparently the Allen PMA application to the FDA included it but the published study did not so we weren't able to review that for this technology assessment.

But what you see listed are the types of morbidities that people described and typically they describe it in the intervention group, but again, we don't have it in the control group.

But the one-year mortality in the TMR only RCTs really, again, showed no significant difference between the intervention and the

control group. The five-year mortality in the one five-year follow-up by Allen did show a significant difference, so that the Allen five-year follow-up showed a survival benefit, if you will, in the TMR group compared to the control group.

What you do find is long-term morbidity benefit in the TMR RCTs, the seven RCTs. All seven showed an improvement of angina class at one year and there were various measures of how they measured that, percentage in class III-IV, percentage free of angina symptoms, et cetera. Two of the studies showed reductions in hospitalization or coronary events at one year, two showed improved exercise time at one year, and all four that measured quality of life showed improved quality of life at one year. So this is where you're seeing the benefit, or the main benefit in the TMR only studies.

Again, the Allen five-year follow-up to his one-year RCT actually showed an increased survival in the TMR group, decrease in angina at five years in the TMR group compared to the control group, and a decrease in post-enrollment cardiac intervention.

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So now we move on to the combination of TMR plus CABG and here we're looking at studies that look at TMR plus CABG compared to CABG-alone. And the issue is people who are undergoing CABG but have areas of the myocardium that are viable but are not amenable to revascularization, and the question is whether doing TMR in addition to the CABG has a health benefit.

So the perioperative mortality, the 30-day mortality was lower in the TMR plus CABG group compared to the CABG-alone group, and there hasn't been a lot of discussion that I've seen in the literature about what might be an explanation for that, but it's known that having areas of the myocardium that are not amenable to revascularization, having diffuse disease, when you're doing a CABG is a perioperative risk factor.

There's a few comments in the literature about how perhaps the CABG-only group, that the surgeons were attempting to be a little more aggressive because they saw areas of the myocardium that they were trying to revascularize and might have attempted things that carried a little more risk, but I think that as far as I can

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tell that is all speculation, but that is a survival benefit that was found in that RCT. The one-year survival was not significantly different between the two groups. The freedom from major adverse cardiac events was different, so the TMR plus CABG did better. Allen has impressed a five-year follow-up of his study which, the 218 over 263 belongs in the title line, I'm sorry for that. He followed up 218 of the original 263 patients in that study, found a lower mean angina score, actually several measures showing improved angina status at the five-year mark, and no difference in survival with various statistical methods of looking at survival over the five years. So whereas there was no real morbidity benefit in the shorter-term studies for the TMR plus CABG, there was at the five-year mark.

Now we look at the PMR RCTs. So with PMR, none of the studies showed a mortality benefit of PMR versus the control condition. Several of the studies showed an angina benefit. Three of the seven studies were double blind trials, which would give you greater confidence, especially in the measures of angina and other

subjective measures. Of these, two showed no angina benefit but one did show an angina benefit, so the studies are mixed there in terms of angina benefit.

Things to consider when you look at the PMR literature. There is a lot of heterogeneity in the patients who were studied, the specifics of the procedure, how the follow-up was done, what the findings were in terms of early morbidity and mortality and late morbidity and mortality. So this literature is a little bit harder to synthesize in terms of having an overall message.

Then there are the observational studies which you can see in the technology assessment and these are useful for looking at characteristics of the patients. In some of these studies they are different from the patients in the RCTs in a variety of ways. There is a greater variety of surgical centers that are doing the procedure, the specifics of the procedure, and some of them have longer-term outcomes.

So, comments. For TMR alone, again, trying to come up with metamessages here, the 30-day mortality was up to about 5 percent in RCTs and up to about 15 percent in observational

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studies, so there's some perioperative risk of doing this procedure. It has been shown that there's factors that you can use to distinguish the higher risk patients from the lower risk patients. In particular, the highest risk is in those with a recent cardiac event, diminished left ventricular function, unstable angina. There has been found to be an improvement in angina with some studies showing that it has a duration of several years and other authors talking about a diminution of the benefit over several years. But again, the Allen five-year follow-up did show continued improvement.

There is no improvement in survival at one year with TMR alone but there was the improved survival found at five years in the Allen follow-up. There was improved exercise tolerance and quality of life at one year, so again, you're talking about symptom measures at one year have shown an improvement with TMR alone, but then there were no consistent trends for things like angina, admissions, medication use, cardiac events.

TMR plus CABG, there's a decreased perioperative mortality; I discussed thoughts

about the explanation for that. No change in angina symptoms until the longer-term follow-up, and then there have been some documentation of improved symptomatic status in those patients. PMR, improved angina symptoms with no evidence of improved survival is sort of the big picture findings in these things.

Comments on utilization. What you find, again, looking at the Peterson study, which is a report of an analysis of the STS database, that a good percentage of the patients are less severe than what would be recommended, I think it was 20 to 25 percent did not have class III or IV angina, people who were getting this procedure. Similarly, or on the other hand, he says one in two patients were more severe than what would be recommended, they either had an MI within the last 20 days or had unstable angina, or had other things that would generally be considered to put them at higher risk.

There were a large number of providers across the country doing this procedure, some with low volumes, and he reported a trend in the sort of volume-outcome relationship showing that the centers with lower volume had a trend towards a

higher perioperative mortality than the centers with higher volumes. So this is something of concern that's raised in that study.
The other thing was the very large number, in fact the vast majority of these procedures were combined with other cardiac procedures and again, raised concern about, other than the Allen study, a lack of clinical trial data talking about that. There was also some attempt in the Peterson article to look at the mortality issue in the combination of TMR plus CABG, and there was some intent to find a control group within the study and try to compare and try to sort of replicate the Allen finding, which they did not replicate. But that's also been criticized in terms of whether the sort of internal case control group that they identified was appropriate, and so we didn't actually put a lot of weight on that, but it does tell you something about what perioperative mortality is occurring in the community.
So, I think I'll stop there.
DR. DAVIS: Thank you. I think we have about six or seven minutes if we want to try to get back on track for questions. Does anybody

have any questions for Dr. Zarin?
DR. AKLOG: I have a quick question.
When you reviewed the literature on PMR, you noted that the studies were mixed, but in the final study you included improved angina in the broad summary of that result. I'm just curious how you reconcile that.
DR. ZARIN: The people doing the technology felt that enough of the study showed some angina benefit that they felt confident, not extremely confident but sort of with a moderate degree of confidence, with the caveat that there was variety in the patients as well.
DR. DAVIS: Other questions? Yes, Dr. Cooper?
DR. COOPER: You alluded to the fact that there might be a placebo effect from the procedure. Did you review the literature of many of the placebo operations or operations now recognized to be either sham or placebo to look at characteristics, duration of benefit? The literature is replete with such studies in which a subjective benefit was observed but without objective corollaries. These things generally were discarded ultimately and didn't stand the

test of time. Did you evaluate placebo effect in various procedures and try to look at the pattern of placebo effect, things that have been done in the past for angina or other things to see whether or not this pattern was similar?

DR. ZARIN: We didn't really do that, but I think that's certainly a reasonable point, it was sort of outside of the scope, given the time frame for this assessment. But I think that just in reflecting what people have said in the literature, again, there is some concern at the 30-day mark, there seems to be a lot less concern when the angina benefit was found longer than that.

DR. DAVIS: Other questions? Yes.

DR. ROSE: In the mechanism of action discussion, one of the things that didn't seem to be considered was that there was no action, because the assumption for all four hypotheses was that something was actually happening. An alternative explanation is that nothing is happening physiologically and mechanistically there is really nothing to explain other than --

DR. ZARIN: I guess that's why placebo effect was listed under possible mechanisms of

action.
DR. ROSE: But using the term mechanism of action implies, I think, that it works.
DR. ZARIN: I guess perhaps a better title might have been explanation of findings or rationale for the use, and that point is well taken.
DR. DAVIS: Yes, Dr. Aklog.
DR. AKLOG: I notice you didn't spend a lot of time discussing the regional perfusion data, the actual objective data that Dr. Cooper alluded to. What was the sense of the group on that, whether there was increased perfusion or not?
DR. ZARIN: Again, I wasn't the primary person to do this, but I do recall that there were some studies that were able to show improved perfusion and many that didn't show improved perfusion. There's debate in the literature about whether the techniques for measuring perfusion were good enough to find it, et cetera, so I think that I'm going to leave it to you cardiologists to debate the meaning of that. But nobody has been able to directly correlate in a consistent way as far as I understand symptomatic relief with hard

evidence of improved perfusion in those areas, I think that would be safe to say.

DR. DAVIS: Dr. Cooper?

DR. COOPER: Is there any autopsy data, any data in the literature anecdotal or systematic on evaluating the hearts of individuals who've had this procedure but may have succumbed in the first six to 12 months as to what effect it may or may not have had on those hearts in the areas of myocardial revascularization, or of laser treatment?

DR. ZARIN: I would have to look through the literature, I don't recall that, but again, I'll look into that.

DR. DAVIS: Dr. Zarin, I had a question or two, if I may. Was there any discussion about the value of trying to pool the data across the different studies for certain clinical outcomes, or was it felt that the studies were too heterogeneous to do that?

DR. ZARIN: I think it was considered every place where there were several RCTs, meaning TMR alone or PMR alone. And the PMR alone, as I understand it, they were considered to be too heterogeneous to do that in terms of the patients

and follow-up time and how they measured the outcomes. The TMR alone, again, I think a similar consideration was made, it was felt that doing a metaanalysis wasn't going to add anything, for example, to the conclusions.

DR. DAVIS: And also, the evidence report indicated on page 59 that frequent lack of blinding in outcomes assessment, quote, could lead to an apparent increased therapeutic effect of TMR/PMR, end of quote. There wasn't more detailed discussion of the likelihood or potential extent of bias as I read through the evidence report. I'm wondering if you have had any further discussion about that, about how important any bias might have been in leading to the findings that were reported.

DR. ZARIN: I think that with the 30-day morbidity measures, in particular the angina assessment, some of the reports blinded the assessor but the patients weren't blinded, so there was a concern that even when the assessor was blinded, if you're asking the patient about a subjective measure that their own belief system and their sort of internal attribution of symptoms might affect that assessment, whereas again,

longer term there was less concern about that.
DR. DAVIS: Thank you. Any further questions? Thank you very much.
We'll move on now to scheduled public comments, and members of the committee do have a list which I'm looking for as I'm speaking of the people who are scheduled to give public comment during this portion of the meeting, and they are also listed on the agenda, and I believe we'll begin with Dr. Ferguson.
DR. FERGUSON: Good morning. My name is Bruce Ferguson. I am professor of surgery and physiology at LSU Health Sciences Center in New Orleans, and I am chair of the Council on Quality Research and Patient Advocacy for the Society of Thoracic Surgeons. I have no financial interests to disclose. I am on the, I was a member of the writing committee for the ACCHA guidelines on the update on the treatment of chronic stable angina last year and I am here representing the Society of Thoracic Surgeons and have discussed this topic with a variety of physician and non-physician individuals with relevant interests in TMR and TMR plus CABG.
I would like to thank the panel for

their proactive approach in evaluating the evidence behind the two procedures of TMR and TMR plus CABG. In addition to these disclosures, I was also the senior author on the Peterson paper that was published in JACC last fall.

My task this morning is to lay the groundwork for Dr. Horvath's and Dr. Guyton's discussions on TMR, and in particular to provide information on the STS national database to the panel. This database infrastructure is a critically important mechanism by which cardiothoracic surgeons and the STS evaluate clinical performance and improve the quality of cardiovascular care. In addition, this infrastructure embodies an opportunity to evaluate current and future technology in cardiothoracic surgery.

The national database is the largest clinical aggregation of its kind in medicine, with over 2.5 million patient records harvested from over 600 heart surgery centers across the nation. The Duke Clinical Research Institute is the warehouse and analysis facility for the database, bringing scientific credibility and objectivity to the database effort. Semiannual site-specific

feedback on processes and outcomes of care benchmarked against national metrics are fed back to participant sites twice a year. There is an extensive data managers network, thus involving allied health personnel at the sites in this process. With improvement in data quality through an aggressive system of data quality checks and feedback, no evidence of overcoding of preoperative risk is now demonstrable. This voluntary database has been audited by the Iowa Quality Improvement Organization on a regional basis with greater than 95 percent concordance of site harvested data and CMS audited data. A recent report compared the STS dataset with Medicare data for isolated coronary bypass surgery between 1994 and 1999. There was no evidence of undercoding of procedure volume or mortality in the clinical STS set compared to the Medicare DRG administrative data. I will use these characteristics of the STS database to in part lay the groundwork for the subsequent discussion about and evaluation of TMR and TMR plus CABG. One of the issues on the table today is the procedure of combined TMR plus CABG. To evaluate these data, elucidation of the current

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status of coronary surgical revascularization is important.
One of the fundamental tenets of surgical revascularization since the early days of CABG has been the completeness of revascularization. Surgeons have known for years that incomplete surgical revascularization where one or more areas of the myocardium are left without new blood supply at the completion of the operation is associated with a higher operative mortality and poorer overall outcomes. Shown here are Medicare data from over 600,000 patients harvested into the STS from 1990 through 1999. Complete surgical revascularization was achieved in the vast majority of these patients.
In this trend analysis of mortality and expected risk, the risk-adjusted mortality for coronary bypass grafting over this decade was documented to decline by over 41 percent. Also demonstrated in this unique trend analysis for interventional procedure was the fact that the expected mortality based on the STS trend risk model developed for this analysis increased by 33 percent. CABG patients were indeed documented to be getting older and to be presenting with more

comorbidities. Despite this, the overall quality of CABG as assessed by mortality improved by 74 percent between 1990 and 1999. Parenthetically, the reimbursement for coronary revascularization in three vessel disease patients declined almost in parallel to the decline in mortality. This improvement has continued, as evidenced by these data from the spring 2004 national database executive summary that is posted on the sts.org web site. At the end of 2003, the overall risk-adjusted mortality for isolated coronary bypass grafting was 2 percent. In some subsets such as patients with three-vessel disease undergoing complete revascularization using off-pump technology in experienced centers, the risk-adjusted mortality is 1.1 percent. Grafting in patients over the age of 75 was documented in large observational analyses using propensity matching statistical techniques. We have broadened this national database effort to evaluate this specialty society platform as a mechanism for continuous quality improvement in medicine. This AHRQ-sponsored trial randomized 359 sites to a CQI intervention

over an 18-month time interval. In short, we tested the ability of a specialty society to influence national care practices through this national database mechanism. Sites were randomized to receive information about preoperative beta blocker therapy, IMA grafting in patients over the age of 75, or to receive no intervention.

These trial results were published last summer and this platform was demonstrated to be successful in changing cardiac surgical clinical practice on a national scale within an 18-month time interval. Note, the scientific data linking these process measures to improve mortality were not published until the end of the trial intervention.

One of the most important aspects of this quality evaluation platform is in the ability to incorporate new technical advances into this database mechanism such that they can be analyzed and benchmarked against national norms of existing technology. This was the case for TMR in 2002 when the analysis for the Peterson paper was performed. The authors and the FDA, which funded that study, felt the opportunity to do this

evaluation of a new technical procedure on a validated CQI platform of national scope was unique.

With respect to new technology, this CQI platform provides an ongoing registry of clinical data and performance that complements clinical trial data. The combination of the two, quote, narrows the gap, closed quote, between trial results and everyday clinical practice. As Dr. Rob Kalik from DCRI has suggested, this platform allows for the incorporation of quality into the development cycle of technology.

The STS database doesn't collect longitudinal clinical data on individual patients, but as demonstrated earlier with CABG, it can collect longitudinal data on surgical interventional procedures tracking technology performance, use and impact on care processes and outcomes over time.

It is important to keep in mind the limitations of these observational database analyses, however. By definition, there is a lack of control populations. Clinical and institutional bias can be present as well as clinical factors that are not completely

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understood. An example from the TMR arena would be the optimal method of protection of the microvascular circulation in patients with severe end stage coronary artery disease, as is seen in TMR plus CABG candidates. Most importantly, some variables can't be quantified, such as the diffuseness of epicardial coronary disease. This was a major factor affecting the Peterson analysis that was acknowledged in the JACC paper but not in the New York Times interpretation of that study. This depiction of graftable disease on the left and non-graftable disease to the right is illustrative, but from a database perspective both patients would be classified as having three-vessel coronary artery disease.

This slide provides an update to the Peterson JACC analysis from the STS database from 1998 through 2003, thus adding a little over two years of additional data. The Peterson TMR plus CABG group is shown here on the right. This total of 5,600 patients in the update represents 0.6 percent of all CABG cases collected into the database during this time interval, and does not represent an exponential increase in the use of TMR.

In sites with the capability of performing TMR, demographics for their CABG-only population are identical to the overall STS dataset, indicating that these sites were probably not being overly aggressive or inappropriate in their use of TMR as a combined procedure. Finally, the clinical profile of the TMR plus CABG patients was substantially more characteristic of patients with diffuse coronary disease, including the risk factors of insulin-dependent diabetes, hypertension, prior stroke, peripheral vascular disease, and renal insufficiency. This difference in preoperative risk factors would be expected to be associated with a higher operative mortality regardless of the procedure performed. Among the things that large observational databases can do well, perhaps the most valuable is tracking trends in care practices and being able to risk-adjust processes and outcomes with clinical data. As demonstrated with CABG, this platform can indeed make procedures safer and better. This should extend the post-market data collection and analysis of new technology as evidenced by this current discussion

on TMR.
Objectively, the Peterson paper and the follow-up analysis that Dr. Horvath will present in greater detail provide important post-market information that without the STS infrastructure would probably not even exist. Understanding the attributes and limits of observational analyses is necessary to put these data into the proper perspective for objective scientific evaluation, alongside of clinical trial data.
In the initial and ongoing evaluation of technology in medicine, the combination of trials data and CQI-based observational data can be additive in determining benefit, value and safety. This is particularly true as we work hard to transition cardiovascular care from an intervention based paradigm to the long-term management of a chronic disease process. TMR and TMR plus CABG are excellent examples of this. This works best if there is engagement of all of the stakeholders at the table. Most importantly, through this mechanism we can continue to document the degree of efficacy of TMR and TMR plus CABG in these patients for whom there is no other therapeutic alternative available.

Thank you.
DR. DAVIS: Thank you, Dr. Ferguson. I think we'll just proceed with the others who are scheduled to follow you and then we will have time for questions from the committee. Dr. Horvath.
DR. HORVATH: I would like to echo the thanks that you have already received, both to the panel members for taking their time to evaluate this and for CMS for arranging this not only specific to TMR, but to the care of our patients in general.
DR. DAVIS: Dr. Horvath, as you're getting ready, let me ask you and the other members of the public who are speaking to please follow through with the disclosure statement.
DR. HORVATH: As these are being loaded, the disclosure I would say is that I have no financial interests with PLC or Cardiogenesis, as was asked on the first two questions. The third question, the answer is that I have not served on panels or committees. I have been contacted by the Society of Thoracic Surgeons to present these data to Blue Cross Blue Shield, and have discussed these data with other members of the society, as well as patients and industry.

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DR. DAVIS: Thank you.
DR. HORVATH: Sure. My intent today is to discuss the clinical results that we have seen with TMR and specifically in this title, the diffuse coronary disease that we are facing in trying to treat patients.
Maybe a fuller disclosure on this slide indicates that as noted, I am a member of the Society of Thoracic Surgeons, and I have served on the work force on coding and nomenclature that deals with reimbursement, as well as on the work force on national databases. I've practiced TMR for the last 15 years, and I have served as a consultant to Edwards on the wide spectrum of cardiovascular devices and therapies that they have, and that predates any of their involvement with TMR. My research has not been funded by industry but in fact has been funded by the American College of Surgeons, the American Heart Association and the National Institutes of Health, and I am here on my own credit card.
Diffuse coronary disease is a significant and growing problem and it particularly applies to the Medicare population. It has been shown in numerous studies to be an

independent predictor of mortality and that incomplete revascularization leads to more complications.

I have been asked on many occasions if I believe in TMR and I don't believe that this is a faith-based initiative. I know that TMR works and the backbone of that knowledge comes from the randomized controlled trials, the demographics of which are summarized here. There have been five randomized controlled trials that have looked at sole therapy TMR studying the effects of TMR in isolation, versus medical management, and as you can see, the trials total 937 patients that have been enrolled.

There are very significant similarities between the trials, they had similar ages of patients, but also there was some significant differences. Patients in class IV ranged from 100 percent to 27 percent. Patients with unstable angina, in most trials there weren't any but at least in one there were 11 percent. Myocardial infarctions, previous bypass surgery, angioplasty, again, all very prevalent for this population. And the prevalence of diabetes, again, another surrogate of diffuse disease was a little bit

different between these trials, and some of these reasons demographically may be reasons for differences in the outcomes.

One outcome that has been demonstrated repeatedly through every one of these trials is that there is significant angina relief, and using the definition of a decrease in angina class of two or more, all of these trials demonstrated at 12 months a significant improvement in symptoms, and metaanalysis of all of these trials as shown here had a summary odds ratio of 9.3. This from a coverage point of view has led to fewer hospitalizations, patients that were treated with TMR were less likely to be readmitted to the hospital than those with medical management.

And looking at specifically some of the trials in detail, the major adverse cardiac events, again, there were far fewer TMR patients that suffered death, myocardial infarction or unstable angina than those in the medical management cohort. Quality of life was also demonstrated using validated instruments and has previously been mentioned, in trials that used these tools, significant improvement in quality of life was noted for the TMR treated patients.

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These quality of life measures were not just in areas that might be directly influenced by the placebo effect, sort of the mental response to the treatment. There were also quality of life indices along with physical limitation and functional ability that for the TMR-treated patients was far improved as opposed to those that continued with their medications alone. More objective evidence comes from improvement in exercise tolerance. In this study from the U.K., there was, significantly more of the patients in the medical management arm had angina while on the treadmill, and not surprisingly in an additional analysis of exercise tolerance, more of them had angina during a 12-minute walk. Improvement in exercise tolerance was also shown by a multi-institutional trial here in the United States where the improvement in exercise tolerance, the percent change from baseline was significant for the TMR-treated patients and as would be expected with the natural history of the disease, the exercise tolerance worsened for the medical management patients. This exercise tolerance was also shown in the Norwegian study in an absolute improvement

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of 66 seconds from baseline for the TMR-treated patients and really no significant improvement at all for those in the medical management group. Those are some of the objective results. What about perfusion? That has been brought up earlier. The trial from the United States indicates that there was in fact a 20 percent improvement in perfusion in the ischemic areas of the myocardium, those areas treated with the laser, whereas the medical management patients at one year had a 27 percent worsening of the ischemic areas of their myocardium. This leads to a 47 percent swing, and I would ask as well that it be understood that improvement in perfusion and a direct correlation with symptom improvement is difficult. We all see patients that have diffuse coronary disease that may have few symptoms and other patients that have a single branch vessel that gives them tremendous chest pain. Having said that, this improvement in ischemic perfusion did not come at an increase in infarction, so it was not the laser creating infarcts that led to the symptom improvement that was seen. Additional perfusion benefit is

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demonstrated from the single institutional trial from the U.K. This analysis was done in a slightly different fashion, all of these segments of all of the patients' myocardiums were pooled together. And as you can see here when you do that, you can then divide those segments up into either normally perfused, infarcted tissue, or ischemic myocardium. And one of the conclusions that was drawn was that while there's a decrease in the ischemic areas in the TMR treated patients, it appears there's a similar decrease in the medical management patients. But a closer look at this data indicates that these TMR-treated patients had ischemic segments that now became normal. There was not a significant change in the infarcted tissue in these patients whereas there was over doubling of the infarctions in the medical management patients. So the decrease in ischemic segments was led to infarction not because these patients now had normally perfused myocardium.

Other objective evidence of perfusion comes from PET scanning. This is an example of one such scan from the Texas Heart Institute, the upper panel being the preoperative state for this

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particular patient and the lower panel the postoperative state. Improvement in perfusion metabolism as indicated by white or red, as you can plainly see, is greater in the postoperative situation, and a pooling of these data and specifically using each patient as an internal control, looking at the septum which was not directly treated with the laser, versus the left ventricular free wall, and even more importantly looking at the subendocardial perfusion versus the subepicardial perfusion and generating ratios, you see that there is no significant change in the unlased portions of the myocardium, where there was a dramatically significant improvement in that ratio for those that were treated with TMR. Other evidence of objective improvement comes from functional data using echo. Dobutamine stress echos done before and six months after a CO-2 TMR shows improved wall motion stroke index at rest, and this improvement was even more marked with stress. As you would expect, there was a decrease in the ischemic segments, no change in the infarcted segments, and from a symptom point of view, improved stress tolerance.

