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CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare Coverage Advisory Committee

March 12, 2003

Baltimore Convention Center
100 West Pratt Street
Baltimore, Maryland

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Panelists

Chairperson
Harold C. Sox, MD

Voting Members
Wade M. Aubry, MD
Norman Daniels, PhD
Alan M. Garber, MD, PhD
Clifford Goodman, PhD
Tracy R. Gordy, MD
Mark Slaughter, MD
Louise Woerner

Consumer Representative
Linda A. Bergthold, PhD

Industry Representative
Eileen C. Helzner, MD

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Panelists (Continued)

Non-Voting Guest Panelists
George J. Agich, PhD
Stephen Gottlieb, MD
Joanne Lynn, MD, MA, MS
Ileana L. Pina, MD
Julie Swain, MD

CMS Liaison
Steve E. Phurrough, MD, MPA

Executive Secretary
Kimberly Long

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PANEL PROCEEDINGS

(The meeting was called to order at 8:04 a.m., Wednesday, March 12, 2003.)

Ms. Long: Good morning and welcome, committee chairperson, members and guests. I am Kimberly Long, 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 a ventricular assist device as destination therapy in end-stage heart failure patients who are not eligible for a heart transplant.

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

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includes direct financial investments, consulting fees and significant institutional support.

Now I would like to turn the meeting over to Dr. Steve Phurrough.

Dr. Phurrough: Thank you, Kim. I am Steve Phurrough, I am the acting director for the coverage and analysis group at the Center for Medicare and Medicaid Services, and we want to thank all the panel members for the efforts they have made to be part of this meeting today.

It's a very timely and exciting topic, a topic that we think will generate a significant amount of discussion today, and we look forward to your comments and recommendations as to the evidence that's going to be presented here today.

I want to make a special welcome to the new members of the MCAC who are attending for the first time today and hope you will find this a very challenging and exciting time, and challenge you to be members in the future also.

I would like to remind the guests and the members in the audience today that we do have two times for public comments, one for those who have previous to this meeting requested time, and then there is an open public comment time period. For both groups of people, there are disclosure forms that you need to have in hand that you will read prior to your comments, whether it's during the scheduled time or

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during the open public time. If you don't have those forms,

they are out at the front desk and you can get them.
Again, thank you very much for your attendance, and now I would like to introduce the panel chairman, Dr. Hal Sox.
Dr. Sox: Well, we're going to start off by introducing the panel members, or allowing them to introduce themselves and then we'll go right into the presentation and the data.
I'm going to, in terms of running the meeting, if you'll just put your hand up when you want to be recognized, I will note your name and try to take people in order. And I prefer informality, so I'm going to call you by first name if I can. So, what I would like to do now is have each of the panel members introduce themselves by name, state your major affiliation, your employer and what you do, and then it's real important that you state for the public record any financial interests that you have from Thoratec or a competitor, and also if you've served on any other advisory panel that's considered the topic of left ventricular assist devices, this is the time to let everybody know about it. And with the exception of the MCAC consumer and industry reps, if you have been contacted by anybody with a financial interest in this meeting, you should so state at this point so we have that all on the public record.

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So Joanne, do you want to start?
Dr. Lynn: I'm Joanne Lynn. I am a physician. I work with the Washington Home Center for Palliative Care Studies and the Rand Corporation. I have no stock in Thoratec or a competitor's company. I have no financial support from Thoratec or a competitor. I don't serve on any other panel that has considered this issue and I have not been contacted by any party prior to the meeting to discuss today's topic.
Dr. Gottlieb: I'm Steven Gottlieb, director of heart failure and transplantation at the University of Maryland. I do not have any stock or other formal financial interest. I am a co-investigator of the Intrepid trial at the University of Maryland. And I am not on any committees and have had no contacts.
Dr. Sox: Anybody contacted you?
Dr. Gottlieb: No.
Dr. Pina: I'm Ileana Pina. I'm director of heart failure transplant, Case Western Reserve University in Cleveland and University Hospitals of Cleveland. I have no stock or any financial interests in Thoratec or any

competitor's company, and I have no financial support from Thoratec. I served on the FDA advisory panel for devices which looked at and approved at the LVAD as destination therapy. I have not been contacted by anyone.

Dr. Agich: I am George Agich. I'm chairman of the department of bioethics at the Cleveland Clinic Foundation. I have no stock in Thoratec or a competitor company. I have not received financial support from Thoratec or a competitor, and I have not served on any other advisory panel and have not been contacted by anyone prior to this meeting.

Dr. Swain: I'm Julie Swain, a cardiovascular surgeon, and I