We at Northwestern have used MRI to

confirm these studies. This is an example of one such patient that underwent sole therapy TMR, preoperative and postoperative MRI. I think the contractility improvement is plainly evident. The other reason that we used MRI was that with MRI we have a tool that can detect infarcts down to the level of one or one-and-a-half millimeters. There's a concern that TMR causes injury and that these microinfarctions may be the mechanism whereby the patients are having symptom relief. What we found in using not only the Cine MRI, which you've previously seen, but hyperenhancement studies of contrast-enhanced MRIs, there was no change in the number of infarcted segments, there was no extension of infarcts in patients that had previous areas of their myocardium that were infarcted. There was in fact, as you saw, improvement in segmental wall motion and certainly no worsening of wall motion, and correlating with this, angina improvement.
That being, focusing on the short-term results, not only the symptom but functional results that we have seen, there has been long-term follow-up and a combined over 2,000

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years of patient follow-up looking at the sole therapy TMR patients. These are extensions of the randomized controlled trials and combinations of randomized and nonrandomized patients, that being the lower study here, specifically looking at the patients that did not have any reinterventions over that period of time. The Aaberge trial looked at patients that stayed in their groups throughout the period of follow-up where no cross-over was used, and Allen's group giving us the largest series of data in long-term follow-up. His report shows that the initial angina improvement that is seen in sole therapy TMR is maintained to over five years. This is particularly dramatic when you look at the fact that twice as many of the patients had a two or greater class improvement in angina if treated with TMR at five years of follow-up, and three times as many TMR patients were angina-free. A survival curve indicates that there was higher survival at five years for patients treated with TMR compared to those in the medical management group. Inverting this and looking at a cumulative hazard analysis, especially once you go beyond that first year, that survival benefit is

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perhaps more dramatic with an annualized mortality of 8 versus 13 percent in TMR versus medical management.

Long-term angina relief, as mentioned, was also studied by Aaberge at four years of follow-up, and the key of this study is that both groups were kept intact, so we have a nice demonstration of a control group that is being followed for an extended period of time. And while there was a significant improvement in angina relief for the TMR patients that was maintained over that period of time, whereas, as one would expect, a worsening of symptoms for patients treated with just medications alone.

We have also demonstrated long-term angina relief and sustained angina relief with TMR as sole therapy at one year and at five years, and these patients had no other intervention other than the initial TMR over this period of time.

And looking at this in a different way, looking at the distribution of improvement in angina class, which may give a little more insight in it to exactly how these patients are doing, 75 percent of the patients had a two, three or four class angina decrease over the first year of follow-up

and at the long-term follow-up there was a slight shift but not significant, in that 68 percent of the patients still had that two, three or four class angina decrease.

Now based on these sole therapy data, the FDA approved the device and the labeling as you've already heard, was for areas of the myocardium not amenable to direct coronary revascularization. As a result, surgeons then applied this in combination with bypass surgery and this was further, the results of this approach was further illustrated using two different randomized controlled trials that have been reported as short-term results by Allen and the longer-term results which are in press. The results from Frazier at the Texas Heart Institute are also in press at the present time.

As you can see, 300 patients were randomized and one can easily appreciate that those from Texas Heart had higher risk factors going into their operations with more patients with unstable angina, heart failure and diabetes.

This long-term angina relief has been demonstrated with TMR plus CABG versus CABG-alone. Both therapies work in relieving angina. Not

surprisingly, we saw a decrease in the average angina class from 2.8 as was seen on the previous slide to less than one, .5 as an average angina class for both groups, but this was not sustained for the CABG-only group, it was for those who received TMR in addition to their CABG.

Looking at this in slightly more detail, the patients with severe angina, class III or class IV, none of the patients that had TMR plus CABG were in those classes, whereas 10 percent of those that had CABG alone were.

And diabetes, again, another indicator of the diffuseness of their disease, this angina-free state was greater in the diabetic patients than in those that had CABG alone as opposed to TMR in an adjunctive use.

The five-year survival curve, as has been mentioned, there was an early mortality benefit that was demonstrated at five years, and really not much before that. There is convergence of these curves but that should not be surprising considering the type of patients that we're discussing.

Long-term angina relief has been demonstrated by the Texas Heart Group as well.

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Patients with repeat revascularization at four years were none in the TMR plus CABG group, and 24 percent of those that had CABG alone needed some other type of revascularization in that period of time. And as far as event-free survival is concerned, freedom from deaths, repeat revascularization and recurring angina, much higher in event-free survival for the TMR plus CABG patients versus those that just had CABG. You've seen slides like this and you will see more of the diffuseness of disease and the difficulty in matching such patients, and while on paper these may appear the same, I think you can readily appreciate that their angiograms are markedly different and that they are not equal. So attempting to do this in some sort of case match analysis is probably not the best way to review these patients.

As a result of the Peterson paper and as a result of the need to update that information, we've gone back to the STS database and given a better picture, I believe, of what is in fact happening in the community. Over the five years of follow-up that we have from the database, the number of bypass patients done in that period

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of time was 930,000, the number of TMR plus CABGs done in that period of time was 5,618. As you've heard, this is .6 percent of the revascularization that is being done in both the community and academic centers.

The important factor on this slide is that for every surrogate of diffuse disease and many of the high risk preoperative factors that we would attribute to an increase in perioperative mortality, the TMR plus CABG patients had those factors, significant differences between both groups with the TMR plus CABG patients on every measurable parameter being sicker, if you will, than those undergoing CABG alone.

So the results then, in updating those data, show that the raw mortality, not surprisingly, was higher for TMR plus CABG patients at 3.8 percent versus 2.7 percent for CABG alone. But if you attempt to try to get perhaps a more valid comparison and even more importantly, a clinically applicable comparison, the comparison of patients that had three-vessel disease but received fewer than three bypass grafts, what you would consider under-revascularized, show that the mortality was 5.2

percent for TMR plus CABG and 4.3 percent for CABG alone, an insignificant difference. And if you take the unstable angina patients out of that analysis, the TMR plus CABG mortality was decreased to 2.7 percent, exactly the same as we saw for the population that underwent CABG alone and the ODE ratio was .87. Now this mortality issue is an important one and there has to be some perspective applied to this. For CABG alone, 30-day mortality, as you heard, is 4 to 2.7 percent. For TMR plus CABG, the initial Peterson paper, as his follow-up indicates, is in that range. For CABG alone with unstable angina, it's a bit higher, at 5.8 percent. And for reoperative CABG, it is in fact reported to be somewhat higher than that. The one-year mortality after CABG alone in diabetics has been reported at 10 percent, for re-op CABG alone in the 10 to 15 percent range, and in a more recent study that I think gets to the core of this problem for these patients and patients with diffuse disease. And in this study they looked at coronary flow reserve, that the one-year mortality of patients with microvascular disease was 8 percent, for those same patients

with diabetes it was 33 percent. And as highlighted here, at one year the patients with such diffuse disease are six times as likely to die as those without. So the net health benefit may have been achieved if these types of data were used as the comparison.

In summary, the randomized controlled trials across the board, and I've included the combination and sole therapy use and I've also included the short-term and long-term follow-up of all of these studies, a number of studies, number of investigators, these have shown angina relief. But more important, in addition to that symptomatic improvement, all of them have shown an improvement in objective measures following TMR either as sole therapy or in combination. Observational data as well, including several more institutions and hundreds more patients, has demonstrated the same symptom relief and in the majority of these studies, a significant improvement in objective measurements. As a result of all of this data, there have been a number of evidence-based recommendations regarding TMR both as sole therapy and in combination with CABG and this has, as

outlined here, let to CMS coverage in 1999, a Blue Cross Blue Shield assessment in 2001, and a recent reassessment where they stand by their coverage decision from 2001, has led to guidelines from various societies, the American College of Cardiology and the American Heart Association task force, as well as independent assessments from the Emergency Care Research Institute that does this for the Defense Department in the TriCare health dependents, and most recently from the Society of Thoracic Surgeons work force, putting together practice guidelines. During that development of those guidelines, Dr. Guyton was the president of the STS and he will now follow with his thoughts on this topic.

DR. DAVIS: Thank you. Dr. Guyton.

DR. GUYTON: Thank you. It's my privilege to speak today on behalf of the Society of Thoracic Surgeons. With regard to disclosure, I have no conflicting financial interests, although one of my faculty members does have investigative research support from Cardiogenesis. I was recruited to -- I have not served previously on an advisory panel or committee considering this topic. I was recruited to speak here today by the

Society of Thoracic Surgeons and in preparation I consulted with multiple parties, including surgeons, cardiologists and the industry.

My qualifications in brief. I've been a member of the Society of Thoracic Surgeons executive committee for the last nine years, I'm an active clinical surgeon, I'm an active educator, and I'm currently co-chairperson of the ACC/AHA committee on guidelines for coronary artery bypass.

The Society of Thoracic Surgeons has a mission and that mission is to help cardiothoracic surgeons serve patients better. To serve our patients, we will work to develop, to refine and to bring to clinical practice advances in molecular biology, pharmacology, information technology, operative techniques, and surgical devices. But as we work to implement innovation, we're ever mindful that innovation has an important challenge. As stated in this slide taken from my presidential address given just six months ago, the challenge of innovation is that our number one priority must be to remain patient-centered. We must evaluate and reevaluate new technology, and we must maintain a constant

focus on patient benefit.
The Society of Thoracic Surgeons has taken an active role in new technology with a focus on patient benefit. Along with the American Association for Thoracic Surgery, we've had an active work force on new technology. We've established a work force on evidence-based medicine, which developed a guideline for the use of TMR, included as part of our submitted testimony. The most important part of our continuing evaluation of new technology is our adult cardiac database described by Dr. Ferguson earlier today.
Now to get to the specific business of the day, the Society of Thoracic Surgeons and transmyocardial revascularization. I'll discuss the following points: We believe that TMR as sole therapy is strongly supported by multiple randomized controlled trials and observational studies. Our guidelines committee, representing the official position of the society after careful consideration, felt that the use of TMR as sole therapy for patients with disabling angina who had no other revascularization options warranted a class I recommendation for use, with an A level of

evidence.
TMR plus coronary bypass has less data and is more difficult to interpret, as I will discuss. Our committee felt that the data warranted a class II-A recommendation with a B level of evidence.
Percutaneous techniques are rarely performed by our surgeons and there will be no comment from our society on PMR and we urge that PMR be separately considered from TMR.
Now we must begin with the patient perspective. Who are these patients? As Keith pointed out, these are patients with diffuse coronary disease, disabled by angina, not amenable to percutaneous therapy or coronary bypass. This diffuse disease is found in up to 12 percent of patients with coronary artery disease and is the cause of incomplete revascularization in 15 to 25 percent of coronary bypass patients.
Now is this incomplete revascularization significant? You bet it is. Incomplete revascularization due to small and diffusely diseased vessels significantly increases the risk of late cardiac events, a fact documented by multiple studies and indeed, quoted by the AHRQ

evaluation earlier today.
TMR is specifically focused on these patients with diffuse coronary disease. This is not a new technology; it's been over 20 years in development. Clinical studies began in 1990, 14 years ago. Six years ago seven randomized controlled trials were reported with one-year follow-up.
First, let's consider TMR as sole therapy for disabling angina. As stated earlier, there are 937 randomized patients in five controlled trials. The early mortality for stable angina patients is 1 to 5 percent. For unstable patients in the randomized controlled trials, the early mortality was 9 to 22 percent. Now this mortality sounds high but it's very important for the panel to understand that the definition of unstable angina in these randomized controlled trials is very different than the usual cardiology definition of unstable angina. These were not unstable angina patients who came in and were stabilized or could be stabilized. These were patients who had continuing requirements for intravenous medication, intravenous Heparin or nitroglycerin. They are patients who could not be

weaned from intravenous therapy. So there's a different definition of unstable angina leading to this 9 to 22 percent mortality.

The one-year outcomes revealed that mortality, including perioperative deaths, was equal to medical management. The morbidity even with this big operation at one year was equal to medical management. As stated earlier by Dr. Horvath, the data showed improved prospectively defined event free survival, improved quality of life, and a dramatic improvement of angina class.

This from the ECRI technology assessment shows that the five randomized controlled trials agreed emphatically with a reduction in angina in these patients.

Now, was this sustained by one year, that's the question asked frequently today. Dr. Allen's trial at five years shows that indeed it is sustained. 88 percent of the patients at five years with diffuse coronary disease undergoing sole therapy had freedom from class III or IV angina at five years, a dramatic improvement compared to the patients treated medically. This is true whether you use this as an intention to treat analysis or as actual treatment analysis.

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In addition, Allen's five-year follow-up showed a significant benefit for these patients with a 13 percent absolute mortality benefit, which is a 27 percent relative mortality benefit for TMR. With regard to sole therapy from the patient's perspective, for the patient who is disabled with class IV angina with diffuse coronary disease, at one year there is a dramatic symptom improvement, with a three out of four chance of freedom from disabling angina. This benefit with minimal downside; there was no difference in one-year mortality or morbidity. At five years, there was a sustained symptom improvement with an 88 percent chance of freedom from disabling angina at five years and a 27 percent five-year relative mortality benefit with TMR versus medical management. From the patient's perspective, this is a definition of a no brainer, no downside and a huge upside with relief from disabling angina.

Now what about adjunctive TMR? This is a much more difficult issue. The data are not clean, the variables cannot be isolated. TMR is being added to a therapy directed at the same symptom. Because the potential benefit is

incremental, one would expect many more patients would be needed to show benefit. The control group cannot be created by case matching or propensity score analysis because diffuse coronary disease is very difficult to quantify or even identify in databases. We know that diffuse coronary disease has a very negative impact on long-term outcomes and it's present in essentially all TMR patients, and only 20 percent of our other coronary bypass patients.

So what do we have as far as data regarding adjunctive TMR? We do have two randomized controlled trials and observational data, the largest bit of observational data from the STS database as has been discussed earlier. We do have excellent follow-up from one of the randomized controlled trials at five years. This is the data shown earlier by Dr. Horvath in a different form. This is Allen's trial at five years comparing TMR CABG with coronary bypass alone, showing a significant angina relief benefit at five years. Now this benefit looks small unless you have angina, and then it's not small. As Dr. Horvath showed, 10 percent of the patients in the medically treated group or the patients

treated with coronary bypass alone had class IV angina, compared to no patients in the group treated with TMR plus a coronary bypass. The addition of TMR significantly benefitted these patients with regard to symptoms. Symptom relief is the upside. From the patient perspective again, what is the downside? Does TMR added to coronary bypass increase the mortality of the procedure? Indeed, Allen's trials showed a significant decrease in one-year mortality with TMR when it was added to coronary bypass. The five-year survival curves converge, as all survival curves eventually do, and there was not a significant difference at five years.

Now I think it's very important for this panel to understand one of the reasons that we don't have more data, more robust randomized data with regard to adjunctive TMR. This study, Allen's study, the largest study was stopped prior to completion of enrollment by its data safety and monitoring board because of a significant 30-day mortality difference in the two groups. When that difference reached a P value of .02 the study was stopped. I think the data safety and monitoring board thought that the TMR group was going to have

the higher mortality; indeed, it turned out that the TMR group had a mortality of 1.5 percent, the CABG-alone group had a mortality of 7.6 percent, and the study was stopped.

This is important. The Blue Cross Blue Shield panel in particular asked why we don't have more data. When we go to our IRB and say we want to do a study of TMR-CABG, they say you want us to approve a study that's already been stopped by a data safety monitoring board? And it's hard to get that through your IRB. And so I think it's important to realize that when we say why are there not continuing study, I think you've got to go back to this large trial that was stopped by its data safety and monitoring board.

No, the randomized controlled trial showed a 30-day and one-year survival benefit. Peterson's observational study failed to confirm the 30-day survival benefit, but the Peterson study did nail down the fact that the addition of TMR to coronary bypass does not increase the risk of the procedure. Mortality and morbidity were not increased when TMR was added to coronary bypass and the randomized controlled trial showed a significant five-year symptom benefit.

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Again, from the patient's perspective, consider a patient with disabling angina scheduled to undergo coronary bypass but with a large region of diffuse coronary disease likely not amenable to coronary bypass. I always discuss with these patients the risks, the benefits and the alternatives. The incremental risks, as we've seen, is essentially none of adding TMR to coronary bypass shown by both randomized trials and observational studies, no increased mortality or morbidity. The incremental benefit is a significant, possible significant early survival benefit, significant in the randomized trials, and is statistically probable, a 95 percent probable late benefit in angina relief.

What's the alternative? The alternative is incomplete revascularization with coronary bypass alone, known to be associated with increased operative and long-term risk compared to complete revascularization. Looking at this from this patient's perspective, you can make a pretty strong case for saying with no downside and a 95 percent statistically probable upside, please add TMR to my coronary bypass if my vessels cannot be grafted.

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From the perspective of a clinical cardiac surgeon, I confess that for years I've been a skeptic that the channels don't stay open. I have resisted TMR for years and if ever there was a physician wedded to system physiology, it's Robert Guyton. I have told the companies again and again, come back and talk to me again when you have five-year data. Well, indeed, about a year ago they came back and talked to me with the five-year data that you've seen today and it was pretty persuasive.

Beyond that, I'm also persuaded by some local clinical observations. One of our great cardiologists, Steve Sigmund, said to me last year, hey Guyton, come and look at this. He showed me this PET scan of a patient whose disabling angina was treated by one of our faculty with sole TMR. This is his preoperative PET scan, and you can see the stress defect in the apex of the ventricle, and this is his scan after sole TMR two years later, showing dramatic improvement in the atrial defect. This was accompanied by dramatic relief of his disabling angina. We went back and called the ten patients that we had with TMR as sole therapy who had good preoperative PET

scans, and seven of ten came back. Perfusion improvement with this high resolution PET scan, and we have a great PET scan unit, was seen in six of the ten. The patient without clinical improvement was the one without perfusion improvement. Our retrospective TMR study now submitted for publication did not show a change in the size of the defect, but it did show a change in the severity times the size of the defect that was significant. As all of you know, if you can get significance with seven patients it usually is a pretty good difference; it's pretty tough to get significance with seven patients.

We did see a very small but statistically significant increase in scar, this was only 2 percent of them, so a very small increase in scar. Now, does this all make sense to me? I really think it does. I think there's a very small perhaps increase in scar because we are causing a controlled injury to the heart. We are causing a controlled injury that does not lead to diminished myocardial function because we're going to very tiny regions of injury, but that area of injury is enough to elicit the response to injury that we have in every organ and that response

leads to angiogenesis, and it requires the resolution of modern scanning techniques to see that, which I think is part of the reason that some of the studies didn't show it seven or eight years ago. So for me, this makes physiologic sense with controlled injury leading to angiogenesis, and this is added to the hard data that we have discussed.

To summarize, TMR as sole therapy for disabling angina both stable and unstable, has a low risk and a great benefit as established by multiple randomized controlled trials and observational studies. TMR plus coronary bypass for disabling angina with an area of myocardium not amenable to intervention or coronary bypass has essentially no incremental risk compared to coronary bypass alone and it has a statistically significant, statistically likely, a 95 percent likely benefit in long-term symptom relief.

Our society believes that CMS coverage needs to continue, that TMR addresses an otherwise unmet need in this subset of severely disabled patients. Thank you for the opportunity to present these thoughts.

DR. DAVIS: Thank you, Dr. Guyton.

Dr. Popp.

DR. POPP: Thank you for the opportunity to address you today. I am Richard Popp from Stanford. I'm past president of the American College of Cardiology but I am not representing them here today. I am a consultant to Cardiogenesis Corporation but I have no financial interest in the company. I have received some financial support as part of the medical review panel. I was paid for my time for that, but I volunteered to come here, but the company paid for my air fare and hotel last night. I presented on this subject to the FDA and I have discussed with Cardiogenesis the generation of passing over my slides to them so they could be brought here today.

I'm going to specifically talk about PMR and I would like to talk specifically about the Cardiogenesis system. There are three studies that especially were reviewed by the medical review panel, it was a panel chaired by Dr. Eric Topel and myself, several other investigators that were brought together by the company and with the charge to objectively review the data and to tell them what we thought about it and how they should

go further. We paid special attention to the Oesterle study, which is called the PACIFIC trial, the Gray study from England, the Salem study, and the BELIEF study, which is one I will spend a lot of time on because it was from Norway, not sponsored by the company, a double blind sham-controlled study. We didn't give much attention to the Whitlow study that came from the Eclipse system, or the system that Dr. Cohen is familiar with, the Biosense system, as we felt that they were somewhat different. And I'm sure that Mr. Lacey will understand that there are differences in equipment certainly, that can be demonstrated. In terms of the data and the evidence, interestingly, in Oesterle's study there was a greater than two class, or two class angina improvement in 46 percent of the treated patients versus 11 percent of the medically managed patients. This was true with the blinded assessment as well as with further, a larger number which were not done with blinded assessment, but the blinded assessment showed this.

I would like to take a few minutes to talk about the BELIEF trial in Norway because it's

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a very striking trial and addresses perhaps what Dr. Cooper was talking about earlier. That is, this was a trial in which the government asked for assessment of the technology. They agreed, and the hospitals agreed to do a sham-controlled study. The sham controls had the catheter placed just as one would do for the PMR procedure. The only person who knew whether the catheter was connected to the box that actually sent the energy out was a technician, so that when the operator stepped on the pedal to activate the device the machine made the same noise, light came out, everything happened exactly the same, nobody could tell whether the patient got the therapy or not. And this was maintained so that the patients didn't know if they were treated, the physicians didn't know if they were treated, the assessors didn't know if they were treated. And with only 42 patients, there was a 35 percent reduction in angina class, I'm sorry, 35 percent had a greater than two class angina improvement in the treated patients, and only 14 percent.

Now, the 14 percent I would say is an assessment that there is a potential placebo effect. The patients had a procedure that they

underwent, so I believe that that improvement assesses that, but it is clearly a much greater improvement in the patients who actually got the therapy.

Also, there are some other outcomes. In all these studies, the quality of life improved, there was an increase in exercise tolerance assessed by a blinded core lab in the PACIFIC study as well.

Now one of the issues to be addressed is the question of mortality in these randomized controlled studies. I think nobody is claiming mortality benefit here. The question is, are we hurting patients? In the PACIFIC trial there was a 7.2 percent 12-year mortality of the treated patients. There was a 2.7 percent mortality in the controlled patients. However, if one looks at the controls of almost 600 other patients in many of these other studies and from our own clinical experience, we expect about a 5 to 10 percent, 5 to 15 percent mortality over 12 months in these desperately ill patients. The patients in the PACIFIC study were especially fortunate. It doesn't make it easy for the company to prove that it was helpful, but in fact it's great for the

patients that they had an anomalously low mortality.
I think the bottom line for me is that these patients, again, should have some options, and the product is really for selected patients with no other option. Prospectively to find end points in these studies were met, and two very, very good studies, the PACIFIC study and the BELIEF study from Norway, that sham-controlled study is very impressive to me, and if we look at Weinberg or other kinds of procedures, this is the kind of things that killed those procedures because it showed that they didn't work. Here in 40 percent of the patients it shows that it does work.
I don't think we should ignore the ancillary information very important to the patients regarding quality of life and how much better they feel about their condition.
In watching this over the time I've joined the medical review panel and through the FDA and now looking at all the data coming up to this, I believe that the background and attitude conditions that one brings to look at these data actually conditions the interpretation of

scientific data. And if you think about what you do reviewing an article or what Dr. Zarin's group and others are meant to do, they are meant to look at it and see how could it be better, what's wrong, what defects do we see. I think that's a natural and understandable situation, but I think we have to look at the evidence for evidence-based decisions, and the evidence is really the data that we have.

Part of my job at Stanford now is ethics, and I must say that I'm concerned that we probably will not ever be able to have another sham-controlled study after the BELIEF study because it so clearly shows benefit. And so I'm not sure exactly how we're going to get further with what I would consider ideal studies. On the other hand, there is the issue of protecting patients and providing for patients, as opposed to being overly protective, and once again I would just echo what others have said. These are patients who are extremely ill. Some of them can't take a shower, there are not a lot of these patients in any of our practices and I think that these procedures might be best done in centers where the experience can be accumulated. But I

really think it's very important that we have these procedures available to the patients and I think that the PMR studies, while we need more data, so far they have been very positive. I think that's all we can say about PMR is that so far it has been very positive. Thank you.

DR. DAVIS: Thank you. We have about 20 minutes available for questions from the panel, and would anybody like to begin? Obviously they can be directed to any of this morning's speakers.

DR. AKLOG: This is for Dr. Popp. You described these as no option patients. In the past they have been generally referred to as no option with regard to revascularization, but given sort of the lag in the accumulation of data for surgical TMR versus PMR, I would assume that no option would include that many of these patients are candidates for surgical TMR. You described them as being sick and debilitated by their angina. Don't you think -- I guess there's two parts. One is, how do you define no option, and the second is, are we at a point, given that the data for surgical TMR is larger and a little bit more robust, that the control group could be surgical TMR as opposed to medical therapy?

DR. POPP: Thank you, I should have addressed that point. Really the only option for the patients that we're talking about for PMR is TMR. And while I think most of us would accept that the morbidity-mortality of having the surgery is expected to be higher than having the PMR procedure, just because it's a noninvasive procedure without having to open the chest in any way, I think that's the issue. I don't think we know that yet. I think we could construct such a study. Certainly that would not exempt us from the issue of placebo effect as to going to surgery versus having the noninvasive procedure. But I think that is clearly, we need to define what no option means. In this case it's a question of sending the patients for TMR or having the PMR procedure, and it's not established yet, but I think that is the point, if the patients can't have PMR, eventually TMR is their option. Thank you for pointing that out.

DR. DAVIS: Dr. Cooper.

DR. COOPER: First of all, I realize I should probably add two more disclosures. Number one is, although I am head of cardiothoracic surgery, I do not do cardiac surgery, and I

suppose that's a relevant disclosure. The other thing is, I am a proud member of the Society of Thoracic Surgeons, though I have not been involved in these deliberations.

Dr. Popp, you pointed out that in a particular study you referred to, the control group mortality was below what you -- you showed a bar graph and you showed that there was a difference between control and treated in favor of the controlled group, but you correctly I think pointed out that maybe in the particular study the control group did not give the anticipated result and you showed that on other studies showing that this may be one of those cases where this particular group was, for some reason, didn't follow the usual control expectation.

That's a very relevant issue whenever you have two groups and do a randomized trial. It's the reverse of what was shown I think by Dr. Guyton and Dr. Horvath in what I believe was referred to as the Allen paper, and perhaps unexplained difference in mortality where the CABG group alone had a 30-day mortality of 7.5 percent and the CABG plus TMR had a 30-day mortality of I think 1.8 or 2, and that difference in fact

explained the one-year difference in mortality. Is it possible, and I was going to ask Dr. Guyton the same question, that this just happens to be, as we've all seen, an aberration that happens, that something may be wrong with the control group, it just doesn't match up what you would expect, that in the Allen group the mortality of 7.5 percent or 7 percent at 30 days in CABG-alone isn't quite what you would expect if you compare that, and I think Dr. Horvath pointed out some CABG-alone figures of 2.7 percent mortality. Whenever you do a control or randomized trial you're subject to the possibility that the control group may just not track historically and that the explanation is a random one, that one out of either every 20 studies that we do will have a P .05 value merely by chance. What is your impression, therefore, of how we should view the 30-day mortality both with the PMR, the study that you pointed out, and with the CABG-TMR difference in the Allen group? Do you think it is fair to say probably those are aberrations and we don't have to take those into great consideration because they don't track what one would expect?

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DR. POPP: First of all, the difference in PMR in the control group and the treated group is not a statistically significant difference. I was pointing out that in my own experience and if you looked at the literature, then I would expect a higher number, but it just didn't come out that way. And I think your point is well taken that the play of chance can happen where there is a reduced number for control. However, it was not statistically significant. I think that's different and either Dr. Guyton or one of the other may want to comment.

DR. COOPER: I was going to ask Dr. Guyton the same question. How do you think we should look at the evidence in that particular, the Allen trial, do you think it's fair to say, well, it's interesting that there was 30-day mortality, but we don't really have an explanation and it may just be one of those things that happens.

DR. GUYTON: I think regarding the control group in the Allen trial, these are patients with diffuse coronary disease and as Keith showed with the slide that had the P less than .01 all down the right side, that the

expected mortality in the control group would be 5 to 6 percent, maybe not 7.5 percent, but the expected mortality for this group of coronary bypass patients would be in the 5 to 6 percent. And I think that if the enrollment had been allowed to go out to the full 380 patients that were expected, there probably would have been a difference between the expected mortality in the TMR group and the control group. So in that particular instance, the control group wasn't that far off.

DR. COOPER: May I just ask a follow-up question?

DR. DAVIS: Sure.

DR. COOPER: Do you, a technical question since I don't do cardiac surgery, in the design of the CABG plus the TMR versus CABG and no TMR, was the randomization done after the surgeon had completed as much revascularization as he possibly could, and then he drew an envelope and was told either do or do not proceed with TMR in what's left behind, or was the surgeon aware in those trials before he started doing revascularization that this patient had been randomized to TMR or non-TMR, and could that have

influenced, if the randomization was done before he had said okay, I've now done my revascularization, now I'll draw the envelope, could that have influenced in fact the conduct of the revascularization? And specifically, I suppose you could look at how many grafts were done because if they did the complete revascularization and then drew the randomization, one would expect the same number of grafts in both groups of patients, CABG plus TMR or CABG without TMR. Do you understand what I'm asking?

DR. GUYTON: Yes, and I think it's probably better for Dr. Horvath to answer that than myself, as I didn't participate in that trial. I'm a recent convert to TMR, having been skeptical for a number of years, and based on the data have changed my opinion in the last couple of years, so I will ask Keith to respond.

DR. COOPER: Thank you.

DR. HORVATH: It's a very good question and highlights one of the points that we have with doing additional trials, is when do you do that randomization and when is the best time to do that. There are problems with picking the right end points as well. In that particular trial, the

randomization was done based on the angiogram, and the patients were then randomized at that point, not in the operating room. But, should they be randomized in the operating room after the vessel is opened, after a probe is put down, after a graft is done and flow is then measured and at some blood pressure or some threshold, those are all interesting scientifically, but practically speaking, I think that's one of the problems we have with those types of trials.

DR. COOPER: Thank you.

DR. DAVIS: Dr. McNeil and then Dr. Rose.

DR. MCNEIL: I think my question may be very similar to the one Joel just asked, but in the TMR plus CABG versus TMR, the assumption is that we are asking what the benefit is of TMR as an incremental procedure, so that would assume that the CABG is the same in both arms; otherwise, we aren't looking at incremental, we're looking at some difference in CABG plus this TMR procedure. And that's actually where I'm having trouble, because I can't be convinced, or I'm not convinced yet on the basis of what I've read or heard, that the bypass approach in both arms of that trial was

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the same, I think Joel was getting at the same thing. Therefore, it's very hard for me to answer the question, is TMR providing an incremental benefit because I don't think the baseline, or I'm not convinced that the baseline is the same. Could some one of you elaborate on that?

DR. GUYTON: I think a better design might be similar to the design that we used for off pump versus on pump, where we chose the targeted vessels preop and then had an index of what vessels we bypass versus what we said before the operation we would bypass, and we made that choice of which vessels might be bypassed before randomization. In the trial, however, that was performed, even though that preoperative determination was not made, the number of bypass grafts performed in the control group and the TMR plus CABG group was the same, so the number of bypasses performed, it's my understanding, was the same in both the control group and the TMR plus coronary bypass group.

DR. COOPER: I'm sorry, I may be wrong and the reason I asked the question, and again, I may have misread. In one of the papers I thought that I did see two point something versus three

point something, and perhaps I misread it or didn't understand it. I agree with you, if the same number of bypasses were done, that would --
DR. MCNEIL: They are definitely different.
SPEAKER: 3.1 and 3.4.
DR. HORVATH: Both the short-term and long-term follow-up have, it's clearly listed that the number of bypasses for the CABG-alone group was 3.4 and for the CABG plus TMR was 3.1, which was not statistically significant. Nor was the distribution of those graphs to the various territories of the heart different for any of the patients.
DR. GUYTON: So, I think based on that, I guess perhaps there was a more aggressive approach taken in the control group and I think that the question perhaps remains whether that more aggressive approach may have led to a longer time struggling to do small distals or something of that sort.
DR. DAVIS: Dr. Zarin, did you want to make a point on this?
DR. ZARIN: I was just going to offer table two in Allen, in the original report of his

RCT has time on bypass, number of vessels bypassed, coronary arteries grafted, and none of the differences are statistically significant, but I could just hand it to you.

DR. COOPER: Thank you.

DR. ZARIN: There are differences but they are not statistically significant.

DR. DAVIS: Dr. Rose and then Dr. Cohen.

DR. ROSE: I want to add to the mix the discussion of Direct trial. I am a cardiac surgeon, I've worked with a number of lasers in the laboratory. I think that arguably the channels that are created with each of the different energy sources are really not much different. They look the same, they all close up. The best trial at least from the point of view of looking at making holes in the heart with the laser with a sham control group is the Direct trial, much larger than the Cardiogenesis trial. And a look at essentially all the outcomes in that well-powered sham-controlled trial with even two doses of laser holes drilled into the areas at risk show that there was no difference in essentially any of the important

outcomes. Unfortunately the manuscript for the trial, the detailed manuscript has not made it to print. Some of us have been able to see drafts of that in preparation for this meeting just by contacting some of the investigators trying to find out what's happened with it. But arguably, this is the best designed trial in the field to test the hypothesis that drilling laser holes in the heart does or does not have important impact on outcomes, and the data seem overwhelming, at least in that best test, that there is no difference.

DR. POPP: Well, if I can respond to that?

DR. DAVIS: Yes, Dr. Popp.

DR. POPP: As far as I know it really isn't published, and so it's very difficult to assess it. I think the trial design as far as I understand it is a very good trial design. However, just as the paper is not published yet, there are data that I'm aware of where the devices really aren't different. The spot size is a lot smaller with the PMR device, the penetration is much less, it does not sit against the myocardium or penetrate into it, and so there really are

quite good differences demonstrable. Just as you're aware of some unpublished things, Dr. Laske at UCLA has done a comparison of the two, I've seen that data, and the injury to the myocardium is really quite different. So that's the basis on which I'm saying I don't want to equate the two because I think there really are equipment differences. In terms of the design of the study, I think as far as I understand it, and the slides that one can see on the web from the presentation, it looks like a very well designed study, but I don't think that we can necessarily say that the two pieces of equipment are the same at all.

DR. DAVIS: Dr. Cohen.

DR. COHEN: This was a question mainly in relation to, I think Dr. Guyton's statement about the essential ethics of a future trial of TMR plus CABG versus CABG alone. My main concern about rejecting that as unethical is it seems to be the surgeons voting with their feet and their hands, in that I don't see very many cardiac surgeons doing TMR plus CABG on a routine basis, and so I really dispute the claim that it would be unethical or difficult to get that study done.

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And I'd just be curious as to those comments, in particular in relation to the fact that you were unconvinced, obviously, about the mortality benefits, and said wait until five years and I will be convinced by the symptom benefit.

DR. GUYTON: Right. I think that we have run into increasing difficulty with our IRB in attempting to, because they look at prior trials and if we have a trial that's identical to a prior trial that was stopped by a data safety and monitoring board, that's a red flag for our IRB. Dr. Horvath has in fact floated this before his IRB and they told him that they couldn't let him do that at his institution.

Now we all know that IRBs can be persuaded and that I think that it indeed may be possible to do the trial, and I think that that's a possibility. I wouldn't rule it out. I didn't really make the statement that it was unethical. I think that that was a leap from the statement that I made, and the statement that I made was that it is problematic for IRBs. But I don't think it's unethical and I think it is something that I would potentially like to see happen.

I think the concept of a good PMR trial

in one arm and a TMR trial, or CABG alone as a three-arm study is particularly intriguing for me.

DR. DAVIS: Dr. Aklog.

DR. AKLOG: Actually, this is also for Dr. Guyton. One of the things in terms of the challenges of doing a combined TMR and CABG trial that I don't think has come up is really the full spectrum of patients who might be candidates for combined CABG and TMR, all the way from those who may not even be, or are borderline CABG candidates may get one or two grafts but you're encouraged to go in because you know you have the option of adjunctive TMR, to those who are getting two, three, maybe even four grafts but have one discrete area of myocardium. So it seems to me like there is quite a broad spectrum of potential adjunctive patients. Isn't that an additional --

DR. GUYTON: Right. I think very much if we start expanding this -- the approval, at least for one device, is only for class IV angina, and indeed the trial that showed a three-month survival difference was only for patients with class IV angina, so you could certainly make your argument that we should extend this to patients with class II or class III angina and then you

have eliminated the concern, perhaps, of the IRB that this is something that has already been done, and I think that there are certainly opportunities for trials.

Now, the problem is that we are looking for a greater than two angina class relief and if you start with an average angina class of 2.5, you're doomed as far as showing that two angina class relief, and that's the reason that Allen's trial in particular looked solely at patients with class IV angina.

If I could make one other comment about Allen's trial, and that was the previous, the AHRQ summary showed that the five-year follow-up was only on 218 patients, the original was on 263. I would point that that was not from poor follow-up, it was because the institutions dropped out since some of the institutions chose not to participate in the five-year follow-up, so it was institutions dropping out by institution, not individual patients dropping out because they couldn't be found or so forth.

DR. DAVIS: Yes, Dr. Goodman.

DR. GOODMAN: I want to ask two quick questions and I don't know who best to answer

them, maybe Dr. Horvath or Dr. Guyton. First, is there any -- what do you see as the evidence about the, either mechanistically or from the trials, about the distinction between any of the types of lasers that can be used for TMR?

And two, do you see any issue, there are relatively a few number of women in these trials, which reflects the patient population probably. Do you see any reason to think or to know that the results from these trials couldn't be generalized to a much larger population which could involve, or have a higher number of women?

DR. HORVATH: As far as the laser-tissue interactions, there are differences, but I think in answering Dr. Rose's question, I think what we're seeing to some degree is a dose response curve. And as Dr. Popp pointed out, there are differences even with the various percutaneous devices, and if you imagine that a partial thickness channel may give you one type of response and particularly if you get one that the laser doesn't even engage the myocardium and then you take the other end of the spectrum of surgical TMR giving you a full thickness channel, you can envision where that would give you a completely

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different response.
The mechanistic differences, though, I think are points of future studies in the animal lab and part of ongoing studies that I and others have been involved in, but from a clinical point of view as you have seen time and time again, we're not seeing dramatic differences between the types of laser, at least in the surgical community, as far as the clinical results.
As far as the approach to treating women, there was no exclusion in doing that and I think it reflects, as you mention, the patient population that we're seeing, and in doing retrospective analysis of the data that has been collected, the outcomes for women have not been any different, and gender was not a risk factor either for success or failure of the treatments.
DR. DAVIS: Dr. Black.
DR. BLACK: I think maybe I will start with Dr. Popp on this in terms of the no-option patients, and I don't mean to muddy the water by bringing in another technology, but just in terms, as I'm thinking about the questions, I'd appreciate comments from you and one of the TMR folks.

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There is a noninvasive approach that CMS provides coverage for called external counter pulsation, which has been also used in treatment of patients with angina that is refractory to standard therapy. I wonder if you can make any -- and I don't believe any of the studies talked about comparisons, I'm not aware of any trials. I wondered if you felt comfortable making any comments about where EECP or the external counter pulsation may or may not fit into the treatment of these patients.

DR. POPP: Well, I can just comment about my general knowledge of it. I have had discussions fairly extensively with Richard Conte, who has had quite a large experience with it at Florida, and my impression from him and talking to other colleagues is that it is effective in the short term. It is, as you know, if you're familiar with the procedure, it's a fairly intensive therapy, you have to come in every day for a number of weeks and then there is residual effect which then fades away relatively rapidly. So in terms of the long-term effect and trying to actually make a difference for the patients longer term, I think it is a short-term answer and it can

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be repeated but it's not generally considered, at least by most of my colleagues, to be a highly desirable one just because of that.

I think it's analogous in that we don't know why it works. There are theories about why it works, but frankly, I mean, I keep going back to the fact that when I first saw angioplasty, I thought it was the craziest thing I ever saw. I mean, you break open the vessel and let the cholesterol out and stretch everything and then it's supposed to work. Well, it taught us a lot, the angioplasty, and I think there are lessons here both in the external pulsation and in what we have here with the somewhat unknown effect, and I think that's one of the reasons we need to study this carefully in both situations, because then we're going to learn something that right now as scientists we just have trouble with.

DR. GUYTON: I think that's an interesting comparison and the comparison is important because the FDA has held, I think, the two devices to two different standards, in that they are asking for a one angina classification benefit with EECP and a two angina class benefit with PMR and TMR, which I find interesting.

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The other thing is that I would be very concerned about the placebo effect with EECP. If you ask a patient, do you still have angina and if you still have angina you're going to go back and get this pounding on your chest three times a week. And also the fact that the benefit seems to be there while they're having the therapy and then it's short lived makes me, I think there is an increased concern about the placebo effect in that situation. I do think that, I certainly have had patients who have been considered for TMR who have had EECP and some of them swear by it and they go through it and they're happy with it, and then a couple years later may go back and go through it again. But I think these are desperate patients and it may be that placebo effect is a benefit, whatever makes it work seems to help some of these patients and they can walk across the room and they can take showers, and they can get out of their house if they get EECP. And I think that it's relatively noninvasive, even though it seems brutal, and it doesn't seem to cause much damage, and it does have minimal downside and some upside for these patients.

DR. DAVIS: We're about ready to move

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into our break, but before we do that we'll hear a question from Mr. Queenan and then Dr. Phurrough will have a comment to make, and then we will take a ten-minute break.

MR. QUEENAN: I actually have two questions, one is short and one is a little longer. The first one is to Dr. Guyton, if I might. I will characterize this as a 30,000-foot question as the consumer rep, but in your summary slides, your first slide you came out pretty strongly, I think, in support of TMR, but you mentioned that TMR and CABG was unclear. Yet when I listened to your presentation as a lay observer, I came away with the conclusion that you were actually pretty strongly in favor of TMR plus CABG, at least with respect that there was an angina improvement and there was no downside in terms of risk. Did I summarize that correctly?

DR. GUYTON: That is correct. The reason that I said it was less clear is that we're looking at five to seven trials with sole therapy and we're essentially looking at one to two trials with the TMR plus CABG, so I think that the level of evidence is different. There's no question that the level of evidence is different between

the two, so I think the evidence is pointing the same direction and it is a good randomized controlled trial that we have five-year follow-up on, but it would be nice if we had multiple trials, as Dr. Aklog has pointed out.

MR. QUEENAN: Thank you. The next question is for I think Dr. Ferguson, although a number of you mentioned this issue. You talked about the Peterson trial and the STS update and made the observation that the difficulty of comparing the CABG-alone people versus CABG plus TMR because of the sickness of the patients. And you also mentioned that the update suggested that there was not any overuse, I think, or not an exponential increase in TMR plus CABG, I assume compared just to the number of patients treated with CABG alone. My question is, because it was mentioned earlier that the CABG alone was potentially a different population in terms of sickness, one of the questions I would have would be, can you tell from that data whether the patients that received CABG plus TMR, whether there is any trend or difference in the sickness of those patients with respect to the criteria, the FDA criteria for actually applying TMR plus

CABG. In other words, is there a trend towards patients who don't fit the actual labeled indication for TMR based on that data, or can you tell?

DR. FERGUSON: What we know based on the observational data and the updated analysis of the data that were in the Peterson paper were put together, which was a study done at the onset of the adoption of a new technical procedure in cardiac surgery, and it's important to put that analysis in the context of the fact that in 1999 to 2001, which is the time interval that the Peterson paper analyzed, even though it was a retrospective analysis, that was the point in time where TMR had just been approved by the FDA and was becoming available for use in the community, as opposed to the data to its use in the randomized clinical trials.

So not only does it reflect more community use of that technology, but it reflects the learning curve of the community use of that technology, as opposed to the reanalysis, which is a more mature analysis of how it's actually being utilized in the community setting, at least as referenced to the STS sites that submitted data.

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As is indicated, it's a very very small percentage of patients in the overall context of the number of patients who get revascularized for coronary artery disease. .6 percent is a very small percentage. The increase between 2,400 and 5,400 in the two-and-a-half years between the Peterson cutoff and the cutoff through 2003 that was used in the update is a very small increase in the overall context.

The fact that there was no difference in the risk profiles of the sites that had TMR capability but were using TMR in patients they selected prospectively based on the indications at their own individual sites, the fact that their CABG-only population had the same preoperative risk profile, which is the only thing we can really measure in addition to outcomes in the STS database is I think suggestive of the fact that they're not applying TMR to a widely disparate population of patients in that the patients who don't get TMR in that institution mirror the patients who get CABG only in sites that don't have the opportunity to do TMR in the first place.

The corollary to that is that the TMR plus CABG patients in those sites who have the

ability to do TMR are considerably different based on their preoperative risk. They have higher diabetes, higher insulin-dependent diabetes, they have greater preoperative stroke indices, they have greater peripheral vascular disease, they have greater incidents of preoperative renal failure. All of those variables are important variables in the risk model for mortality from isolated coronary bypass surgery.

So we expect those subsets of people who end up getting TMR in the sites that are able to do TMR plus CABG to have a higher preoperative risk based on those risk factors alone.

DR. DAVIS: Yes, Dr. Goodman.

DR. GOODMAN: I just have two quick questions. One, I actually wasn't aware that the first Allen study was stopped. I was just looking through the paper, maybe I missed it, but it wasn't stated there, and that's relevant because when studies are stopped, they are known to be biased high for whatever end point they're stopped on. And the issue of the slightly higher observed mortality rate which can't be explained is, can't be easily explained has to be interpreted in the context of having been stopped early.

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Now, there were a couple of things that were said and I just want to have them reconciled. The Allen study was said to produce evidence of mortality benefit and angina benefit, but in fact it seems that on its face, it produces results that are not consistent or not completely consistent with the sole TMR studies in that it didn't show an angina effect in the first year or even three years, and showed a surprising mortality effect. Where the mortality effect seems to diminish and the angina effect only emerged after three years, which is completely inexplicable, occurs, there's a slight deviation. So I would like to just get that explicated and not leave the statement on the table that the Allen study with the follow-up showed both survival benefit and angina benefit. The short-term and long-term showed somewhat different and not completely consistent results. In the last sentence of the Allen study which has been stated has made it difficult to mount similar studies says that the operative and one-year survival benefits require confirmation by a larger validation study which is ongoing. So the author of that study himself said that another

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study was needed. So it would seem to me that that could also be brought to bear in justifying the need for another study, and I would just be interested in knowing what the other study he was referring to that he said was ongoing at that time was.

DR. HORVATH: Unfortunately, Dr. Allen is unable to attend today for family reasons, but I can answer your questions. The patients that got treated in that study had a CABG plus their TMR. The CABG is going to have some beneficial effect, in fact a dramatic one. So if there is going to be an angina benefit, which there was, one would not expect to see that early on. It was only over time, years in fact of time, that we saw --

DR. GOODMAN: Well, five years and not three years, really many years.

DR. HORVATH: I think that should be expected because we've seen this already when you compare angioplasty to bypass surgery. The benefits of those types of operations are going to be, for the bypass in particular are going to be over years. And it should not be a tremendous leap to understand that if you're using an

operation that we know has benefits, that being the CABG, and you add TMR, and the profound effect of the CABG is going to limit how soon you can see that incremental benefit. Additional years of follow-up may be the only way to see that.

And as far as the comment at the end of the paper with ongoing studies, there were in fact ongoing studies. Dr. Frazier was in the midst of compiling his study at the Texas Heart Institute, and I think the main reason that that was included in that paper, as is true of most papers that generate what would be a surprising result is in essence, yes, we found this, we believe it's important, and we would like to see it confirmed, but it may not be able to be confirmed, and I think it is somewhat irrelevant that that statement is there.

DR. GOODMAN: Well, I only brought it up because it was said that this study made it difficult to mount further statements. And I think the statement is correct, it's completely correct and I'm glad he made it, but it would seem puzzling that that the study, even though I understand the dynamics of IRBs, would be taken as something that made further study more difficult

when the investigator in the study himself said that further studies and larger studies were required.

DR. HORVATH: I think that the difficulties were not only in making a larger study but also what has come up and as was alluded to personally, have not been able to get this through an IRB, and a lot of it comes from exactly what point do you randomize such patients, as I mentioned earlier, and then what end point are you going to show that are going to demonstrate a clear benefit. And I think what we've been able to show with thousands of patients in the STS database is that there is a net health benefit if you look in the opposite direction. If you take these same patients with diffuse coronary disease, the mortality rate which is a hard end point is expected to be and has been demonstrated to be much higher, and combining it with TMR, that mortality rate is decreased.

DR. DAVIS: Dr. Guyton.

DR. GUYTON: I may have, probably gave the impression that all other studies might be difficult. I agree with Dr. Aklog that if it were not an identical study, that it is very likely

that such studies could be conducted and indeed an expansion of the indications or comparison against PMR certainly would be appropriate. But I do feel like knowing the dynamics of an IRB, that trying to do an identical study when a relatively large study has been stopped is a problem, at least it certainly is in our institution.

DR. DAVIS: Dr. Phurrough.

DR. PHURROUGH: Just before we take our break, and we'll have time later on for further questions, as the people in this room are aware, any time CMS decides to have an MCAC, there is a lot of interest, particularly on the part of those who have some interests or are part of that particular technology. In this case the STS and the companies after our announcement of this particular MCAC requested a fairly large amount of time to present their comments today, several hours worth of time. And I wanted to thank the STS and the companies and their consultants for working very hard to take what was several hours of comments and condense that down to what I thought was a very good presentation in the amount of time that we had to give them, and I appreciate the cooperation and collaboration that occurred

with that, so thank you for that.
DR. DAVIS: Thank you. I will also add my note of appreciation to our colleagues from the Society for Thoracic Surgery. So thank you for those informative presentations and for answering all the questions.
Just to lay out the rest of the morning, we're going to take a ten-minute break in a few moments and after that we'll have until 11:30 to continue with public comment. We're going to begin after the break with presentations by Dr. Gardin and Dr. Wehberg, and after that we expect to hear from others who are now in the audience. So let me ask that others besides Drs. Gardin and Wehberg who wish to give verbal testimony after our break, please see Michelle Atkinson outside in the hallway during the break so that she will have an idea of how many people wish to speak and can apportion the next 45 minutes or 50 minutes or so among those who wish to speak.
So with that, we will take a break and let me ask the members of the committee to try and be back here promptly in ten minutes.
(Recess.)

DR. DAVIS: We're going to start back with the public comment session, and we will begin with Dr. Gardin, and let me ask presenters again to disclose any potential conflicts of interest and answer those questions that were referenced earlier.

DR. GARDIN: Yes, thank you, and thanks for allowing me to address the group here. I am Julius Gardin, currently chief of cardiology at St. John Hospital in Detroit and professor of medicine at Wayne State University. I have no financial interests to disclose nor have I received financial support from the companies listed, nor was I contacted by industry groups prior to this presentation. I have served on the American College of Cardiology's committee, a writing group on chronic stable angina, and also two years ago on the update that was prepared by the ACC and then endorsed by the American Heart Association on chronic stable angina, and part of my responsibility was to work on the section on TMR and PTMR. So therefore, I believe that's why Mike Wulk, the president of the American College of Cardiology, asked me a few weeks ago to come and represent the American College of Cardiology

at this meeting.
Now, I would say in terms of the chronic stable angina, initial guidelines in the update, what we considered as a group were only randomized clinical trials, so although I have recently had the opportunity to read the Duke assessment which I received last Friday, our analysis was based really on the randomized trials.
I was also asked to use this format, the evaluative questions here, so I will go over this and I will just point out that under question two, where it has long-term and short-term survival under how likely is it that TMR will improve this outcome, those numbers are transposed. So in other words, the short-term --
DR. DAVIS: We have copies of that in our packet, so members of the committee can find that in their folders if they like. Could you explain again what's transposed?
THE WITNESS: This three and this one, for long-term and short-term mortality, I'm sorry. Short-term mortality one and long-term mortality three.
So I will try to go through these and

just focus on some comments, hopefully some will be not redundant to previous speakers, but I'll try to at least give our position on this. The first question was how well does the evidence address the effectiveness of TMR in the treatment of chronic refractory angina and our position was based on the review of the data that with a moderate degree of confidence, we felt that it certainly did, and especially as was pointed out earlier, in the areas of improvement in morbidity and quality of life. In terms of the short-term mortality, Dr. Zarin noted earlier and I would just refer to the studies of Frazier and Schofield that there was really no benefit that we were able to detect in terms of short-term mortality which was defined in terms of the request to me as 30-day mortality.

In terms of long-term survival, certainly there is the Allen study that was commented on earlier that there was a clear mortality benefit at five years. However, I would point out that among the randomized clinical trials, there were a number of others in which there was no mortality benefit, including the ones by Frazier, Schofield, Jones, Hoopshum, and also

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the Norwegian trial by Aaberge. So again, although the Allen trial would influence this as sort of moderately confident, I'm not really sure given the fact that there are these other studies that we can be conclusive just based on that one study. And I would point out that the Aaberge study, the Norwegian trial was a 43-month study as well, so there was no mortality benefit at that point.

In terms of morbidity, there are a lot of studies that document improvement in event-free survival and also some angina exercise testing. I would want to point out related to comments that Dr. Guyton made earlier and others, in terms of perfusion, that although there's certainly been studies showing improvement in perfusion, a study by Allen in '99 showed no difference in myocardial perfusion using TMR. And also I would point out that the Norwegian study -- oh, in the Allen study there was an N of 275. I'd also point out that the Norwegian trial, at least the publication in 2001 by Aaberge, of which there was an N of 100, showed that post-TMR there was an increase in resting wall motion abnormalities in nonviable LV segments.

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So I think that the whole issue of perfusion is still out there, and you know, I agree with Dr. Guyton that we have newer techniques to evaluate that that perhaps were not applied to these previous studies, but the level of evidence out there is just not sufficient to say that there is increased perfusion maybe with PET scanning studies, maybe with nuclear viability studies, maybe with dobutamine echo. So to that extent, that's an issue in terms of mechanism.

In terms of, moving onward here, how confident are you that TMR will produce a clinically important health benefit in the treatment of chronic refractory angina, again, I think certainly in terms of angina relief and some of the other tests in terms of, say, exercise duration and that, we can certainly be at least moderately confident that it will produce this benefit.

And how, question four relates to generalizability, first of all to the Medicare population. I think certainly the studies have covered the age range that would be likely seen in the Medicare population. In terms of providers and community practice, that's always a little bit

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of an issue in terms of making sure that they use the same criteria that were incorporated into these studies. For example, is the myocardium that they're going to try to use TMR on viable, has it been shown to be viable and ischemic? So I think that this is the concern, of course, in introducing it out into the community, to make sure that people follow the indications that have been proven.

Now in terms of, moving on, in terms of TMR and CABG, again, we have, although less evidence, a moderate degree of confidence that this will be a useful technology and effective in a selected group of patients, and I would emphasize the whole issue of selected group and will get into that in just a minute.

In terms of the short-term mortality, again, we do have the study by Allen that there was a significant mortality benefit at 30 days.

In terms of long-term survivals, I think that this has been pointed out before, you have a positive benefit at five years by Allen, I'm sorry, at one year but not at five years. So again, depending on how long term is long term, these are the data we need to deal with.

In terms of morbidity, the small amount of evidence that there is certainly supports a decrease in angina and morbidity in events. And also in terms of quality of life, notably again with the paucity of data of the Allen study. So, at this point, we are moderately confident that the combination of TMR and CABG would produce a clinically important net health benefit for selected patients with chronic refractory angina, and again, that the data would be applicable to the Medicare population with moderate confidence.

But in terms of providers, I think the issue is even more so here in terms of an issue of whether the technique will be appropriately utilized and the issue is, as has been pointed out by a number of speakers, if a patient is already going in for a coronary bypass surgery and then they don't get complete revascularization, but I would submit that another issue is whether the area that has not been revascularized by CABG and that you're considering for TMR is actually viable. So I think it's very important that as this technology becomes more widespread that we hold ourselves as practitioners to fulfilling the

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standards of showing that there's actually, we're attacking something that's actually viable, because again, we don't know exactly how the technique works and we need more data on that. Now moving on to PMR, again, how well does the evidence address the effectiveness? Again, there is certainly an emerging body of evidence that suggests that in selected individuals that there is a moderate degree of confidence that this is a helpful technique. However, as has been pointed out before, there does not seem to be any mortality benefit either in the short term or the long term. In fact in the PACIFIC trial, although this was not statistically significant, there was an increased mortality trend, which has been commented on before perhaps some of the reasons for that. So we're really not talking about, as has been pointed out, an improvement in mortality. What we're looking at is morbidity and quality of life. In terms of those issues, however, the data are a little bit mixed. As really pointed out in the Duke technology assessment, there was really no improvement in the Leon and Stone studies, but there was improvement in the study by Salem. And

the question of course that has been raised is does this have to do with either different technologies being used or some other differences in the study. And there's clearly just not enough data yet to make that call because of the divergence there and because of the evolving technology.

On the other hand, the quality of life does seem to, the preponderance suggests that there is a benefit, but I would only be moderately confident about that.

Now in terms of the applicability to the Medicare population, I believe that it's reasonably likely that the data so far will be applicable to the Medicare population, but again, we have the issue of what about the providers in community practice. There will need to be an assurance that whatever is the best technique, if there turns out to be a difference between these devices, is utilized and that the same issues about looking at, trying to treat viable myocardium are adhered to in this group. So, I think my main concern is in terms of the diffusion of the technology, that it be properly used in the groups for which we really have good data.

I would also just point out parenthetically, although this may have been just the luck of the draw and the fact that it was a small study, the PACIFIC trial did have a trend towards increased mortality at 12 months, with eight deaths in the PTMR group and only three deaths in medical therapy. But again as Dr. Cooper pointed out earlier, this may have been the luck of the draw in more than just this trial. So I think in summary, in terms of PTMR, we're really looking for additional data, additional definition of perhaps differences between the technologies, and of course we don't have a lot of long-term follow-up. Thanks very much.

DR. DAVIS: Thank you, Dr. Gardin. Dr. Wehberg.

DR. WEHBERG: While we're getting the technology started, I'll just give my disclosures. My name is Dr. Kurt Wehberg, I am a community cardiothoracic surgeon in Salisbury, Maryland. I'm also a member of the Society of Thoracic Surgeons. I do not hold stock in any medical company. I have been elected to the advisory board of directors for Cardiogenesis Corporation

in January 2004. I strongly believe that the technology, interaction and working relationship with the industry will benefit my patients. I do not serve on any committees or panels that have discussed this topic. I have discussed this talk today with a few of my patients who will also give their testimony and I have also discussed my slides with Cardiogenesis.

The purpose of my presentation today is to address specifically to the panel the questions regarding the generalization of CABG plus TMR data, and I want to address these and thank the panel for giving a community physician the opportunity to speak about the outcomes, specifically the 30-day outcomes of CABG plus TMR. This study, this trial which I will discuss has been published and is our initial experience in the community of CABG plus TMR. We looked at a total of 250 patients over a six-month period at a single institution. 36 of those patients were completely revascularized by CABG plus TMR, 219 patients were revascularized by CABG alone. The indications and the exclusions for each of the group were identical. Indications for surgery were they had to have class III or IV,

Canadian Class score of angina. They had to have a left ventricular function of greater than 30 percent.

The interoperative decision was made both on a preoperative angiogram as well as the judgment of the surgeon, basically if the target was less than one millimeter in diameter and also if the cardiologist felt preoperatively that they were not a candidate for PCI. In both groups the exclusion criteria included emergency procedure, anyone with unstable angina that was in intravenous nitrates or platelet inhibitors, and any patient who had an acute MI within 72 hours.

In looking at the results, the baseline characteristics and demographics of the patients in the two groups were similar. The ejection fractions were approximately 50 percent in both groups. The number of grafts in both groups were not statistically different; in the CABG-alone group it was 3.1, the CABG plus TMR group was 2.9.

The operative time was similar in both groups. We compared the outcomes of both patients.

In terms of intensive care unit stay, patients with CABG plus TMR had a significantly shorter stay, 1.6 days versus 2.1 days. In terms

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of overall postoperative length of stay, again, significance in the CABG plus TMR group, significantly different and a decrease from the CABG-alone group. In terms of 30-day readmissions for all causes, not only cardiac events but for all causes, there was a significant reduction in the readmission rate with the CABG plus TMR group as compared to the CABG-alone group. In terms of postoperative atrial fibrillation in the hospital, there was a significant reduction in atrial fibrillation rate, almost half of what it was in the CABG plus TMR group compared with the CABG-alone group. And finally, mortality, 30-day mortality, for these first 36 patients we have had no mortality. That's compared to a 2.3 percent mortality rate with the CABG-alone group. There was no statistical significance with this. In conclusion, CABG plus TMR as compared to CABG alone in vary carefully selected patients is associated with a reduced intensive care unit stay, postoperative lengths of stay, postoperative atrial fibrillation, and may also provide a benefit for operative survival as well as rehospitalizations as compared to CABG alone.

This paper was accepted in a peer review journal about the early experience in a community setting of CABG plus TMR. We have now a cumulative experience of over 250 CABG plus TMR patients with a 30-day operative mortality rate of 0.5 percent. I would like to emphasize that the community physicians who are performing CABG plus TMR strongly believe that the 30-day outcomes are improved as compared to a subset of patients that are possibly even healthier with CABG alone. Thank you.

DR. DAVIS: Thank you very much. Perhaps if any of the committee members have some quick questions of these last two presenters, we can take those now and then we will have public comments from four other people who have signed up, and so if we don't take too long, we can offer them three or four minutes each before we go into our lunch break. Dr. Cooper.

DR. COOPER: Dr. Gardin, two questions. Would you agree that angina in itself is not a reliable surrogate for ventricular function?

DR. GARDIN: Absolutely.

DR. COOPER: Secondly, if through whatever mechanism TMR relieves angina for a

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period of time, six to nine months, is it possible that the relief of angina would have a secondary effect on the patient and ultimately on their physiology by allowing them to do more, be more comfortable in their exercise activities, is it possible that by whatever mechanism one could relieve angina for a period of time, that that might translate into long-term benefit allowing the patient to be more active, do more exercise, and could that secondarily improve vascularization, ventricular function, by a secondary effect?

DR. GARDIN: It's certainly possible. And I would also just amplify to say that when I was making the points about possibly one of the studies showing wall motion abnormalities or another study showing increase in heart failure treatment, even though angina was relieved, I wasn't trying to make the point that relief of angina even for six or nine months is not a desirable goal or something that would be worthwhile, merely to point out that since we don't know how the techniques work and because there have been some reports of increased wall motion abnormalities or increased requirement for

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heart failure treatment, it's possible that we may need to keep that in mind.

DR. DAVIS: Dr. McNeil.

DR. MCNEIL: I have a question for Dr. Wehberg. First of all, congratulations for launching a study in a community practice. I know that's quite a big deal.

I didn't quite understand how you chose patients for the combined therapy versus the solo therapy and how thereby you can be sure that you're comparing apples with apples.

DR. WEHBERG: There were two decisions based upon the indications for surgery. One was based upon a cardiologist telling us that it is not angioplastiable or stentable, so that was the one decision for the surgeons, to make a preoperative decision that we're going to go ahead and do TMR in that region of the left ventricle. The other decision was made intraoperatively as a judgment by the surgeon that if he felt the target was not amenable to a bypass and felt that he would harm the patient by doing a bypass, by opening up the artery to do a bypass, then an intraoperative decision was made to perform a TMR in that region rather than a bypass.

I would like to also add, we have performed many procedures where both a bypass and a regional TMR around that bypass have been performed, that's called a belt and suspenders technique. I have excluded those patients in our study to try to make it more clean to find out what the outcome benefits were.

DR. DAVIS: Dr. Aklog.

DR. AKLOG: I have two quick questions, one for each panelist. I'm just curious in your 250-patient experience referring to what I mentioned earlier. Did you find, were any of those patients patients who otherwise were not considered to be candidates for surgery because they had a lot of diffuse disease and you weren't confident going in that you would be able to do an adequate revascularization? Did adjunctive TMR tip those patients into a category where you felt comfortable proceeding in your practice?

DR. WEHBERG: In our community practice we are very strict on our inclusion criteria even now after our initial studies. We try to be very sound on the ejection fraction, about all the criteria of acute myocardial infarction and unstable angina, and we exclude them from getting

it. In other words, if a patient had a target on lateral wall that was not amenable to angioplasty or even a bypass, if they had an acute infarction, we do not perform TMR even though that would probably be the best thing for them.

DR. AKLOG: My question was really more, if you had a patient where you did not have access to the laser, who had such diffuse disease that they were really a borderline candidate for isolated revascularization, did the knowledge that you had the option of supplementing that with TMR lead you to go ahead and proceed with the combined treatment.

DR. WEHBERG: Did the availability of having a laser machine change our strategy?

DR. AKLOG: Yeah. Did it expand the pool of patients who were candidates for surgery?

DR. WEHBERG: I honestly believe it does. I believe it's an extra tool, an alternative tool that a surgeon has in his back pocket to use when a target is not amenable for bypassing. In my practice in our community situation, we believe that if you use TMR, rather than jeopardizing a target with a graft that you're going to do a benefit by not doing

something additional you shouldn't have done in the first place with a graft. We think that the increased mortality associated in Dr. Allen's study in the CABG plus TMR group of 7.5 percent was related to not only incomplete revascularizing those patients in a lateral ventricle, but also because people were trying to put a graft on when they shouldn't be putting a graft on, they should be doing TMR. Does that answer your question?

DR. AKLOG: Yeah.

DR. DAVIS: Thank you very much. We will move on to Lewis Riley. Is Lewis here? And let me remind the next four speakers as well, if they have any conflict of interest disclosure, to please include that in your remarks.

MR. RILEY: Thank you for allowing me to be here today, committee. I have no financial interests, no conflicts that I'm aware of, and I thank you for the opportunity to tell my success story in having been the recipient of the TMR procedure, surgical procedure which was performed by Dr. Wehberg at the Peninsula Regional Center in Salisbury back on August 6th of '02.

I was first diagnosed with heart concerns back in '95 when I had open heart

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surgery. That operation was a success and after nine weeks I resumed my work schedule then, as Maryland Secretary of Agriculture and also as a very active farmer on my son's and my farm operation. I did reasonably well until October of '98 when catheterization resulted again in placement of a stent for blockage, and again in August of 2000 and then in June of 2001 I had another heart catheterization with another stent. These procedures were done in response with almost continuing angina and chest pains, and continual use, and I emphasize continual use of nitro along with other prescribed medications.

So after hearing about the TMR procedure being done at Peninsula and the success rate of pain relief, I obviously became interested after what I had been through. I talked with my surgeon, Dr. Buchness, about the possibility of using this procedure. And then during the last catheterization procedure with my cardiologist, Dr. Jeffrey Whelan, I asked for a consultation with Dr. Wehberg, which took place during my visit while I was in the hospital. He explained the procedure to me and what he could foresee as a probable result, and he strongly emphasized it was

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my decision, as the procedure was relatively new and he was I would say cautiously reassuring. And my decision to proceed was based on the fact that anything was better than the alternatives. I was tired of a daily diet of nitro to alleviate the pain and being grossly restricted in the activities that are necessary in my type of work. Having been a farmer all my life and being so restricted from those types of activities, life was obviously very miserable for me. Let me note the inclusion of my medical purchases, I did submit copies of that, and I thought that was very interesting, the amount of nitro that I was taking for relief. The TMR procedure was performed on August 6, 2002 by Dr. Wehberg, who I believe, if I recall, administered something like 50 laser shots. In six days I was discharged. Eleven days later I was doing light farm work, although he told me not to do anything for 30 days, but I was doing light farm work. Unfortunately the local newspaper printed a picture of me in our poultry operation and it was in the paper before my 30 days were up. But anyhow, that's how reassuring it was for me. My life was renewed. My pain diminished greatly,

frankly almost completely, and the nitro use almost ended. And I have submitted a use from my druggist, this prescription. I want to note that from January 1st of '01 to August 7th of '02 when the TMR was performed, I had acquired 29 prescriptions from the local druggist of nitroglycerin. After August 7th when the TMR was performed until July 4 of '04, this month, I have acquired three nitro prescriptions. I think that's living proof of how the nitro was helping me to survive the pain.

So what more can I say? I basically have my life back, I'm working daily on the farm, I'm caring for my invalid wife, and I feel great about the future. Although I will be 70 years old on my next birthday in February, I have every intention of continuing my activities on the farm and my livelihood in agriculture. I has no aspirations for retiring. You know, in agriculture there's an old saying that a satisfied man is ready to die and I'm just not satisfied yet. I have a lot more to accomplish. I'm a sixth generation farmer on our family farm and folks often say to me, Lew, have you lived all your life on the farm? My answer is, not yet.

There's so much to be said, ladies and gentlemen, for the continued support of this procedure, as well as others that are being researched in the health care field, and I feel that I'm a living example, my experience is living proof that this procedure certainly proved well for me, and I would think it less costly than the route of recovery I was experiencing prior to that August 7th in '02. I will be glad to answer any questions the committee may have, and I just can't be more enthusiastic about my life and what it has meant to me.

DR. DAVIS: I'm sure your family was happy to see your activity level back to where it was, but what about the chickens?

(Laughter.)

MR. RILEY: I think they're delighted too.

DR. DAVIS: Thank you very much. Peter Petkoff.

DR. HORVATH: Permit me to introduce Mr. Petkoff, as he is one of my patients, and the reason is that there are important points of his medical history that I don't think he was even aware of at the time because he was so sick when

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he entered the hospital. He was admitted two years ago just before Christmas with progressive easy fatiguability that had gone to shortness of breath. He was admitted with a non-Q wave myocardial infarction, was close to being intubated at least on one occasion. He had an angiogram that showed he had left main disease and severe other three-vessel disease as well, and he underwent a CABG-TMR procedure. He is a man of few words, being one of the original members of the OSS, but I'll let him take over from this point.

MR. PETKOFF: My name is Peter Petkoff and I'm 85 years old, a Medicare beneficiary. I want to tell you about my experience with TMR. The doctor already told you.

I have no connection with the two companies that are involved in here, except I know one of their employees, and the reason I know him is because my grandchildren play with his children, that's how I know him. I have no connection with everybody, but they do pay my expenses for this trip, and I don't know which one of the companies it is.

I have many experiences in my 85 years

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of life. I am originally born in Bulgaria, and finished high school there but completed one year of engineering school in Czechoslovakia. At the time, in 1938 is when I decided to come to the United States. It was after I had been in Czechoslovakia for one year. I started off on a train from Bulgaria and the train was stopped at the border of Austria because the Germans were invading for the first time Czechoslovakia, as you all remember. I was on my way to join my sister and I continued on my way, and that's how I'm in here today. It changed my life completely. During World War II, I served with an army engineering battalion, but in the middle of the time that I was with them, I joined the OSS. For those of you that don't remember, OSS was the forerunner of CIA today, and as such I was one of the early special services. I'm also a retired structural engineer and in my many years of experience in that I have had the opportunity to work with some of our greatest architects of our time, Eero Saarinen; Minoru Yamasaki, who many of you know of, he's the designer of the Twin Towers in New York; Kevin Roche, who followed Eero Saarinen, and many others, and I'm telling you

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that only to let you know who I am. I have been in very good health all my life, mainly or possibly because of my training with the OSS, which was very demanding. Sometime after I retired, my wife and I moved to Florida, but at some point we decided that we're too far away from our grandchildren, so we joined them in Chicago. And there I see them all the time and I walk with them all the time, I walk, I play, and usually I'm the one that heads the pack. But the Monday just before Christmas of 2001 I was at the end, and my daughter was with us and she reminded me of that, she said you are not that fit today. That same evening I had to go to the emergency hospital and there I was held for about 12 days. During that time Dr. Horvath did the operation, three bypass, including TMR. Now I enjoy walking, walk almost everywhere in the middle of the town of Chicago where we live, and constantly play with my children every time they call, and we play soccer, them and their friends. I never had any problems with my health outside of that. Now two-and-a-half years later after my surgery I feel so well I play soccer with them as I said previously every time that they call, and

they call quite often. Medicare has covered the cost of my surgery, including TMR, and I have been very satisfied with that. Since I have been retired for 20 years, even though when I worked I made a very good living, my ability to pay would be impaired and I couldn't pay for the operation that I got. I would like to tell everybody that I hope your decision will be such that everybody would be entitled if need be to TMR as well as the rest of it.

I thank you very much for the opportunity to speak. Thank you.

DR. DAVIS: Thank you very much. Good to have you with us. I'm glad to see that you're doing so well and thanks for being with us today.

MR. PETKOFF: If there are any questions, I will answer them. Thank you.

DR. DAVIS: Pat Gibbs.

MS. GIBBS: Good morning. On the disclosure statement, my name is Pat Gibbs, I'm a retired federal employee and I have a small amount of stock in TLC, which I shall address later. I am not on any advisory committees, I have not received any financial support from any company,

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and when I was invited to speak today, which is a pleasure, PLC is paying for my accommodations here and they paid for my flight.

I am 75 years of age and I am so appreciative of the opportunity to speak about a subject that I just am passionate about. I can't say too much about PLC and about TMR. I had the only TMR, or TMR only, alone. I have had two, possibly three heart attacks and they severely damaged my heart. I had bypass surgery twice, carotid artery surgery twice, and I'm also a type II diabetic. In 1995 I was told there was nothing more that could be done for me, that I needed a heart transplant.

My health at that time was such that the pain from angina prevented me from walking from my bedroom to my kitchen without stopping to sit down and rest. I had been widowed for two years and was becoming almost housebound. I was afraid to drive or even go out to fill the bird feeder because I had to walk down some stairs.

Pursuing a heart transplant option, I contacted UAB in Birmingham and was told I was too old for a heart transplant. I was told to go home and pray, and I did.

My prayers were answered. Eight years ago I was blessed to be the recipient of a procedure called CO-2 transmyocardial revascularization. It saved my life. My first of many surprises was that I found recovery from the procedure to be more rapid and much less painful than traditional bypass surgery. I felt wonderful and as time passed the previously debilitating angina literally vanished. Since TMR surgery I have enjoyed traveling to many parts of our beautiful country. Unaccompanied, I have flown to Alaska, visited with friends in Anchorage and Fairbanks, I've gone white water rafting and traveled over quite a lot of Alaska enjoying many exciting and strenuous Alaskan adventures. My travels have taken me to many wonderful places which I would never have seen were it not for TMR surgery.

I was so excited by the quality of life that I now enjoy and was so impressed with the TMR laser surgery that for the first time in my life I invested in the stock market, and this is where that little bit of stock comes in. I bought some stock for my children and they will have it when I pass away. I am an avid gardener and I love to

travel. I am a very active volunteer and again, I'm an asset to my community. My family and friends are amazed at the level of energy that I'm able to maintain and what a blessing this is. Because of TMR surgery I no longer struggle to move from one room to another. I can run up the stairs in my house without having any pain in my heart, and I really still hope to take my grandsons skydiving, it's something we've had planned for a long time. Thinking now of my life as it is today compared to what it was before I had TMR surgery, I find it difficult to believe that Medicare would find themselves saving very much money by denying coverage for TMR. I know I would have required a great deal of home care, frequent hospital stays and probably in the condition I was in, special equipment to cope with the disabling effect of the angina. Medicare would have been paying for a lot of these costs and my life really would have been a quite miserable thing.

Today I'm an active volunteer in several organizations and at church and feel again that I am an asset to my family, to my community and to myself. I feel very deeply that it would

be a grievous act for this remarkable procedure to be taken away from those who are suffering with the pain of angina but cannot afford the surgery without the help of Medicare coverage. I implore you to continue offering Medicare coverage for this giver of new life to the people who suffer the terrible pain of angina. To me and to my family, the ensuing results of TMR are tantamount to a miracle.

Thank you. I will be glad to answer any questions anyone might have.

DR. DAVIS: Thank you very much. You mentioned all those vacation spots; have you been to Michigan?

MS. GIBBS: No, but my daughter-in-law is from Michigan.

DR. DAVIS: We don't have any glaciers but we have some beautiful sand dunes and lighthouses, so please come visit.

MS. GIBBS: I'm on my way to Santa Fe in September.

DR. DAVIS: Thank you very much for being with us today.

Charles Turkelson is the last presenter before lunch.

MR. TURKELSON: Yes, I do appreciate the opportunity to be here. I'm Charles Turkelson, I am director of the ECRI evidence-based practice center and its chief research analyst, which in practice means that the technology assessment, systematic reviews and evidence reports are prepared under my close, often very close supervision. My primary purpose in being here today is I understand that you have before you the ECRI report on TMR and PMR. I have no conflict of interests to disclose. ECRI is a nonprofit organization and our conflict of interest rules prohibit accepting funding from manufacturers, pharmaceuticals and the like. Indeed, our tax returns are audited every year. I should mention that 60 reprints of this report were purchased by a manufacturer but manufacturers are not allowed to commission reports from us.

Indeed, the history of the report that you have before you is that we first undertook it for our own private sector clients in 1998. Subsequent to that, specifically in the fall of 2003 TriCare commissioned a report from us on this topic, it was essentially a complete rewrite of

the report, and then the report you have before you, I believe, is the January 2001 version. This version was updated to include the data from the Peterson study.

The report does examine TMR, TMR plus CABG, and PMR, and looks at 11 outcomes for each of the technologies. There is obviously not the time to recount all of the results of that report, I would just like to highlight a couple features of our report, going perhaps more into methodology, and then by way of that talk about a couple of results.

I would like to point out that we do not just judge the quality of evidence, we judge what is called the strength of the evidence following the AHRQ report system to rate the strength of the scientific evidence. That takes into consideration the quality, the quantity and the consistency of the evidence. I bring this up to show some of the lengths we go to to prevent bias in our reports, because quality, quantity and consistency in our report, they were defined a priori and how these three weighed together were also defined by a priori rules that tend to prevent reviewer bias.

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There is a formal possibility, because our report was prepared prior to the publication of two new trials, that indeed the strength of evidence factor would be higher than what you see in the report because of the addition of new quantity of evidence. So for the methodologists in the crowd, I think we have been rather scrupulous in determining the strength of the evidence.

I would like to point out too that we did a series of metaanalyses in this report. I think it's appropriate to discuss our approach to metaanalysis. It is I think in general entirely difficult to find identically conducted trials that enrolled identical patients, and oftentimes very easy to say that the differences between trials are too substantial to permit a metaanalysis. That tends to be a rather, or can be a very subjective reason for not combining trials, so we take an empirical approach. We will combine the trials and let the statistics tell us whether we should have done that or not.

The other option is actually an interesting statistical conundrum and that is when one begins a metaanalysis by concluding the trials

are sufficiently alike to combine, one is actually engaged in a de facto acceptance of the null hypothesis. So again, that is another reason for, I think, the statistical approach that we take to determine whether trials should be combined. Throughout most of the metaanalyses in the report you see before you, there is little empirical support for the notion that the trials should not be combined, that is the test for heterogeneity in particular, the I squared test, which is meant to operate with very few trials, suggests that patient differences and studied differences notwithstanding, these trials are indeed combinable. In the one case where they were not combinable or were said to be heterogeneous, we sought to explore the heterogeneity.

I will briefly mention just an undercurrent of our report and that manifests itself in the metaanalysis for TMR alone of survival data. Our concern was that indeed we confess that the mechanism of action is unknown here. One proposed mechanism of action is denervation, which I think we were concerned that this could result in perhaps delays in patients getting to the hospital. So we were conducting a

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metaanalysis of long-term one-year survival in an effort to determine whether TMR was in fact harmful to patients. The advantage of conducting a metaanalysis there is we gained the statistical power of pooling results, that you don't have when you look at the studies alone. And indeed with that added power, we still see no trend towards excess mortality in the face of TMR.

The other claims of metaanalyses we did are best, I think, illustrated by TMR alone and again, on our one-year metaanalysis data of greater than or equal to two class reduction, the purposes of these metaanalyses is not so much to arrive at a single summary statistic, but rather to bracket the potential effectiveness. One of the reasons for doing so, indeed, has to do with crossovers. As you're aware, two of the trials did allow crossovers. The interesting fact here is that of course a patient cannot cross over from the TMR to the medical management group, but only from the medical management group to the TMR group. What that has the potential of doing is leaving the healthier patients in the TMR group and shunting the sicker -- I'm sorry, the healthier patients in the control group and

shunting the sicker patient to the TMR group, which could indeed create a potential bias against TMR in these studies. Indeed, in two other studies there are also potential biases against TMR in that it looked like the control group patients were a little sicker.

So we conducted a series of metaanalyses, three in particular on angina reduction, to bracket what the potential odds ratio might be; it ranged from 5 to 9 depending on the assumptions one made, and each sensitivity analysis was backed up, or each metaanalysis was backed up by sensitivity analyses. It certainly did not overturn the quality or conclusions.

That brief overview is I think where I should stop my summary. My primary purpose here is really to, A, give that flavor of the report that I just gave you, and B, to answer any questions about this report that you or anybody else might have.

DR. DAVIS: Any questions? We did receive a copy of the report electronically before we came here. Thank you very much.

Well, we're at the time for our lunch break. We are scheduled to take a one-hour break,

we're a little bit behind schedule, but I'm confident that we will be able to make that up in this afternoon's session, perhaps through modifying the way in which we were going to do our voting process. I think we can talk about that when we reconvene after lunch. So please be back here in about 60 minutes. Thank you.

(Luncheon recess.)

DR. MCNEIL: Dr. Davis is delayed a bit, so why don't we start this session and I will start off as moderator and the minute he comes back I'll pass the baton.

We now have open panel deliberations and I think this would be an opportunity for the panel really to raise any issues that we want before we go to the last part of the day, which will be filling out the questionnaire. So, questions? Comments? David.

DR. COHEN: My question is, are we supposed to ask questions of each other or are we allowed to ask questions of the folks if we have remaining questions from earlier?

DR. PHURROUGH: Either/or, or talk among yourselves.

DR. BLACK: I wonder if it might not

make sense to try to go through topic by topic. There's going to be some overlapping things, but rather than being all over the place, if we were to talk about TMR first and then go on, I mean some of it will be relevant, but I'm just concerned that if we potentially bounce back and forth, we lose the ability to come to closure, or we may be able to close one topic fairly quickly and then get that behind us and move on.

DR. MCNEIL: Actually I wonder, could we even consider taking a vote, answer the questions, I'm sorry, after we discuss one topic, or do we need to go through all three of them before we answer any of the questions.

DR. DAVIS: Let me just mention, and I apologize for being late, but let me just mention the thought I had about how to conduct the voting, and then we can come back to this issue about how to structure the discussion. My thought for the voting was to do it in the following way, which I think will help make it more efficient. I thought we would take it treatment by treatment and we would start out with TMR, for example, and we go through it question by question. So we would begin with question one, and I would go through

the response choices and then ask people to give me a show of hands when I got to their number. So you can see on the questions, one is limited evidence, three is moderate, five is complete, so I would just start out for example at one, and I would say just say one, two, and just pausing after each waiting to see if there are any hands that go up. And then somebody who's not voting, like Michelle, can keep a tally of how the votes go on that particular question. Then we would move on to question two and do the same thing for two, three and four.

And then we would stop and then go around the table and let each member of the committee comment if they like on why they voted the way they did, which is done traditionally for this committee. And then we'd repeat that process for TMR plus CABG, and then repeat that process for PMR. Now if we do that, we could also follow that same process for the discussion, so we could do the discussion for TMR, then do the voting for TMR like I laid out, and then move on to the other two treatment areas.

But let me just open it up for comments from the committee. And I want to mention at the

outset that this is the first time that this committee is using this structure of questions, so we haven't done this before and we're learning by doing in some respects. Dr. Cooper.

DR. COOPER: It seems to me one of the values is to be able to ask other members of the panel who are from other disciplines and have other points of view some of the questions that we haven't maybe had a chance to address when discussing with the presenters this morning. So I think it might be helpful to have a little period of discussion among ourselves before doing the actual voting if time allows.

DR. DAVIS: That was the plan. We will have a full round of discussion before we get to the point of voting, but I would encourage you to start thinking about how you will cast your votes if you haven't already begun to think about it, as we move into the discussion phase. What would people like to do for the discussion part of it, would you like to divide the question, so to speak, for the discussion portion as well as the voting portion? I see a lot of nodding of heads. Yes, Mr. Queenan.

MR. QUEENAN: I don't have a problem

with doing that but I think that certainly from my point of view, it is also worth discussing perhaps at a general level across all of the other areas what we mean or what people think of when they answer complete or limited or moderate, in other words, what the basis, what the benchmark for that assessment would be, because it seems to me that's going to be critical for CMS to really interpret what our votes mean, and I suspect it could be a matter of some differing points of view among the committee members, and that doesn't fit into any single area, that's sort of a generic area that I think would be worthwhile.

DR. DAVIS: Good point. We can start out with some general discussion that would cut across the three different treatment areas and then move on to a divided discussion and voting. And also, I think the nuance that you pointed out is the kind of thing that people might want to explain after they vote to explain why they voted the way they did. Because you're right, people may interpret these adjectives like limited and moderate in different ways. Dr. Phurrough, are you comfortable with us proceeding in that way?

DR. PHURROUGH: Very.

DR. DAVIS: Good. Barbara?
DR. MCNEIL: Yes.
DR. DAVIS: Okay. Well, let's open it up for general discussion that would cut across these three different treatment areas, recognizing that if you have a comment on a specific area, perhaps you could hold that off until we get to the specific discussions. Yes, Dr. Aklog?
DR. AKLOG: Maybe I'll start by asking the other members of the panel as a surgeon, do other members of the panel see a difference in terms of the levels of evidence, the burden of proof, the types of studies and so forth that are necessary to evaluate surgical procedures where the challenges of doing very rigorous studies are greater than perhaps medical therapy, are we operating with surgical therapies in a different realm?
DR. BLACK: Let me try and then certainly others, since you asked the entire panel I'll start out. I think the one issue that's very difficult that's already been alluded a lot is the idea of blinding, so we know that for a number of surgical procedures it's very difficult to do the blinding. And you can do it depending on the

surgical technique and, you know, who the investigators are, it can be set up in various ways. So while I think the level of evidence that we're looking for should be the same, I think the blinding around surgical procedures, what we talked about earlier this morning, the questions about what do we know about the placebo effect and its durability and the extent to what we might see are important, so I think there are particular challenges. But I think in terms of sort of the evidence we're looking for, we ought to strive, from my perspective, I think we ought to strive to have it as similar as possible.

DR. DAVIS: Barbara?

DR. MCNEIL: Just to amplify, I don't think we would find it acceptable to use observational data to come to rigorous conclusions.

DR. DAVIS: This committee, which is now, what, almost five years old, developed a guideline for how to evaluate and weight the evidence and I don't know if you've seen that document, it has gone through some iterations, it's available on the MCAC web site, but it does talk about the familiar sort of hierarchy of

evidence with RCTs being the gold standard and so on down the ladder. I don't recall it making any distinction between, for example, medical treatments and surgical treatments. I don't think we made an allowance for that so I don't know that they could be treated substantially differently.

DR. GOODMAN: There is no objective reason why they should be treated differently. Even in a situation which this is not really at, where you literally could not do an RCT in surgery, I think one would just have to acknowledge that the evidence in that case was less than it might be in either other surgical cases or other pharmaceutical cases. So the fact that it's the best that you can do in this discipline doesn't necessarily mean that it's very strong evidence. I think we have to separate those two. So, I think we could acknowledge that this may be, and we may or not say it's the best we could do, but it still may not be good enough, or vice versa.

DR. DAVIS: And to just add a comment to that, we need to remind ourselves that we are rendering judgments on the quality of the evidence and the generalizability of the findings and those

kinds of things, but we're not making recommendations on coverage. So CMS can take our conclusions on evidence and decide because an RCT isn't practical in a particular area, they may be comfortable accepting consistent and valid observational data or they may not, but that would get into the realm of some policy decision-making as to whether, for example, an RCT can be done in a particular area.

DR. AKLOG: I think that may be true with regard to the level of evidence, but in terms of practical matters of actually providing therapies, like Dr. Guyton said, actually looking at the patient and providing the opportunity to give our patients therapies that may be beneficial, I think if we set the bar too high with regard to the level of evidence, we could be in danger of withholding therapies that may potentially be beneficial. I think the way the questions have been structured, like we talked about at lunch, has allowed us some ability to separate the strength and the volume of the evidence versus the likelihood of there being a benefit, and so I think you can vote separately on those two. But as someone who has been involved

in trying to set up surgical trials, it's very difficult to reach the level of, you know, a trial of two different pills for example.

DR. PHURROUGH: I think Ron was right on point in that what we're asking from you is not to tell us what we should do as a payer, but to give us your best assessment of what the literature demonstrates. And then in the policy-making arena, we weight your discussions, as Ron said, based on the ability to collect the data, what the potential impact is on beneficiaries, so those are all weighted at the policy level and our preference is they not be weighed here. That whatever the bar is, whether it's high or low, that it's consistent across the technologies, and the only differences in technologies that I think the MCAC guidance has is between therapeutics and diagnostics, but within therapeutics there wasn't any distinction.

DR. GOODMAN: I also think we have to make a clear distinction between clinical decision-making and evidence evaluation. It can be completely reasonable to have a certain, to make a certain clinical decision in a setting where everybody would acknowledge the evidence is

yet inconclusive or imperfect but the physician has to make a decision. So I think we should try as best we can to not ignore the clinical setting but keep those two evaluations separate.

DR. DAVIS: Dr. Cooper.

DR. COOPER: In getting to the general subject of TMR, the real question, and I think it applies to all the subquestions is in fact, is TMR with or without CABG the emperor's new clothes? Is there anything whatsoever to suggest that it's other than a sham operation and are we just trying to throw a physiologic cloak over the emperor, or is there a rationale? I think Dr. Guyton and I have shared a certain skepticism which exists in the community because over the years there have been many operations proposed for the relief of subjective symptoms which did not have a physiologic rationale or an objective correlate to measure, and which initially seemed to produce tremendous benefit, but ultimately it did not stand the test of time. And literature is replete with that, and that's why I asked some of the questions earlier today. So to me that's the basic issue.

Dr. Guyton, I think, feels that having

been a skeptic like myself, he now perhaps sees some objective correlate which would help explain what it is, but I think it's useful to review. Some of the most famous sham operations were ligation of the internal mammary artery reported in the New England Journal in 1959, rigorously applied, all patients seriously affected by angina, usually to the point of disability, a true sham operation that we could no longer do a true randomized trial, taking to the operating room, an envelope drawn, all the patients had cuts upon them to relieve angina. The patients weren't even told that it was a randomized trial, that we are evaluating something to see if it works. And at six months, both the control and the noncontrol group had a 40 percent reduction in the amount of nitroglycerin, exercise improvement, and 60 percent of both groups had a greater than 40 percent improvement in angina. But we know -- and that's both the sham group who had the incisions and didn't.

Glomectamine for asthma and emphysema, thousands reported, initially out of Japan and then Overholt, again, a subjective symptom, and there was between a 60 and 70 percent six-month

improvement in both the sham group, all of them got cuts on the neck, and those who didn't have the carotid body removed had the sternal mastoid muscle biopsied. So it was a similar technical procedure.

And so for someone who knows the history of operations done to relief symptoms and much touted but without a physiologic rationale or an objective correlate, the question becomes, is TMR similar? There are not many operations that I can think of, if any, which don't produce either something you can objectively measure which explains why there is subjective benefit, or has a physiologic rationale. So the question to me, and I think to a lot of individuals is, are we just relieving angina by a sham effect?

And I was a little distressed as I began to look into this. I mean, it's not really randomized trial, it may be the best we can do, but half the patients knew they had nothing done, they had medical management, and half went to the operating room, had a general anesthetic, a thoracotomy, that is a major intervention and can carry with it a very significant sham effect. And if you look at the sham operations for both

subjective dyspnea and for angina, they all carry with them a 40 to 60 percent six-month significant benefit. So it seems to me that the question is, can we find an explanation for this.

And I think what puzzles my colleagues as I talk with them is, everyone recognizes there's this great benefit to reduce angina by any means, I don't care whether it's sham or not sham. It can have a very big effect on patients. They are no longer anxious, they can exercise more, they have a better quality of life, they are not as concerned about the symptom, be it breathlessness or chest pain, and that can have a long-term very beneficial effect. And I'm not poo-pooing something, I don't care how it does it, to make the patient better. The question really, is it the cheapest way of doing it, is it the most effective way of doing it. And so on the one hand I have real reservations about this and it seems to me to fall into the category of sham operations historically.

Now we see perhaps increasing evidence that there may be some objective corollary. One of the problems I think with Medicare, and I think you're to be greatly congratulated for this

process, I for one have pushed Medicare to not take ten years to make decisions. And that means if you're going to make decisions in favor of the patients who have no alternative, maybe you're going to make it some time on the basis of less than ironclad evidence, but then you have to be able to reevaluate it and decide, hey, it hasn't worked out. And so number one, I think this process is terrific, I think you have proved this procedure fairly early on and now you're reevaluating it.

I suspect it would be difficult to undo something that you have approved but I think the consensus I have among the individuals I have spoken with involved in the field, many of whom have been involved in the trials, many of whom have had a financial interest, is that they have an uneasiness because we can't find a mechanism, and if you don't have a mechanism, you don't have an explanation, you wonder whether it's a sham operation.

So in conclusion, the consequence of what Medicare decides is very important. My sense is that no one would want to see this thing totally stopped without the opportunity of further

evaluating it just in case there is something here that can benefit these patients, and yet, many of us are uneasy about the quality of the evidence and whether or not it should be widely disseminated. I think Medicare in the past has not had a good mechanism for evaluating new technologies and procedures under controlled circumstances, and I think maybe one of the things that is being developed is the opportunity to introduce new technologies, you don't have to ration it, but study it well.

And then I can only say if there is any mechanism by which Medicare can employ that mechanism for new technologies, allow it to be tried under controlled circumstances, rigorous scientific evaluation, and then after an interim period of time, decision-making. I would just strongly encourage it and I'm very impressed with the procedure. I'm just a guest panelist, I don't get to vote, but this is very transparent, in fact a little more transparent than I would like maybe; you know, when you ask for transparency you've got a problem, because I'm sort of intellectually streaking in front of some of my distinguished colleagues.

DR. DAVIS: Would anybody like to respond to that before we move into any other areas? Not the streaking part.

DR. COHEN: I actually had a question for Dr. Cooper which came up this morning that I never got to ask, which related to one of the arguments that this was more than a sham that had been put forward at least, had been the durability of the benefit on angina relief. And it seems like this morning you may have reviewed the literature more closely than I have and know something about the durability of some of these formerly practiced procedures and how well they stood up over time. Do you have any information about that?

DR. COOPER: The angina one only had six-month data. The glomectomies were out to 18 months with very significant benefit. And one of the things about the ligation of internal mammary artery which is so striking is the fact that exercise tolerance improved, some people's electrocardiogram improved. One patient who had been unable to work because of heart disease was almost immediately rehabilitated and was able to return to his former occupation; at one year he

reported a 75 percent improvement; he didn't have his internal mammary artery ligated. It's a small study. You know, you can always criticize them, but it does tell you that anything you do to make the patient feel better not only makes them feel better, but in the case of cardiac and lung disease, I personally believe, can have a significant beneficial impact in the long run on their health by providing an interim period of protection time during which time they're more willing to get themselves in shape.

DR. DAVIS: Yes, Dr. Aklog?

DR. AKLOG: Just a couple of things. I agree that there is a disagreement within the specialty as to what the status of this procedure is and among surgeons, if you poll surgeons there will be different opinions, and the fact that the penetration has not been earth shattering I think reflects that. However, I think the fact that the first STS consensus statement to be presented was with regard to this and really in an objective way, at least speaking for a portion of the specialty, has come to a conclusion that there is something more to this than just sham surgery. And I think a couple other comments.

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One is with regard to the mechanism of action. I'm not sure it's really fair to imply that there is no evidence. I mean, there is certainly no definitive evidence, and we continue to come up with the list of possible mechanisms as to why this may exist, but there is plenty of laboratory evidence that at least would suggest that the angiogenesis mechanism is in fact perhaps contributing to this with regard to, you know, in multiple different, measuring it in multiple different ways, whether it's vessel count, whether it's actual blood flow perfusion, so on and so forth. It's not definitive, it's not definitive in clinical patients, but there is, I think there is certainly some evidence even though it's not definitive.

And the fact that I don't, there are many other areas of therapy, whether it be surgical or medical, where we learn about new mechanisms, we learn about why things work after we know that they do work. I mean, we're learning that they do many many things that we never ever expected them to do, and that some of the benefits from certain drugs may be from things that we never really ever suspected.

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And I think this goes back a little bit to my original comment, that I'm still pretty puzzled that there is a sense that the level of evidence for this procedure is still sort of butting up against the edges of being sham surgery. There are very few things that we do in surgery that are, that reach a level of evidence that we can, you know -- I mean if you think of coronary bypass surgery, there is no randomized sham-controlled trial that shows that there's a benefit. We have a strong physiologic basis for it, there's obviously a large cumulative body of evidence that suggests that it is in fact viable. But I go back to my original statement that within surgery the vast majority of the things that we do are based on a fundamental understanding of the biology, as much evidence as we're able to gather, and a strong emphasis on the data with regard to safety, and I think there is no opportunity to compromise on that, and we're not hurting patients.

I guess I'll go back and say it again.

I am surprised that we are still discussing this procedure in the realm of possible sham operations when you have five-year durability. I don't know

of any sham procedure, pill, any other intervention whatsoever that has a placebo effect that can be demonstrated out to five years.

DR. COOPER: I agree, but in coronary bypass, you at least have objective improvement of vascularization and the logic that if you improve blood supply, it's not illogical to think that it might lead to functional and symptomatic improvement, and you have postulates, you have objective things that you can follow, and you can then make a leap of faith that yes, if I can revascularize, then I can explain why the patient's heart works better.

It's the absence of that mechanism here, I think, which causes the problem. But I would have to agree with you, if you truly believe that the data supports a five-year benefit, that's not a sham operation. The question is could an initial sham effect lasting for a year translate into some benefit in the long term by allowing a person to have a different life style and improve.

I think it's good for the public to hear what we do among ourselves all the time. I mean, what you're hearing today is no different than we do, only maybe a little more aggressively

behind closed doors, and I think that's in the patient's best interest to try to kind of flesh it out.

DR. DAVIS: Dr. Rose.

DR. ROSE: I just want to expand, I do think it's worth continuing to discuss the issue of whether or not this is a sham effect, for the reason additionally that this is not a cure for refractory angina. I mean, if you have this, it does not disappear and you're well forever. And the results, even if there is a positive benefit, and I think at best it's modest, if it's there at all. If you want to improve it, it's hard to imagine how you could improve it unless you understand the mechanism in the first place. It's not something that we're going to refine, you know, do we drill more holes or should it be a different laser. I don't even know how to begin to address those issues around how to improve it. So I have the sense that at best it's a moderate effect with a relative unimprovable if not totally unimprovable technology until there is a lot more to be known.

I think it's worth addressing also the issue, this is not of the level of evidence

equivalent to coronary artery bypass grafting. In particular, a number of randomized trials of coronary artery bypass grafting looked at objective end points like survival, which I think it's hard to argue placebo effect when you're counting heads as an end point. And it sorted out a good deal of the practice of coronary bypass surgery, which began with treating patients with single vessel disease, for example, with bypass surgery, and in whom now it's almost never done, and for whom there is no survival benefit in most subsets.

The only somewhat hard, and I wouldn't even call it hard, the only end point here that I think has to give you pause is the reduction in angina. And how objective and how important is the decrement of two classes of angina and how reliable is the measurement? The other thing is that we're dealing with a moving target, compared to the treatment of angina or coronary artery disease a few years ago with the use of statistics for what arguably could have an impact. I don't think medical therapy in the late or mid '90s for chronic angina is what it is now. You know, with LDLs below a hundred, I don't know what's going to

happen to chronic angina. I think all of us have the sense that unstable angina and anginal syndromes in general are a lot more controllable clinically than they used to be, and that still raises the sham operation question.

DR. DAVIS: Yes.

DR. BLACK: And again, I'm wrestling like I think many of us are with this issue of, I'll use the word placebo effect and how that fits through there. And I think what I tried to do as much as I could as I looked at the paper is to say what were the measures that were less subjective and more objective, and there seemed to be a few, but they really were a few compared to the assessment of angina. So I think one of the things I think we all would look forward to or if this panel reconvenes on this topic in a few years is what are some of the new studies? I mean, we saw some comments this morning that perhaps PET scanning is a better technique or a different way to look at sort of what was an intensity times time as a way to do that. Some of the MR images that were being done. I mean, I think we need to continually challenge, even if we say, you know, we really think there is

a reasonable evidence base, not to be comfortable and say that the case is closed. So I think that's a challenge to folks in the room who are involved with it.

The other thing in terms of durability and what sort of, again, one of the things that went through my mind is there was a lot of not blinding going on, there were a lot of people that knew exactly what had and hadn't happened to the patients and what impact did that have over three or five years of follow-up in terms of the activity of the surgeons or the cardiologists, or the patients. I mean, I don't know, but when you're talking about durability, what's our level of confidence that durability is from the procedure versus the patients were treated differently? And then you add on to that, and by the way, we treat coronary artery disease a lot differently than we did in '99, '97, when some of these studies were done.

So I mean, it's like always when you ask questions, you get some answers but it seems like we often raise more questions.

DR. DAVIS: Yes, Mr. Queenan.

MR. QUEENAN: If I could sort of

respond or amplify on that, and it really goes back to the comment I had about sort of how one evaluates what level of evidence is adequate or not. I think there was a comment made with respect to sort of CMS making decisions in favor of the patients, and I think it's important to take that point of view, not surprising I suppose given my role here, but I think that's a really important statement.

And in that regard I don't know that something, because we don't understand the mechanism of action perfectly today, and as you point out, that doesn't mean that we don't know a lot about the mechanism of action, but because that is still perhaps controversial, that shouldn't count against, as it were, evidence that suggests that there is a benefit to a patient and particularly in the context of where a decision has already been made to cover the procedure. It would seem to me that if you take the point of view of making a decision in favor of the patient, the evidence suggesting that there is a real question ought to be particularly compelling, and it sounds to me like in this case what we have heard today is the new evidence, if anything, is

making the case stronger, not weaker in favor of TMR or TMR plus CABG.

So I think, again, the point of view that one takes is particularly important and I can't imagine that any one of the patients who spoke to us this morning care a whole lot if they don't know the mechanism of action. What they care about is how they feel and that to me is a pretty important point.

DR. DAVIS: Dr. Goodman.

DR. GOODMAN: Just to address that point, I think the reason the mechanism is so important is because of this blinding issue. If we had perfectly blinded studies with this degree of evidence, you're absolutely right, that would outweigh the sort of higher bar that empirical studies have to jump over when you don't know how things work. How things work, even though the jargon of evidence-based medicine has sort of hijacked the word evidence for only empirical studies, I do think that knowledge of the biology and physiology when it's reliable brings us a long way. I think that that is highly relevant evidence and shouldn't be discarded.

I think, however, in the absence of

that, that the empirical results have to be that much higher, and in this case we have this particular issue of the placebo effect, and if that wasn't an issue I think this TMR alone certainly would have already surpassed any reasonable objections due to not knowing what the mechanism was. It's really that, that's the issue, it's in the presence of what we will call incompletely controlled assessments or reports, do we have information from the biology that helps convince us that this is really working or not, and that's why it's relevant. It's because in a sense the trials in some way, even unavoidably, are somewhat imperfect.

MR. QUEENAN: If I could just respond quickly to that, I don't disagree that in principle you would want to know more about mechanism and that that would be very helpful and that this could be a case where you would like to learn a lot more about that. But again, I think there is a point of view that because you don't understand the mechanism but in the face of studies that are telling us that there is a benefit to the patient, which I think we've heard from, that we ought to work in favor of that and

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the standard, as it were, would be to rebut that based on new evidence, as opposed to the other direction. We shouldn't say that we've got to know everything about the mechanism before we can agree that we have enough. I think it ought to be the other way around. If there's information that tells us that we have enough evidence to know there is a benefit but don't understand the mechanism, we ought to look more about the mechanism but it ought to be from the perspective of revisiting the issue to say that this doesn't work down the road as opposed to the other way around.

DR. AKLOG: I'm also concerned that we haven't really in any structured way looked at the data with regard to the mechanism. We haven't really reviewed the laboratory data, and I think there's sort of this general sense that we don't know what the mechanism is and that's certainly true to a level of certainty, but there are numerous studies as I've said before that do give us a sense of what's going on here, and that's going to be a significant factor in trying to balance against some of the issues with regard to design of trials that you mention, and I'm

concerned that we haven't reviewed that adequately to basically perform that balance.

DR. DAVIS: Dr. Cooper and then Mr. Lacey.

DR. COOPER: The point of mechanism I would agree is not the essential thing if you have objective measurements of improvement. If you had survival, if you had functional improvement, ejection fraction or something that you can work with and help develop new procedures, you know, whenever you're trying to evolve procedures you've got to have something to measure. And the concern, obviously that I and other people have is that if all you have is relief of angina, we all know that that can be the subject of a sham effect, as many others.

So even if you don't have the mechanism, I agree. We may not know how cigarettes kill people, but we damned well know that if you smoke two packs of cigarettes a day, we know it has an effect on incidence of heart attacks and strokes and life expectancy, et cetera. And it may take a while to work out the mechanism, but you have an objective measurement. And I think that's what I and others

are grappling with, something consistent and objective that is produced by the procedure other than subjective relief of pain, and then you may not know the mechanism but at least you can be more secure in the notion that the benefit, which is, after all, the patient doesn't come to you and say I have terrible vascularization in my heart. You know, I can't walk, I've got terrible chest pain, and if you can relieve that chest pain, that's fantastic.

But you want to believe, and surgeons don't want to do something unless they really think that they're benefitting the patient, so I agree that you may not know the mechanism, but it would be nice to have either a mechanism or a consistent objective benefit across the various studies, and I just don't know that it's there yet.

DR. AKLOG: You certainly need more objective data, and I think obviously the future studies with PET scan and so forth are necessary, but there is some objective evidence. I mean, the Frazier study did show a quite significant one-year improvement in perfusion in the lased patients and a decrement in perfusion in the

corresponding areas in the medical therapy area. So it's not definitive, but there is some. I'm not sure it's fair to say that there's no objective correlate to what we're seeing functionally.

MR. LACEY: I would just add to that, the one question I would have is wouldn't consistency of results on the angina across multiple studies have some weight with the panel in terms of the trend and so forth? So we didn't really have a chance to see the ECRI study for example, but presumably in the metaanalysis we'd be able to see at least where the consistency of that results, and that would be very relevant to seeing, even though parts of the angina assessment are subjective, parts of it are not, and I'm just wondering if that would be something that would be very relevant here.

And then what other kinds of mechanism of action study designs would you be suggesting besides the PET scan? You know, if we recognize that perhaps the ultimate study design is not possible in this particular population, what would be some of the confirmatory evidence that you would be looking for in a nonclinical type study?

DR. DAVIS: You know, I can respond to that first question. Some of this discussion gets at the issue of causal inference and in epidemiology we talk about criteria for causality to help us know when an association is causal or just coincidental, and consistency is one of the criteria, strength of the association is another, biological plausibility is another, which is an issue we have been kicking around. Specificity of the association is another. So this gets down to a balancing act typically where some of the criteria are met fully, some are met partially, and then you have to make a somewhat subjective determination at the end of the day. Dr. Cohen.

DR. COHEN: I just want to go back to the objective data issue and raise this concern that I think Dr. Cooper alluded to earlier, which is that I think in the absence of properly blinded studies I'm not sure I even believe the objective data, frankly, because we have seen that you can take patients, you can relieve their angina with whatever mechanism, then they can exercise more, they can do more and they can develop their own collaterals, and they can improve perfusion. And we have in fact in our own

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institution seen this with, again, going back to our experience with the Biosense DMR system, which was proven in a sham-controlled trial not to be any more effective than placebo, we saw plenty of these patients have improvement in MRI wall thickening, improvements in wall motion, improvements in SD depression on the EKG, simply by virtue of the fact that somehow we had enabled them to get beyond whatever was limiting them before. And maybe that's good, maybe that's a reasonable goal, maybe this is a good way to achieve that. You know, there just might be other ways to achieve the same sort of thing.

DR. AKLOG: Isn't that a little bit of a stretch? I mean, you're saying that a placebo effect gives you a window of opportunity where your angina is relieved so that you can exercise and so forth and ultimately develop collaterals.

DR. COHEN: I'm only saying that because of the data we have seen to the effect of, we did a sham-controlled trial, we saw exactly comparable angina relief among people who got nothing done and people who had the laser applied, and in a parallel population, not the same population, a parallel population of patients who

had had the laser done, we saw improvement in objective measure. I agree there is a slight --
DR. AKLOG: Was this anecdotal?
DR. COHEN: No, published data with reputable scientific journals with no control group of objective improvements in myocardial performance perfusion.
DR. DAVIS: Dr. Black.
DR. BLACK: I just wonder and would appreciate comments from folks on the panel about the mortality rates, particularly some of the early mortality rates with this procedure. I don't think any of the studies showed that there was any early mortality, that in any of the studies the TMR group, and I'm talking specifically about TMR here, but in any of the studies the TMR mortality was higher, but yet if you looked over the large studies it was 4 percent higher, 2 percent higher, 3 percent higher, and so I guess I begin to wonder about type II errors. And then you begin to look at the observational studies where the -- and again, you don't want to make decisions based on observational studies but I think observational studies may reflect what goes on in the real world and some of the

mortality rates for TMR are significantly higher. And again, how much does that need to play, come into our decision-making? In some ways this is almost some tradeoffs where, you know, your chances of dying if you get TMR might be slightly higher, but if you get through it, then you do better of, so you're almost trading some things short term for potential long term. I mean, did anybody besides myself have questions or concerns about what seemed to be across many of the studies a slightly higher 30-day mortality rate in the TMR patients?

DR. COHEN: The only thing that I was concerned, I looked at that and didn't see the same trend. I looked and I saw some studies that went one way and some went the other. Maybe I was looking more at the one-year data, not at the 30-day data, but sort of just in aggregate, so the one-year data looked to me to be balanced out. The concern that I was a little bit concerned about in regard to the mortality, we saw at least one piece of data this morning that suggested from the long-term follow-up, I think one of the Allen trials in TMR that there was actually a mortality benefit to TMR. And I just,

a question in my own mind looking at how those patients were ultimately managed, if a lot of that mortality benefit wasn't due to the fact that because these patients were having fewer symptoms, they didn't get crossed over and get other procedures that were risky for them, such as late bypass operations. I mean, clearly in the data in that paper, there were excessive procedures in the group that had gotten maximum medical therapy, including late TMR procedures by the way, as a potential mechanism for that mortality benefit. So again, I wasn't concerned about a lot of excess mortality, but I certainly wanted to raise this as a possible explanation for why there might be reduced mortality.

DR. AKLOG: That was true for the 30-day data. I don't think this was --

DR. COHEN: No, the five-year data.

DR. AKLOG: But the most dramatic difference was in the 30-day mortality.

DR. COHEN: I'm not talking about the TMR plus CABG, I'm talking about the isolated, the five-year follow-up on the isolated TMR study, because it was the one outlier where there seemed to be this mortality benefit.

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DR. DAVIS: Dr. Cooper.
DR. COOPER: I was just going to once again address, I don't know whether it's going to be in the purview to have additional trials or additional data, but again, I'm interested in the part of the panel as to looking at CABG plus TMR, which seems to be even fuzzier, how you feel about the design of the study where I think, but I'm not sure the patient actually knew that they got TMR, the decision was made before surgery, and would a better design and would you have been more comfortable if you told the surgeon, revascularize what you normally would do, and now flip a coin and decide whether you're going to add something. I'd just be interested from the people who really are cardiac surgeons here whether that's a feasible type study, would you be any more comfortable with that design than the design in which both maybe the patient and the surgeon knew in advance before going into the operating room that he was going to or not going to do TMR, or would that affect your determination?
DR. DAVIS: Dr. McNeil.
DR. MCNEIL: As I said earlier this morning, I would have been more comfortable with

this because determining the incremental benefit of TMR in this situation requires that the underlying procedure be the same in both arms of the trial, and I realize that the differences in the number of grafts was not significantly different, but that still doesn't make me feel totally convinced that the procedures were actually the same. So that would have made me feel a lot better had the trial been done that way.

DR. DAVIS: Would any of the STS representatives here like to comment on that, the possible design issue?

DR. HORVATH: Certainly I would be happy to comment on that. I think that we have tried for years to decide what would be the best way to design such a trial and the randomization points are not easy, and I would agree that the patients didn't necessarily get the same operation because they weren't the same patients. The diffusity of disease is not easy to control for and it's very hard to quantify and qualify before you enroll any patient in such a trial.

Now if you consider randomization by angiogram as was done in that trial, that is one

way to do it. But there are other ways that unfortunately I think, if you work out an algorithm, border on being impractical. Inspection in the operating room of the coronary artery, whether that's visual or after the artery is open and the diameter of the artery may be assessed, or after the diffuseness of disease in that artery, depending on how far a probe can be passed down the artery, or let's say that it's done where the artery is grafted and you then measure flow through that graft, and there is a threshold at which you cut off and say that that graft is unlikely to stay open and we should use TMR in that area. These are all questions that have been discussed, and from a randomization point of view, I think have proved very very difficult to conduct such a trial. The end points too, as well, I think are going to be difficult to achieve even with this complex randomization. But I would be very remiss on behalf of the Society of Thoracic Surgeons, myself and my patients not to address what has already been discussed, and I know that's not why I was asked to come up here. But in 1959 there were no perfusion scans that were used in this trial. The

few patients that Gray and Diamond report on did not have one-year, let alone five-year symptom relief. So, the objective evidence is there, it's been presented, it's been shown in five randomized controlled trials of sole therapy, as well as in two randomized controlled trials of CABG plus TMR. And if the suggestion that all of this is a sham is really what we're talking about, then it seems incongruous that the FDA as well as the Society of Thoracic Surgeons, which has put together a consensus statement on this procedure, would say that we want to promulgate a sham procedure on our patients. And I appreciate your opinions with regard to this, but the data argue completely in the opposite direction.

DR. GUYTON: If I may, let me comment specifically to your question about the design of the study, and I think there is a conflict in that when you're designing clinical trials you have to reach a compromise between what may occur after the trial is accomplished in clinical reality, versus what you can do in the animal laboratory where you can isolate variables and say this is what we're going to do in this group and we're only going to do this in that group, and then

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we're going to add just this little piece to these patients.
Because in fact, if I'm operating on a patient that has a large region of viable myocardium that I know is ischemic, or know by my PET scan preoperatively is ischemic, because that's what the surgeon had access to in his data bank, and he knows this patient has class IV angina, is going to the operating room, class III or IV angina going to the operating room, has a large area of viable myocardium that is ischemic, to ask that surgeon to abstain from making every attempt to revascularize that area is difficult, because the surgeon, the option is what operation is the patient going to get if they have TMR available or if they don't have TMR available. And if the TMR is not available, the surgeon is going to make extra efforts to bypass that area of the heart that is causing that patient's disabling injury. You can't ask the surgeon not to do that. And that's the conflict, the trials mimicked what was likely to happen in clinical reality where the surgeon has TMR available for this ischemic area or doesn't.
DR. AKLOG: If I could just expand on

that real quick, because I think he's on to something which I --

DR. MCNEIL: You could, but could I just follow up?

DR. AKLOG: Go ahead, sure.

DR. MCNEIL: I still don't quite get it because I would have thought that it would not be unreasonable in the design of a clinical trial to say to the surgeon, do your best shot at bypassing vessels into ischemic areas. Okay, done. And then say all right, now we have the TMR procedure here, we believe that's going to provide incremental benefit, particularly with regard to angina relief and maybe survival if we take the Allen data out five years. Go add some more clatter, add 50 more channels, or whatever. I don't understand the logistical difficulty there, and I know it was mentioned by Dr. Horvath as well as by you.

DR. GUYTON: Yes. I think when you are looking at a vessel on the heart and you're saying should I revascularize this vessel or not, you recognize that if you start working on a very difficult vessel, you may spend 25 minutes trying to revascularize this very difficult vessel and

end up potentially making it worse because you've worked with a vessel that you may not successfully revascularize, but you've disrupted the endotheliums, you've ended up making a long cut, you've extended the operation by 20 minutes. And if you have TMR available, you are likely to say my chance of successfully revascularizing this vessel is only 50 percent. Therefore, since it's a 50 percent chance of successfully revascularizing this vessel, I'm going to use TMR. If on the other hand TMR is not available to you in the patients that were not randomized to TMR or if TMR were not available in your institution, and you knew that this was the region causing this patient's disability, it is very hard not to make every effort to either revascularize that area or potentially to infarct it by trying to revascularize that area. I think it's very difficult to ask surgeons not to treat an area of the heart that they are pretty well persuaded is the cause of this patient's angina, and I think that's the difficulty.

DR. AKLOG: Why is that important, I guess is my question. Why is it important that we know what the incremental benefit if we go all the

way to complete the CABG and add a TMR, versus the strategy of, we have two tools, we have revascularization and TMR, the strategy of combined therapy versus CABG?

DR. COOPER: But I thought the whole point of what we're trying to do is assume that we don't know, assume it has no benefit, now let's show that it does. Your strategy is presuming that it has benefit and how can you prove that something has benefit if your assumption to start off with is that you're going to change your practice because you believe it has benefit. So that's the difference. You should approach this, it seems to me, particularly without a mechanism, is gosh, I don't see any reason why it should work, but maybe it does, so let's do a randomized trial, do the best we can, and then half the patients will get the additional treatment.

DR. ROSE: And the reason to do that, if the reason is to relieve their angina, the data don't show that at all. If the reason to do that is to make them more likely to survive the operation, I don't think the data show that either. I think what they do show is that something bad happened in the control group, not

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that something good was happening with TMR.
DR. GUYTON: If every ten minutes we're going to say without a mechanism, I would invite the panel to let Dr. Horvath spend 15 minutes talking about mechanism, because we weren't asked to address that and that repeatedly comes up, and there is expertise in this room about mechanism, and we are hearing that every five minutes, without a mechanism, and I think that's a misconception.
DR. MCNEIL: That wasn't my question, though, I wasn't going to the mechanistic viewpoint.
DR. GUYTON: I understand, but Dr. Cooper's response, again, said without a mechanism, and I'm having problems with that "without a mechanism" over and over and over again.
DR. MCNEIL: I understand that. But even if we took and just erased all those questions about mechanism just for a moment, delete, delete, delete, and talked about the design, I'm still not convinced, and I'm trying to keep as open a mind here as possible, that the way the Allen study has been designed is really

convincing me that the addition of TMR is on top of two comparably established patient groups, and if they are not comparable in whatever ways we deem appropriate, I'm totally putting aside the objectivity of the end point, which is a separate issue, but if we cannot say those are not comparable, then we cannot answer the question, what is the incremental benefit.

DR. AKLOG: Well, they're randomized so the patients are comparable, but a portion of the operation may not be comparable.

DR. GUYTON: Don't you agree, there's a tension between designing the trials so it mimics subsequent clinical practice and designing the trials so it mimics the animal laboratory where you controlled all the variables completely?

DR. MCNEIL: Well, I want to get rid of the animal laboratory in this case. I'm more interested in having the answer to a trial that -- I'm more interested in the trial that answers a very specific question and I don't have it. That's my concern.

DR. GUYTON: I don't think I can satisfactorily answer your question.

DR. DAVIS: I think Dr. Horvath wanted

to chime in and then we'll go to Dr. Cohen.
DR. HORVATH: I think the difficulty that we're all struggling with is that it's very difficult to randomize diffuse disease. You saw angiograms repeatedly today that on paper, those patients have the same coronary artery disease, but let's take the example of an occluded coronary artery which on angiogram we would have no idea what it looks like. It's not until we're in the operating room and evaluating it that we have at least an idea of its caliber and its quality. Unfortunately, even after the artery is opened, when investigating that artery, it may have little to no runoff, so you can't truly randomize the patients well because we cannot quantify or qualify diffuse disease.
DR. COOPER: Didn't you say that you did randomize before you went into the operating room?
DR. HORVATH: That's what was done in that trial, that was the design of that trial.
DR. COOPER: So that's the point that I'm getting too. Aren't you saying the same thing, that you can make a decision in the operating room better than you can make before the

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operating room, and make your decisions, do your surgery and then randomize? If I understood correctly, you told us earlier that the decision was made on the basis of the preoperative angiogram, which you have just said may not reveal what you really find in the operating room.

DR. HORVATH: That's correct.

DR. COHEN: My only statement was that I wanted to try to step back here for a second and clarify, I think echo what Dr. Rose said just a minute ago, I'm just trying to clarify what it is that we're arguing about or discussing here. I think the point is that the study design that Dr. McNeil is trying to advocate for would clearly try to establish the incremental benefit of TMR above and beyond standard of care CABG. The problem with the design as it is is it can't distinguish between benefit of the TMR and harm from an overly aggressive bypass operation, because that's the study design that's been set up.

DR. AKLOG: Why is that a problem? Why do we need to dissect that out? I understand from a purely scientific point of view, it would be nice to know if the patients got the same CABG and

we added the TMR in addition to that, but practically speaking, I don't think you can eliminate the fact that surgical decision-making is a continuous process in the operating room. So the fact that the availability of TMR might modify to some degree the extent of the revascularization I think is something that we have to acknowledge. I don't really understand why it's less rigorous to say that we have a combined modality versus a single modality, that the strategy of entering the operating room with the ability to do the best coronary vascularization that you can, but knowing full well that you have the ability to do TMR, why that's any sort of less rigorous within a normal clinical context.

DR. COHEN: I wouldn't say it's any less rigorous, it simply is defining, I mean the question is different, that's the only point I'm making. You're trying to ask a practical question, saying surgeons are going to do it this way if they don't have TMR and they're going to do it this other way if they have TMR, and let's compare those.

DR. AKLOG: But that's really all they have. I mean, you make your decisions based on a

somewhat artificial construct and then subsequently say okay, either it does or does not work, then you have to acknowledge that, and that's why surgical trials are difficult, there are intraoperative decisions that are always going to be made that have to be sort of an accepted part of reality.

DR. COHEN: All I was trying to do was to clarify what it is we're discussing. I wasn't trying to argue for one trial versus the other as more convincing or anything like that, simply to just make sure we're framing the question correctly and understanding what we're discussing.

DR. DAVIS: We'll go to Drs. Black, Goodman and Rose.

DR. BLACK: I'm okay.

DR. GOODMAN: Let me try to split the difference here and try to sort this out. I agree that the sort of pragmatic question doesn't always require that we know all the components of why something works, so I will agree that even if we didn't know exactly why the combination of TMR plus bypass works better, it would still be a value to demonstrate that. However, if the mechanism -- it is not true, I am not going to

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accept the practical reality that that's what surgeons would use if they knew that the mechanism for the TMR working was simply that they didn't bypass that third dangerous artery. If they knew that, what they would do is they wouldn't stretch as far.

In other words, let's say we did an RCT, let's take TMR off the table completely, just completely, and we randomized and let's just imagine we could construct the criteria and we probably couldn't, but we were able to randomize subjects to getting the Nth degree bypass versus the N minus 1th degree, that is they wouldn't bypass it, there would be criteria for a vessel that they wouldn't even attempt to bypass but sometimes they might try. And we found that the ones who had the Nth degree bypass, that is, they did everything they could, had a higher mortality rate. And therefore, that elucidated that any technology that you introduced into the operating room that made the surgeons a little less aggressive would produce a mortality benefit, even having a million dollar photon gun behind them as a possible adjunct. Just because they feel more secure because they had a safety net they could

use, even though we knew it didn't work. In the presence of that information, they would do a different -- they wouldn't use that other technology. So what we're talking about here, I mean, this relates to what Dr. Cooper was saying, what we're talking about here is what people do in the belief that this third technology works. And you're absolutely right, in the absence of that information, this is what they would do. But I do think that to say that's the pragmatic reality without saying we should still be actively investigating it, so that we should make sure that we're not doing the more dangerous surgical procedure is, it doesn't absolve us from going down that road. You might say in the interim this is what we should do, but you absolutely, I think, need to sort that out if there is a real question about the adjunctive effect of the expensive technology, perhaps not that dangerous.

DR. AKLOG: I think what you're asking is you're asking to randomize -- I mean, I don't, I just really think it's a fantasy that we can dissect surgeon behavior and randomize it like we can, you know, give two pills versus three pills.

I mean, you can't do that, it's not dissectable.
DR. GOODMAN: I still haven't heard why we can't do the study that -- I agree that in real life you can't, but I still haven't absolutely heard why we couldn't do the randomization or reveal the result of the randomization once the bypass part is done. I agree that that's not exactly how it occurred in real life, but with the information that trial would provide, that would affect how surgeons react in real life. So the way they would then proceed may be quite different, and if it was shown that TMR added, then they absolutely maybe would do the less aggressive procedure as well, but if it was showed that it added nothing, then that would change the whole understanding of what's producing the risk and benefit in the operating room, it seems.
DR. DAVIS: Dr. Rose.
DR. ROSE: I think that the study design can be done with pulling the card for the randomization when the bypasses are done, as opposed to doing it beforehand. It was an unanticipated result. I don't think the investigators doing this trial thought there was going to be a mortality difference going into

this, it was not the primary hypothesis of the trial, that mortality was going to be lower in the room having TMR. And the rationale even for doing TMR, as I understand, is still not that. So having made this observation to clarify it, to say is what happened here, did something good happen because of TMR or something bad happened in the control group because of the strategy of doing TMR is still an unanswered question. And if what happened is that something bad happened in the control group, you can't say that the reason for that is because, thank God, we now have TMR.

DR. AKLOG: Why would the control group do worse?

DR. ROSE: Because you changed the character of the operation knowing that you couldn't do TMR, so you stretched it, you did an extra endarterectomy.

DR. AKLOG: Compared to just standard --

DR. ROSE: Well, compared to historical controls, the mortality group in the control group is huge, 8 percent.

DR. AKLOG: Not risk-adjusted.

DR. ROSE: Well, risk adjustment, the

Parsonnet predicted mortality, as I understand, was 6, and the Parsonnet model grossly overestimates risk compared to the more modern models as well, so seven point whatever mortality is a very high mortality rate for patients with bypass surgery with ejection fractions over 30 percent.

DR. DAVIS: I'm going to allow Dr. Horvath to jump in here but I just want to say, explain the process which we're kind of doing by the seat of my pants. This is supposed to be time for the committee to discuss this amongst ourselves. However, I don't want anybody leaving this room when we're dealing with such a complex issue without feeling like they were treated fairly. So we will break protocol and invite our colleagues from this morning to chime in from time to time in our afternoon discussion.

And I also want to give you the opportunity to comment on mechanism, because that was brought up, it's been part of this discussion, and it was part of the evidence report from AHRQ, but in brevity, and I think the AHRQ report mentioned that a detailed discussion of possible mechanisms was beyond the scope of that report.

However, I think we got five or six pages worth of a summary. But if you feel, Dr. Horvath, that that summary did not fairly characterize the evidence on mechanism or that our discussion has not, please feel free to address that as well.

DR. HORVATH: Thank you very much, Dr. Davis, and I particularly appreciate the opportunity to interject in what was supposed to be a private family discussion here. I think that there are a number of issues that have been raised and I can understand from a trialist's point of view it just doesn't make intuitive sense that this randomized controlled trial cannot be done. And I think the approach that's been proffered, that being to graft as much as possible and then decide to just randomly add laser to what territory I'm not sure, but to try to show an incremental benefit as a result of that is going to show likely very little.

I think what you're asking from a trial design is the scientific aspect of what's the incremental benefit of this procedure is that you're going to have to under-revascularize, purposely under-revascularize patients with the bypass, and then add the TMR in those cases. And

what you cannot, in addition to the diffuse disease, what you cannot really randomize or adjust for in variation as one example is the collateral vessels. You can get areas of the heart that are fed remotely that are going to perhaps provide angina relief, perhaps provide survival benefit, et cetera, and that's something that is, I would argue, unknowable.

I think what all of this, and this gets to the mechanism, what for me personally has been revealing is that we understand a lot about the macrocirculation of the heart. We don't understand nearly as much about the microcirculation. And from a mechanistic point of view, TMR has been shown to improve perfusion, it has been shown to increase angiogenesis, and specifically with regard to laser use, that angiogenesis is significant, it's meaningful, it's not just hitting the heart with a track spike and getting a wound-healing response that is unlikely to give you a functional benefit.

In the laboratory where we have a validated animal model, and not just my lab but numerous ones around the country have investigated this and demonstrated the improvement in

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perfusion, the improvement in myocardial function, and as well without a decrement as far as injury is concerned, and with a dramatic improvement as far as angiogenesis is concerned in an isolated. So taking that data, and this is how it all started, we then moved to the clinical arena and worked on the patients as sole therapy, found the same results in general, patients obviously being more heterogeneous than we have with an animal model, and it was then that sole therapy where we knew we had a treatment that worked in isolation without anything else, that it didn't seem to be that great a leap to add it to a bypass operation. And this was discussed at the panel meeting when it got approval as sole therapy. One of the panel members pointed out that everyone there knew that we were going to use this in combination with bypass surgery and therefore, should the labeling be given in that regard. And appropriately the panel decided that no, none of the evidence that they had seen that day which showed the safety and efficacy of TMR was applicable to the combination use because it was all sole therapy data. They did, however, agree that that data plus all of the others that was

presented, including a lot of mechanistic data, indicated to them that they could label it as is as you have in front of you for areas or regions of the myocardium not amenable to revascularization.

That is how we got to some degree where we are and again, it gets back to if you want to talk trial design, I think that's an important thing to do, and I would be happy to discuss that, but I think even -- and I would also be happy to discuss at length the mechanistic evidence that we've seen. And to Dr. Rose's point, there are ways to improve on this procedure. We've added angiogenic growth factors in a matrix that has an adenovirus for FGF-2, and this has been presented at the STS meeting, as well as additional studies relating to the dose response of this procedure, indicating that there is a gradual improvement in perfusion and function depending on the dosage. So all of that evidence is there, but again, the intent today was to discuss the clinical benefit, and that's what we've done.

DR. DAVIS: Thank you. Are people ready to move on to the specific areas of discussion and voting? Why don't we do that? And

also, just to remind you, we're scheduled to adjourn at 4:30 and it's 2:10 on my watch. So, why don't we first begin by focusing in on TMR alone and have some discussion on that before we go to the questions.

DR. COHEN: Let me ask a couple questions about the questions. One of them, I was just sitting around here looking at question 2. One of the four end points we are supposed to judge is morbidity and then we have long-term mortality and short-term mortality, morbidity and quality of life. We had quite a bit of disagreement up here about what actually morbidity meant. My assumption was that morbidity meant intermediate health outcomes other than quality of life such as hospitalizations or nonfatal events, but some people thought maybe it meant angina, and I don't know which it actually means.

DR. DAVIS: Well, in my mind it included angina, but I don't know how CMS or other members of the committee might have interpreted it.

DR. COHEN: If everybody else thinks it includes angina, fine, I'll write angina right next to it.

DR. AKLOG: Is it angina plus?
DR. DAVIS: Everything besides mortality and quality of life.
DR. AKLOG: It's not morbidity of the procedure, I guess that's why we were a little bit confused, it doesn't reflect morbidity of the procedure, so it's really including angina.
DR. COHEN: And can we have clarification of the word validity, it means that it does what it says it does basically? I mean, validity is everywhere in here.
DR. DAVIS: We have somewhere a definition of this. Barbara, why don't you read it?
DR. MCNEIL: Validity in the context of a treatment difference refers to the extent to which that difference can be reasonably attributed to the treatment assigned.
DR. COHEN: Thank you. I should have read my homework.
DR. DAVIS: And I think there is also a definition in there about net health benefit, which speaks to the issue of weighing risks and benefits.
DR. COHEN: I'm sorry to be a nuisance

on this. Is placebo effect considered to be a bias or can placebo effect be a legitimate effect of a medical intervention, by which many medical interventions we know, I mean, many things we do have a substantial component of placebo effect in them. Is that, if you feel that much of an effect of treatment is due to placebo effect but it's real and the patients feel it, is that a bias? I assume that bias means more dealing with how you assess the end point or are the assessors blinded, other sorts of things, but if the patients feel it, even if it's due to a placebo effect, I would not consider that to be a bias. Does anybody around here --

DR. GOODMAN: Most RCTs are designed to eliminate the effect of a placebo effect, not assess the placebo effect.

DR. COHEN: Right, but RCTs are basically to, I thought, designed to eliminate confounding, and placebos are designed to eliminate placebo effects. Correct me if I'm wrong on that. The randomization is balancing the population to get rid of the confounding, gets rid of selection bias, and placebos get rid of the placebo effect. It's different.

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DR. DAVIS: Well, I don't know that it would be fair to say that they get rid of the placebo effect. They allow you to assess the degree of placebo effect so then you can see whether the intervention effect is above and beyond the placebo effect.

DR. COHEN: That's fine.

DR. DAVIS: You know, I guess if you determine that an intervention has the same effect as placebo, then the decision would be that the intervention is no more effective than placebo, and I imagine that CMS would probably, and most other payers would probably not be inclined to pay for something under those circumstances. I hesitate to say that because that starts getting us into the coverage determination, but --

DR. AKLOG: But you can acknowledge that there may be, a component of it may be placebo but that there is benefit above and beyond, that the absolute magnitude of the benefit of that therapy, a portion of that may be placebo, but when you compare it to a placebo group that there's an added benefit. That's probably stating the obvious.

DR. DAVIS: I mean ideally you want to

look at an outcome and say symptoms went down 20 percent on placebo but 40 percent on active drugs, and then you can determine the differential effect, but I don't know that we can do that here.

DR. COHEN: And I guess part of what I struggle with here is that I believe fundamentally there may be something to this, but there also may be a large component of placebo, yet I don't know how to achieve that degree of placebo without this treatment. Frankly, I -- you know, there is a sense of that, you know, because of the nature of the treatment, that it achieves a degree of placebo benefit which is unachievable by pills, by other mechanisms, by simply talking to the patient, and that may be incredibly beneficial to some of our patients. So I wrestle with that in trying to figure out how to answer these questions.

DR. DAVIS: And I agree that there's placebo effect in many cases, in most cases, maybe in all cases of some kind of intervention. I guess the question is whether it's just a portion of the overall effect or the whole effect.

MR. LACEY: Just a point of clarification, short term was 30 days, that was in

the cover letter, but what's the long-term survival defined as, is that one year or three to five?
DR. COHEN: Most of us I don't think would be very happy calling one-year outcomes long-term survival in these sorts of patients.
MR. LACEY: I'm sorry, but to clarify also for morbidity, if you put the angina in morbidity, what's in quality of life, then? I mean, if SAQ and so forth is considered morbidity measures, is it just the SF-36 where it was done, or is there some other kind of utility-based measure in terms of how they're ranking these? What's your sense there?
DR. GOODMAN: I think the ability to carry on activities of daily living, things that affect how you live your life, however that's measured, would validate it, or other kinds of measures.
MR. LACEY: Functional status and things like that.
DR. GOODMAN: Right. They may be profoundly affected, obviously, by the angina, but it's a measure of something somewhat different.
MR. LACEY: Right. I was just thinking

that summary scales include both functional and nonfunctional components and I wanted to kind of separate those out in terms of saying whether there's a strong real life impact in quality of life as opposed to a subjective symptoms-based functional work in morbidity, that's all.

DR. DAVIS: And some measures, it seems, might fall into a gray zone between quality of life and morbidity, like exercise tolerance, so where does that fall? I'm not sure whether that speaks to quality of life or morbidity or both.

DR. COHEN: It's hard for me to conceive of exercise tolerance as being a measure of a patient's quality of life. Quality of life is very intrinsically self-reported and to my way of thinking about it, exercise tolerance, I think, would be morbidity.

DR. DAVIS: Unless it's so limited that you can't climb the stairs or brush your teeth.

DR. COHEN: Right, but then they should also be reflected in some sort of quality of life category too, I would think. I mean, obviously we haven't bled out every single symptom here.

DR. DAVIS: Other discussion on TMR or the questions? Michelle needs to read some

instructions before we proceed.
MS. ATKINSON: For the record, the voting members present for today's meeting are Barbara McNeil, Edgar Black, Steve Goodman, David Cohen and Lashan Aklog.
At this time Dr. Davis will call for a motion and will ask the voting members to vote.
DR. DAVIS: And just to clarify, I guess, as chair I'm asked to vote only if there's a tie. However you define it, it's not going to happen, I'm sure. So once again, the way I'm going to do this is to pose the question question by question, starting with 1 and going through 4.A and 4.B, and we will do it by a show of hands, and I will do it I hope slowly enough so that people don't get lost and so that folks like Michelle can keep a tally. Let me also ask you to record your vote, perhaps on this piece of paper, because CMS has requested to have copies of that submitted to them for their official record.
I am being told that we need a motion to close the discussion and to proceed to voting for this item pertaining to TMR.
DR. MCNEIL: So move.
DR. DAVIS: So Barbara makes that

motion. Is there a second?
DR. AKLOG: I will second it.
DR. DAVIS: Is there any objection to adoption of the motion? Hearing none, the motion is approved.
So we will begin with question 1. For TMR alone, how well does the evidence address the effectiveness of TMR in the treatment of chronic refractory angina in study patients for whom other methods of revascularization are contraindicated? And so, I'm going to start reading the response choices beginning with one and when I get to the number that you have chosen, please raise your hand. One, which is limited. Two. And this would be restricted to those who have a vote. Three.
(Dr. McNeil, Dr. Black, Dr. Goodman and Dr. Cohen raised their hands.)
DR. DAVIS: Four.
(Dr. Aklog raised his hand.)
DR. DAVIS: And five. Thank you.
Moving on to 2.A, how confident are you in the validity of the scientific data for this outcome, ranging from one and two for no confidence, three and four for moderate

confidence, five for high confidence. Beginning with short-term mortality, how confident are you in the validity of the scientific data for the outcome of short-term mortality? Beginning with one, two, three?
(Dr. Black and Dr. Aklog raised their hands.)
DR. DAVIS: Four.
(Dr. McNeil, Dr. Goodman and Dr. Cohen raised their hands.)
DR. DAVIS: And five.
Proceeding to long-term survival, one, two?
(Dr. Goodman raised his hand.)
DR. DAVIS: Three.
(Dr. McNeil, Dr. Black, Dr. Cohen and Dr. Aklog raised their hands.)
DR. DAVIS: Four, and five.
Morbidity, one, two, three?
(Dr. Goodman and Dr. Cohen raised their hands.)
DR. DAVIS: Four.
(Dr. McNeil, Dr. Black and Dr. Aklog raised their hands.)
DR. DAVIS: And five.

Quality of life. One, two, three?
(Dr. McNeil, Dr. Black, Dr. Goodman and Dr. Cohen raised their hands.)
DR. DAVIS: Four.
(Dr. Aklog raised his hand.)
DR. DAVIS: Five.
Moving on to 2.B, how likely is it that TMR will improve this outcome compared to usual care, ranging from one and two for not likely, three and four reasonably likely, and five, very likely. One.
(Dr. McNeil, Dr. Black, Dr. Goodman and Dr. Cohen raised their hands.)
DR. DAVIS: Two.
(Dr. Aklog raised his hand.)
DR. DAVIS: Three, four, five. If we're going too fast, let me know.
Question 3, how confident are you that TMR will produce a -- oh, I forgot those three outcomes. Silly me, I'm racing ahead of myself here. Long-term survival. One.
(Dr. McNeil, Dr. Black, Dr. Goodman and Dr. Cohen raised their hands.)
DR. DAVIS: Two.
(Dr. Aklog raised his hand.)

DR. DAVIS: Three, four, five.
Morbidity. One, two, three?
(Dr. McNeil and Dr. Goodman raised their hands.)
DR. DAVIS: Four.
(Dr. Black and Dr. Cohen raised their hands.)
DR. DAVIS: Five.
(Dr. Aklog raised his hand.)
DR. DAVIS: Quality of life. One, two, three?
(Dr. McNeil, Dr. Black and Dr. Goodman raised their hands.)
DR. DAVIS: Four.
(Dr. Cohen and Dr. Aklog raised their hands.)
DR. DAVIS: Five.
I think we're now ready for question 3. How confident are you that TMR will produce a clinically important net health benefit in the treatment of chronic refractory angina in study patients for whom other methods of revascularization are contraindicated? Ranging from one for no confidence, up to three for moderate confidence, up to five for high

confidence. One? Two?
(Dr. McNeil raised her hand.)
DR. DAVIS: Three.
(Dr. Black and Dr. Goodman raised their hands.)
DR. DAVIS: Four.
(Dr. Cohen and Dr. Aklog raised their hands.)
DR. DAVIS: Five.
Question 4. Based on the literature presented, how likely is it that the results of TMR in the treatment of chronic medically refractory angina can be generalized to, A, the Medicare population, 65 five years and older? Choices ranging from one, not likely, up to three, reasonably likely, up to five, very likely. One? Two? Three? Four?
(Dr. McNeil and Dr. Black raised their hands.)
DR. DAVIS: Five?
(Dr. Goodman, Dr. Cohen and Dr. Aklog raised their hands.)
DR. DAVIS: And 4.B: Generalized to providers (facility/physicians) in community practice, with the same response choices.

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Beginning with one? Two?
(Dr. McNeil, Dr. Black and Dr. Goodman raised their hands.)
DR. DAVIS: Three.
(Dr. Cohen raised his hand.)
DR. DAVIS: Four.
(Dr. Aklog raised his hand.)
DR. DAVIS: And five. Thank you.
I think we're ready to move on to TMR and CABG. We can start out with discussion. Any additional discussion?
DR. COHEN: I had a question actually which maybe, I'm hoping Dr. Horvath can answer related to the late quality of life benefits, or the angina benefits in the Allen study. In the original Allen paper, which is the only one that I had, it said that the patients were blinded for one year. And I didn't, either through fault of my own or perhaps it wasn't given to me, have access to the prepublication version of the other accepted one. Were the patients unblinded after one year? So the blind was maintained even though the other one said they were blinded just for one year? Why?
DR. HORVATH: To see if that

short-term, if one-year is considered short-term result, was reproducible over the long term.
DR. COHEN: So what happened if the patient needed TMR later because they had more angina? Did the docs tell them, or even then they said we'll just do it and not tell you?
DR. HORVATH: That exact question I don't know, but there were very few patients that underwent that, I think there were maybe five to six, so even if it was unblinded, it's hard to believe that would have had a big impact on the results.
DR. COHEN: Thanks.
DR. DAVIS: I neglected during the TMR discussion and voting that we just concluded, I neglected to give you the opportunity to comment and explain why you voted the way you did, which is traditionally a part of these meetings. So if we could back up a moment and allow the voting members to make a comment if they'd like on why they voted the way the did above and beyond any comments that you may have made previously. So, Dr. Aklog?
DR. AKLOG: I think the record probably will reflect most of the comments I've made

already, but I think the level of evidence, the data for this procedure at least in the context of what's achievable with the surgical procedures, I think this is as well a study of the procedure as most anything we do in cardiac surgery except for coronary bypass surgery. And I think the level of evidence, the data on angina at five years I think is really quite compelling to me, I find it hard to accept that there is a placebo effect beyond a year or two. And the safety questions I think are well established, and I think these are patients as we've heard who have very dramatic, very impaired quality of life and who really are debilitated, and I think if we have a procedure that we can do safely with this level of evidence, I believe in it and I would do it, by the way.

DR. DAVIS: Dr. Cohen.

DR. COHEN: Mine simply reflect my earlier comments as well, which is that I'm still not particularly convinced that this is more than a placebo, but I think that it is a tremendously valuable placebo to our patients, which is again, I am convinced that it does improve quality of life and angina for the patients. I just don't know whether it's above and beyond what could have

been accomplished other ways, which is why I said that it certainly would improve outcomes relative to usual care but was a little more skeptical on some of the validity questions.

DR. DAVIS: Dr. Goodman.

DR. GOODMAN: I sympathize and appreciate Dr. Cohen's dilemma with the placebo. I think that this is one area in medicine that has never been dealt well with if we know that we have a therapy that works extremely well but through a placebo effect, do we offer the therapy. And generally the answer has been no, at least not therapies that are very expensive and might involve some morbidity. But it does give you a lot of insight into the power of the medical relationship and you can often search for other ways to achieve that. But in general, I think there's a consensus that we don't offer therapies that we actually think are a sham.

I guess I am, I think that there is a component here of placebo effect, but I also think that there is likely but, you know, there are gradings here and I basically gave it threes. I think that there is a reasonable possibility that there is a meaningful clinical benefit over and

above that placebo effect, so while I don't think that everything we're seeing is due to the intervention, I am convinced that there is enough of a plausible yet still developing understanding of the biology and that at least part of this and probably a clinically meaningful part is due to a real biologic effect, so that's why my vote was both positive but also somewhat intermediate. I think there is still more of this story to be told.

DR. DAVIS: Dr. Black.

DR. BLACK: My comments really echo those of other folks. I think what I wrestled with the most was the blinding and the placebo effect, and how do I weigh that with fairly consistent results, and I think what I tried to do was look at some of the more objective measures that were scattered throughout and give credence to those. I also think that hopefully the way the panel voted sends the message that this is not a closed case but there are significant opportunities to better understand the procedure, to develop some more objective measures of what happens to folks who get this, and to help to begin to understand some of the potential

tradeoffs between some short-term downsides with perhaps and hopefully some longer-term benefits.

DR. DAVIS: Dr. McNeil.

DR. MCNEIL: No other comments.

DR. DAVIS: Thanks. I was just asking Dr. Phurrough something that might be on your minds, and that is, can we get a compilation of the votes sometime soon since most of you have been discussing and voting and not recording, and he assures me that that will be made public as soon as CMS can pull it together.

So let's proceed to TMR and CABG, or to go back to TMR plus CABG and see if there are any additional comments or questions that people would like to make before we go through the voting process.

DR. GOODMAN: I just had one comment, I think it's for Dr. Guyton, or whoever mentioned the fact that this was stopped. That's reflected nowhere in the published paper or in the ensuing discussion. Is that mentioned anywhere in the literature or was it revealed here for the first time, or is it widely known in the thoracic surgery community? Not that this is absolutely critical to any judgment, but it goes to the

strength of the case that the mortality differential might have been caught on a random high.
DR. GUYTON: I checked into this a little bit at lunch, and apparently the goal was 325, I think I misstated that earlier, and when they reached 283, it was stopped and there was a press release, but it's not mentioned in the article, but there was a press release.
DR. GOODMAN: So it was stopped by the DSMB specifically because of that, the short-term mortality difference?
DR. GUYTON: Yes. When it reached the P equals .02 level it was stopped, and the target was 325 patients and they reached 283 patients, so it was close to the end of the study.
DR. GOODMAN: Thank you.
DR. DAVIS: Dr. Cohen.
DR. COHEN: Along the same lines, it's not clear from the paper either what the actual primary end point of the study was when it was designed or why it was designed for 325. I sincerely doubt that it was designed as a mortality trial with that as the primary end point, perhaps that was the case, but if so, it

would seem to be woefully underpowered. So, can you help me understand what the main end point was when it was designed?

DR. HORVATH: I was not involved in the design of that trial but yes, mortality was an end point from the beginning. And I think as has been alluded to, the mortality in the CABG-only population does seem to be higher, and in fact the discussion section of that paper, I commented on that when it was presented. And I think people understood that these were difficult patients with diffuse disease, we could not throw them into the category of our standard CABG-only patient. And I think you will see in looking through the paper that they were equally aggressive on both sides with the patients undergoing endarterectomies in addition to CABG, et cetera. So mortality was an end point, but I think it was, at that time nobody knew if there was going to be a benefit or not, so the hypothesis was that mortality would be one thing that they would look at but they were also looking at symptom relief, but they knew at that time that the symptom relief would probably take years to really start to diverge between the two treatments.

DR. COHEN: I only raise the question because again, the sample size, I mean, you could not in a million years expect to have a 75 percent reduction in mortality as you did in this study, no one would have guessed that. No one would have designed a study to detect that. So presumably the study was designed to look at symptoms, I'm just reading into it, in which case, again -- and then I'm struck by the fact that the five-year follow-up was done only in a subset, as though it were not planned. So it strikes at a lot of inconsistencies and I don't, you know, obviously Dr. Allen would be much better to have him here to answer these questions. I just raise them for the group listening that they bother me.

DR. AKLOG: There was one point that Dr. Goodman mentioned earlier that appeared to be a paradox with regard to the fact that the mortality differences showed up early and the separation in the angina curve seemed to occur late. I would argue that that's not necessarily a paradox in that most of these patients got vein grafts and the linear attrition rate of vein graft occlusions will happen from the start of the operation on through. And I suspect that you

could argue that the reemergence of the angina in the CABG-alone group could have been secondary to vein grafts, cumulative incidence of occluded vein grafts, while the mortality in these incompletely revascularized patients you would assume would happen from more typical acute events, either MI or sudden death in that interval.

DR. GOODMAN: Let me just ask you, though, about the mortality. I'll accept the morbidity explanation, just to take it off the table, and you might be exactly right. But why would you get -- I actually think there's no mortality difference at all, I think it's totally spurious. But if we were going to accept this at face value, why would you get more of a mortality disadvantage, or advantage of TMR in this situation where it's adjunctive to CABG than you would in a TMR-alone setting where you don't see any short-term mortality differential?

DR. AKLOG: I think the mortality benefit I think is a lot harder to really get your hand around, although again, I think the only real way to explain this to some degree is we know that incomplete revascularization with CABG alone does have an increased incidence of short and

medium-term mortality relative to those who get complete revascularization, and perhaps the addition of the TMR does narrow that gap somewhat. But I agree with you, I don't think the mortality data is impenetrable, it certainly has some weaknesses.

But I don't think, if I might, the bigger point was really, I don't think the late onset of a divergence in angina class is really that much of a paradox.

DR. GOODMAN: I can accept that.

DR. DAVIS: Dr. Black.

DR. BLACK: Just some comments and what's sort of floating around in my mind, whether folks can help me or whether there is some additional things to talk about. I mean, my concern is that there are a good number of studies that we've just talked a lot about with TMR. I'm not convinced that you can generalize from the TMR studies to TMR plus CABG. And so as I'm thinking about this grid I'm saying, I think we really have one adequately powered study that we're looking at, that this is a significant problem, that one study actually was stopped because of results that many folks did not anticipate and that many folks

are still having a difficult time explaining or understanding. And so I mean, I think this is a very important question, an important issue. If we can understand, again, if some of this mortality difference could be replicated, I think this is a very powerful message. But I'm concerned on the basis of one study just saying that we have the answer. And it's interesting, but I would almost in some ways say this is to a certain extent hypothesis-generated or maybe the first step of hypothesis proving rather than the end of the story.

DR. DAVIS: Dr. McNeil.

DR. MCNEIL: I may be, in fact I think I am repeating what David Cohen said a few minutes ago, but I just want to say it again, if I am repeating it, David. If the Allen study was powered for something, we agree it couldn't have been powered for mortality. If it was powered for angina or symptom relief at one year, it failed that primary end point. If it was powered for angina or symptom relief at five years, then it met that end point, but it did that with 10 percent or so of the hospitals, or X percent of the patients from Y hospitals, I can't remember

what the numbers were, declining to participate in the long-term study. That doesn't make any sense to me, that if the five-year angina measure was the primary end point, how hospitals would pull out. That would mean they would pull out of the primary end point of the study that they had committed to in a fairly dramatic way, because this is actually a big deal. So I think you probably said all those things, David, but it's just not making sense.

DR. GUYTON: My comment on the hospital issue is that many of these hospitals were not academic institutions. The hospital in Atlanta that participated was St. Joseph's Hospital, which at that time really didn't have a robust research structure. And many community hospitals have difficulty holding together their research team, their clinical nurses over a five-year period. And I believe that among the people who enrolled patients, some of those hospitals, and St. Joseph's is one that didn't follow through on their five-year commitment, the hospitals simply couldn't carry that momentum forward for a five-year period, they just weren't able to do it. It's a different set of institutions than the ones

that we're accustomed to dealing with, but it was an institution dropout rather than a patient dropout.

DR. MCNEIL: But it was your assumption that the primary end point of the study was the five-year angina?

DR. GUYTON: I have no more knowledge than the panel, I apologize.

DR. DAVIS: There were several people who I think wanted to address some of the questions. I think Dr. Horvath.

DR. HORVATH: To answer Dr. Goodman, you talked about why was not the same survival benefits seen short term for the sole therapy TMR. I think that's reasonably well answered by the fact that the medical management patients did not undergo an intervention during that period of time and therefore, not having general anesthesia and an operation, did not have the same mortality in that early period. But as you saw, the lines crossed at one year and so that mortality difference early was compensated for later.

DR. COHEN: Can I ask another question of Dr. Horvath?

DR. DAVIS: Yes.

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DR. COHEN: As one of the people who was more than a little skeptical when the results were published, as evidenced by your discussion in the comments, I mean, two simple questions. Do you think the mortality reduction is real and what do you think accounts for it if it is real, what biologic mechanism? You know, we can't posit angiogenesis or denervation or placebo effect as an explanation for this.

DR. HORVATH: The data's the data, there was a difference, and the difference was very significant. I think that having now dealt with these patients and particularly looking at the long-term follow-up or the update from the STS database, I think what was unappreciated at that time was that these are a completely different subset of patients. And across the board, I would be honest, I was quite impressed with the fact that if you mark down every risk factor that we have going into an operation, the people that underwent TMR plus CABG had higher risk. And so to use what we know for CABG alone, historical controls to try to understand that mortality difference that was shown in that trial, I don't think is really fair. I think it's really a

completely different patient population.
DR. COHEN: Do you have even the foggiest idea of what might be saving their lives?
DR. HORVATH: I think that their hearts were revascularized better and that the risk, that mortality benefit that you saw, the mortality benefit for the TMR plus CABG patients I would say is expected, but the increased mortality for the CABG-alone patients is what appears surprising. And in that case taking those type of patients to the operating room and doing what we assumed was a safer procedure in a very difficult patient population turned out not to be the case. And one of the discussion points that I have had with Dr. Allen when it was presented and since then, is that you could almost argue that those patients should have had TMR as sole therapy, that maybe they were too risky to undergo a CABG operation. But nevertheless, I think that's the essence of the difference that we see.
DR. DAVIS: Yeah, Dr. Goodman.
DR. GOODMAN: I just want to make a few comments about the numbers there. First, the total number of outcomes I think is only 14, I think it's split 12 to 2 or something like that,

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so we're talking about a very small number here that broke a certain way. And while .02 sounds like it's fairly significant, if you're talking about that degree of evidence in the face of a difference that's both implausibly large and surprising, even today, it actually doesn't raise the problem, even if you're going to do a formal calculation and say what's the probability this is true based on that degree of evidence. It's not a 50 to 1 type of strength of evidence that you might think from a P of .02, and it would raise your probability to maybe something like 60 percent or 70 percent if you started out saying that this only had about a 10 or 15 percent chance of being true. So this is by no means a home run, particularly given the very small number of events, the continued lack of -- I would say that even though I acknowledge there's a high probability of a mechanism for the TMR alone in the long-term, I still think the proposed mechanism for the short-term mortality are very very speculative even years later. So that's why I said that I think I would be very surprised, I can only be convinced by data, but I would be very surprised if this in future trials turned out to

be real. It is not such convincing evidence that couldn't be overturned. In fact, this was sort of a classic spurious result, I think, given all those factors, but that's just the way I view it. If we had come to a better understanding over the subsequent years of exactly how this could have occurred, if we had larger numbers, then I wouldn't feel that way, but I felt that way when I first saw this and I feel I'm even more convinced of it now.

DR. DAVIS: Further comments or questions?

DR. AKLOG: I have a question about the first question. It's worded identical to the sole therapy TMR, i.e., refractory angina for patients in whom other methods of revascularization are contraindicated. It seems to me by definition if it's CABG-TMR, they're getting a coronary revascularization as well. Do we agree that that's worded accurately, is that truly the question that we're asking?

DR. COHEN: Yeah. I mean, the question should be something like how well does the evidence address the effect of TMR plus CABG as compared with CABG alone in patients with chronic

coronary artery disease, something simple like that, again, is what the evidence addresses and probably the clinical question at hand, if we're allowed to change it.

DR. PHURROUGH: The expectation would be that the other methods was CABG alone.

DR. COHEN: But they are not contraindicated because --

DR. GUYTON: The FDA approval indicated the region of myocardium for which other methods were contraindicated, so these patients had a region of myocardium for which other methods were indicated, so I think that simplifies it because that parallels the FDA approval for the device. If you change patients to a region of myocardium, then I think that would solve the dilemma.

DR. MCNEIL: No, it wouldn't, because we're talking about a patient level analysis, not an area level analysis.

DR. COHEN: Can we put the question more along the lines that I asked? I think that is the question that most of us would feel more comfortable answering.

DR. AKLOG: But the problem is you're not identifying a subset of patients with coronary

disease in whom, you're not really including what the target population is here if you say patients with chronic coronary disease.

DR. COHEN: Coronary disease with a territory that is poorly suited for alternative, you know, standard revascularization, or something. I mean, I'm working out loud here, but am I getting close?

DR. MCNEIL: David, suppose you said how well did the evidence address the effectiveness of TMR plus CABG compared to CABG alone in the treatment of chronic refractory angina, what's wrong with that?

DR. COHEN: Because that gets to Lishan's issue that it doesn't talk about the population, which is patients with a territory not subject to conventional revascularization.

DR. GOODMAN: In patients for whom TMR might be regarded as appropriate therapy. I mean, if you're considering TMR, presumably that's the group. It's hard to rewrite the question, but I think you're right, I think the implied comparison is here, and we can somehow reflect it in the notes so that CMS knows what we mean is clearly the kind of comparison that was done in the Allen

trial.
DR. AKLOG: Or patients like those in the Allen trial.
SPEAKER: Patients in whom complete revascularization is not achievable through conventional coronary bypass grafting, something along those lines, because that's obviously the group.
DR. COHEN: I don't have any problem with that.
DR. DAVIS: Did you get that down?
DR. COHEN: How well does the evidence address the effectiveness of TMR plus CABG in the treatment of coronary artery disease where complete revascularization cannot be obtained by common means.
DR. AKLOG: I think that leaves it broad enough.
DR. DAVIS: Give that to us slowly. Did you mean to change chronic refractory angina to coronary artery disease?
DR. COHEN: I did.
DR. AKLOG: I think that reflects the fact that not all patients undergoing CABG surgery have chronic refractory angina. There's a broader

indication, list of indications for patients undergoing coronary bypass surgery.
DR. PHURROUGH: But they should be at least class III or IV.
DR. COHEN: That's probably true based on the FDA.
DR. COHEN: All right, so we have to keep chronic refractory angina.
DR. DAVIS: Okay. So continue on then and tell us where the wording would change.
DR. COHEN: I need a piece of paper. How well does the evidence address the effectiveness of TMR plus CABG in the treatment of chronic refractory angina in study patients for whom complete revascularization cannot be obtained by conventional means, i.e., CABG or PCI?
DR. MCNEIL: Can that be read back?
DR. DAVIS: Yeah. What was the last part of it after conventional means?
DR. COHEN: CABG or PCI.
DR. DAVIS: Okay. So what I have is, how well does the evidence address the effectiveness of TMR plus CABG in the treatment of chronic refractory angina in study patients for whom complete revascularization cannot be obtained

by conventional means, i.e., CABG or PCI?
DR. COHEN: Good.
DR. DAVIS: Are people comfortable with that?
DR. BLACK: And I assume then, that it will be the same in question 3, it will have the same wording?
DR. DAVIS: This probably comes up more often than not in MCAC meetings where we're wrestling with the wording at the meeting on the fly, despite all of our efforts to get the wording perfect before the meeting begins. Part of the problem is that these questions are announced publicly ahead of the meeting and speakers are asked to comment, speak to the questions as formulated before the meeting, but we deal with them as best we can.
DR. PHURROUGH: My preference is that the question not change, but that we, you as the panel define what you understand the question to mean, so that the question stays as it is, but for whom other methods of revascularization are contraindicated is meant to be, revascularization cannot be obtained through conventional means.
DR. COHEN: That's fine. I think we're

all just trying to make sure that we are conceptually answering the same question.

DR. BLACK: And I do think the discussion reflected the issues we have been talking about, so I don't think there are any concerns about potentially having one set of questions out there and answering something else. I think the discussion focused on what we're talking about.

DR. DAVIS: Further discussion or questions?

DR. AKLOG: Can I ask another question about 2.B? Actually, I meant to ask this before. When you say how likely is it that it will improve this outcome, is that a reflection of the magnitude in sort of an individual patient, or how likely is it relative to some control group?

DR. COHEN: I think it's an average.

DR. AKLOG: So it's not the magnitude of the effect. I mean, there could be a modest effect in a significant proportion of patients and that would qualify.

DR. DAVIS: I agree with that. I think the size of the effect is taken into account in question 3 where you talk about net health

benefit, because there the magnitude of the benefit will be weighed against the magnitude of the risk, as well as the likelihood of both. Further comments or questions? Okay. Are people ready to vote? Nobody needs a few moments to formulate their votes? If not, we will proceed then.

TMR plus CABG, question 1. You have the original wording, I'll read the revised wording that reflects how people are understanding the question. How well does the evidence address the effectiveness of TMR plus CABG in the treatment of chronic refractory angina in study patients for whom complete revascularization cannot be obtained by conventional means, i.e., CABG or PCI? So again, we'll go from one being limited to five being complete, starting with one.

(Dr. McNeil and Dr. Black raised their hands.)

DR. DAVIS: Two.

(Dr. Cohen raised his hand.)

DR. DAVIS: Three.

(Dr. Goodman and Dr. Aklog raised their hands.)

DR. DAVIS: Four. Five. Okay.

Moving on to question 2, how confident are you in the validity of the scientific data for this outcome, and you see the response choices beginning with short-term mortality. One? Two?
(Dr. McNeil, Dr. Black and Dr. Aklog raised their hands.)
DR. DAVIS: Three.
(Dr. Cohen and Dr. Goodman raised their hands.)
DR. DAVIS: Four. Five.
Moving to long-term survival, confidence in the validity of the scientific data for this outcome, long-term survival. One.
(Dr. Black raised his hand.)
DR. DAVIS: Two.
(Dr. Goodman and Dr. Aklog raised their hands.)
DR. DAVIS: Three.
(Dr. McNeil and Dr. Cohen raised their hands.)
DR. DAVIS: Four. Five.
Morbidity, one.
(Dr. Black raised his hand.)
DR. DAVIS: Two. Three.
(Dr. McNeil, Dr. Goodman and Dr. Cohen

raised their hands.)
DR. DAVIS: Four.
(Dr. Aklog raised his hand.)
DR. DAVIS: And five.
Quality of life. One. Two.
(Dr. Black and Dr. Goodman raised their hands.)
DR. DAVIS: Three.
(Dr. McNeil and Dr. Cohen raised their hands.)
DR. DAVIS: Four.
(Dr. Aklog raised his hand.)
DR. DAVIS: And five.
Question 2.B, how likely is it that TMR plus CABG will improve this outcome compared to usual care, going from not likely as one or two to very likely, five.
Starting with short-term mortality.
One. Two.
(Dr. McNeil, Dr. Goodman, Dr. Cohen and Dr. Aklog raised their hands.)
DR. DAVIS: Three.
(Dr. Black raised his hand.)
DR. DAVIS: Four. Five.
(Discussion off the record.)

DR. DAVIS: Let's do that again. This is for short-term mortality. One. Two.
(Dr. McNeil, Dr. Goodman, Dr. Cohen and Dr. Aklog raised their hands.)
DR. DAVIS: Three. Four.
(Dr. Black raised his hand.)
DR. DAVIS: And five.
Moving on to long-term survival, one.
(Dr. McNeil, Dr. Black and Dr. Cohen raised their hands.)
DR. DAVIS: Two.
(Dr. Goodman raised his hand.)
DR. DAVIS: Three.
(Dr. Aklog raised his hand.)
DR. DAVIS: Four, and five.
Morbidity. One. Two.
(Dr. McNeil, Dr. Cohen, Dr. Goodman and Dr. Black raised their hands.)
DR. DAVIS: Three.
(Dr. Aklog raised his hand.)
DR. DAVIS: Four. Five.
And quality of life. One.
(Dr. Black raised his hand.)
DR. DAVIS: Two.
(Dr. McNeil, Dr. Goodman and Dr. Cohen

raised their hands.)
DR. DAVIS: Three.
(Dr. Aklog raised his hand.)
DR. DAVIS: Four. Five.
Question 3, how confident are you that TMR plus CABG will produce a clinically important net health benefit in the treatment of chronic refractory angina in study patients, and are we using the same wording we did in number one?
Okay. In study patients for whom complete revascularization cannot be obtained by conventional means, i.e., CABG or PCI? Ranging from one equaling no confidence to three equaling moderate confidence, to five equaling high confidence. One.
(Dr. Black raised his hand.)
DR. DAVIS: Two.
(Dr. McNeil, Dr. Goodman and Dr. Cohen raised their hands.)
DR. DAVIS: Three. Four.
(Dr. Aklog raised his hand.)
DR. DAVIS: Five. Should we do some power calculation on this voting strength of five?
(Laughter.)
DR. DAVIS: Four, based on the

literature presented, how likely is it that the results of TMR plus CABG in the treatment of chronic medically refractory angina can be generalized to the medication population, those aged 65 and older, ranging from one for not likely to five, very likely. One. Two. Three.
(Dr. McNeil, Dr, Black and Dr. Cohen raised their hands.)
DR. DAVIS: Four.
(Dr. Goodman and Dr. Aklog raised their hands.)
DR. DAVIS: And five.
And question 4.B, can be generalized to providers (facilities/physicians) in community practice. One. Two.
(Dr. McNeil, Dr. Black and Dr. Goodman raised their hands.)
DR. DAVIS: Three.
(Dr. Cohen raised his hand.)
DR. DAVIS: Four. Five.
(Dr. Aklog raised his hand.)
DR. DAVIS: Thank you. Now let's go around the table again and allow people to offer any comments about why they voted the way they did. Dr. Aklog.

DR. AKLOG: I think in terms of summarizing my views on this, I think clearly we had all agreed that the volume of evidence, the level of the quality of the evidence is lower, but the way I synthesized this I have to incorporate in some way my feelings of the data on sole therapy TMR and acknowledge that this is, that there is an extrapolation going on here, if it works, if there is a mechanism, if it seems to improve angina in the most severe patients, and that is an adjunct to CABG, that we should see a similar mechanism and similar benefits. So I acknowledge that a large amount of my thoughts on this include an extrapolation of the results from the sole therapy.

In terms of just interest, the last question I think, I'm curious on the role of the community providers. I mean, TMR is a very straightforward simple procedure, it's not a high skill procedure that requires a high degree of expertise and certainly as an adjunct to CABG, I don't see any reason why the data is valid at large centers who do a lot of this that is not going to be valid in the community setting as well as an adjunct to CABG. I distinguish that from

sole therapy, where the medical treatment of these, the perioperative treatment of these patients was very tenuous, and the ischemic burden is much more difficult and there may be potentially some differential there, but as an adjunct to CABG I don't see that.

And I clearly made a distinction between, again, benefits with regard to mortality short term or long term, which I think are obviously more difficult to prove and there's a lot of, there certainly are questions that the panel brought up that I think are valid as to that data, and distinguish that from the functional and angina data, which I think is a little bit more compelling.

DR. DAVIS: Dr. Cohen.

DR. COHEN: I think my main concern is that this study just seems like one that's too small with a surprising result and I think the level of confidence is just not there. And I really wish that this study that Dr. Allen alluded to in his paper about the follow-up one to really prove this had been done, because I would have a lot more confidence at that point.

DR. DAVIS: Dr. Goodman.

DR. GOODMAN: I'll just second that. I think it's an interesting first trial that has a lot of the problems that sometimes first trials have, and it cries out for another trial, and I will wait with anticipation, hopefully it will be within my lifetime, for that trial to appear.

DR. BLACK: I think I've already made my points.

DR. MCNEIL: I just didn't know what was doing what.

DR. DAVIS: I think for this third set of votes when we get to it, we'll go in the reverse direction, just to warn you all. We will do comments first and then questions. We could start in the middle; if I had been thinking ahead of time, we would have gone clockwise, counter-clockwise, and then starting in the middle for the third one, but we'll save that for the next MCAC meeting.

I think we're on the last lap actually, reading body language, based on no evidence. Comments or questions on PMR, which in my specialty, means preventive medicine residency, but we won't discuss that today.

DR. BLACK: At the risk of prolonging

things, since I was the one that wanted a break, I think again, it would be interesting if folks had comments. I think we've said that we think there is a reasonable level of evidence for TMR at this point, at least there is some benefit from TMR. Now that we're there, should there be some type, as we're thinking about PMR, should part of PMR coming along, should we be expecting some type of comparative trial? I don't know, I just throw it out for an answer. As a new person on this panel, does the lack of FDA approval, does it or should it have any impact on our decision-making here today?

DR. DAVIS: Dr. Phurrough, do you want to comment on that?

DR. PHURROUGH: If I could quit choking, yes. There are lots of questions as to why we were addressing PMR with this particular discussion in light of it not being FDA-approved, and the answer specific to your question is we would like you to address what the evidence level is at the present time, and not why or why hasn't the FDA made its particular decision. Because this is an information-gathering session for us, we've had discussions with the PMR folks, had the

impression that a number in the field think this is a promising technology, and wanted to see what the base level of information is, and as we have done for the other two, sort of get some advice as to what needs to happen next, what kinds of trials, are the trials out there now adequate, what does need to occur next if the evidence base isn't sufficient.

DR. DAVIS: Dr. Cooper.

DR. COOPER: Would it be possible to take advantage of Dr. Horvath, because I'd be interested in his comment on PMR. Do you have any reason to think that it would or would not produce the same benefit as TMR?

DR. HORVATH: Well, thank you for the opportunity to comment on that. I think that as opposed to TMR which has data, a significant amount of data, both symptom and objective data, we have only seen a little bit of that same type of data for PMR. Is there promise there? I certainly see that that's the case, but I think it gets back to, if you'll permit me a little bit of the mechanism of action, and it's not at all surprising to me that even in the most promising PMR trials, the angina relief was never

to the level of angina relief that we saw with TMR, regardless of what you think the exact mechanism is. A two or three-millimeter divot, perhaps four or five millimeters, on the subendocardial layer with a device that may or may not be able to be easily navigable inside the ventricle is not going to give you the same result as a full thickness channel where the surgeon has the opportunity to view the whole ventricle, and I would argue more precisely place those channels. So, it may be an entire spectrum of treatment for this particular disease, but I would honestly think that more data would be needed to evaluate that.

DR. DAVIS: Dr. Cohen.

DR. COHEN: I just wanted to make a comment in relationship to, this goes back to some of the comments that Dr. Popp made earlier and he didn't get to address them at the time, about there being differences between the devices and one shouldn't generalize across them. And obviously, I mean there clearly are differences between the devices, they look different, they operate differently. The only point that I wanted to make is if one compares the results, the

significant results in the sham-controlled trial from Sweden with I forget which device, the Cardiogenesis I believe, device, and the Biosense trial which had nonsignificant results in its sham-control trial in the United States in a three-times-as-big patient population, the difference does not relate to the difference of the effectiveness in the active arm, it actually relates completely to the difference of the effectiveness of the sham arm, which looked a lot better in the U.S. trial than it did in the Swedish trial. So just by way of information, in terms of trying to understand the differences between the different devices, it doesn't look on the face of it to me like the devices operate differently, it looks like the placebos operated differently.

DR. DAVIS: I just wanted to let the committee members know that Dr. Popp forwarded a note to me indicating that he had to leave shortly after three p.m. to catch a flight, so in his absence, Miss Falls can respond on his behalf regarding details of the studies on PMR. Further discussion or comments, or questions? Are people ready to vote? Okay. Does

the wording for question one work or do we need to modify that? It works? Okay.
Question one is, how well does the evidence address the effectiveness of PMR in the treatment of chronic refractory angina in study patients for whom other methods of revascularization are contraindicated, ranging from one for limited to five for complete.
DR. AKLOG: I apologize, but would that include TMR, surgical TMR as other methods, or conventional methods?
DR. DAVIS: I'm assuming we're not saying that for these patients TMR is contraindicated, we're talking about CABG and PCI; is that correct?
DR. AKLOG: Again, probably stating the obvious.
DR. DAVIS: Right, but good to clear nonetheless. So the implication is that we're talking about conventional methods not including TMR. Okay, we will begin voting. One?
(Dr. McNeil and Dr. Aklog raised their hands.)
DR. DAVIS: Two.
(Dr. Black raised his hand.)

DR. DAVIS: Three.
(Dr. Cohen raised his hand.)
DR. DAVIS: Four.
(Dr. Goodman raised his hand.)
DR. DAVIS: Five.
Moving to question two, how confident are you in the validity of the scientific data for this outcome, ranging from one and two, no confidence, to five for high confidence.
Starting with short-term mortality.
One. Two.
(Dr. Cohen and Dr. Black raised their hands.)
DR. DAVIS: Three.
(Dr. Goodman raised his hand.)
DR. DAVIS: Four.
(Dr. McNeil and Dr. Aklog raised their hands.)
DR. DAVIS: Five.
Long-term survival. One.
(Dr. Aklog raised his hand.)
DR. DAVIS: Two.
(Dr. McNeil, Dr. Black, Dr. Goodman and Dr. Cohen raised their hands.)
DR. DAVIS: I think we're done. Three,

four, five.
Morbidity. One. Two.
(Dr. McNeil, Dr. Goodman, Dr. Cohen and Dr. Aklog raised their hands.)
DR. DAVIS: Three.
(Dr. Black raised his hand.)
DR. DAVIS: Four and five.
Quality of life. One. Two.
(All voting members raised their hands.)
DR. DAVIS: Was that unanimous? Moving towards consensus, that's what I like to see. It only took us about four hours.
Question 2.B. How likely is it that PMR will improve this outcome compared to usual care, ranging from one and two for not likely to five for very likely.
Starting with short-term mortality.
One.
(All voting members raised their hands.)
DR. DAVIS: Unanimous again. Moving on to long-term survival. One.
(All voting members raised their hands.)

DR. DAVIS: Unanimous again.
Morbidity. One. Two.
(Dr. McNeil, Dr. Goodman, Dr. Cohen and Dr. Aklog raised their hands.)
DR. DAVIS: Three.
(Dr. Black raised his hand.)
DR. DAVIS: Four and five.
Quality of life. One. Two.
(All voting members raised their hands.)
DR. DAVIS: Question three, how confident are you that PMR will produce a clinically important net health benefit in the treatment of chronic refractory angina in study patients form whom other conventional methods of revascularization are contraindicated, adding the word conventional there, ranking from one for no confidence to five for high confidence. One.
(Dr. McNeil and Dr. Aklog raised their hands.)
DR. DAVIS: Two.
(Dr. Black, Dr. Goodman and Dr. Cohen raised their hands.)
DR. DAVIS: Three, four, five.
Question four. Based on the literature

presented, how likely is it that the results of PMR in the treatment of chronic medically refractory angina can be generalized to the Medicare population aged 65 and older, ranging from one for not likely to five for very likely. One? Two? Three?

(Dr. McNeil and Dr. Aklog raised their hands.)

DR. DAVIS: Four.

(Dr. Black, Dr. Goodman and Dr. Cohen raised their hands.)

DR. DAVIS: And question 4.B, can we generalize to providers (facilities/physicians) in community practice? One. Two.

(Dr. Black, Dr. Goodman, Dr. Aklog and Dr. Cohen raised their hands.)

DR. DAVIS: Three.

(Dr. McNeil raised her hand.)

DR. DAVIS: Four and five.

Let's start with Dr. McNeil, if she wishes to add any comments to explain her votes.

DR. MCNEIL: Actually, most of my votes were on the one and two side for this one because I think the data were really pretty sparse and that's basically what it came down to.

DR. DAVIS: Dr. Black?
DR. BLACK: Yeah. I think the additional comment that I would have about this in addition to there being limited data is that the data seemed to be conflicted or there were different results, and it was difficult to tease out some of the studies, some were single blinded, some were double, some showed a reduction in angina, others didn't, and so trying to figure out with all the potential variability in techniques, patients, devices, sort of where was the treatment effective or not. So I thought again, some of it was the limited number of patients, but again, I think there were a lot of divergent results that I had a difficult time sorting out.
DR. GOODMAN: Nothing to add.
DR. COHEN: I have nothing to add to my previous comments.
DR. AKLOG: The only thing I would add is that one of the other problems is I don't think that, PMR is not surgical TMR, we're not building on a previous procedure that has some data on it, because fundamentally there are less channels, different channels, the pattern and so forth, and I think we're starting from scratch with PMR and

we can't really extrapolate the data that we did on the surgical side because even though we talk about it in the same context, it's fundamentally very different in terms of what's being done to the myocardium.

DR. DAVIS: Great. Thank you very much, and I would like to thank all the members of the committee for their very careful deliberation of all the evidence and the issues and the engaging discussion, and to also thank all of our presenters and guests here today. I'm going to pass it over to Dr. Phurrough and Michelle Atkinson to close up the meeting.

DR. PHURROUGH: I would like to add my thanks to the panel, I think this was a very excellent discussion today. I appreciate your willingness to be very blunt and open and challenging, and I appreciate those who attended today who are willing to accept those challenges and offer us your opinion. I think this was a very helpful discussion for us.

We will be shortly posting a summary of this meeting with minutes and we will summarize the voting tallies for those whose pens weren't working fast enough to get all those down.

Again, thank you very much, and we look forward to other MCACs that work and produce this kind of information.

MS. ATKINSON: I would like to ask the panel members, please leave your ballots at your chair and I will get them.

To conclude today's session, would someone move that this meeting be adjourned?

DR. BLACK: So moved.

MS. ATKINSON: Will someone second the motion?

DR. COHEN: Second.

MS. ATKINSON: Thank you everyone for your time and participation in today's meeting. Have a good night.

(Whereupon, the meeting adjourned at 3:25 p.m.)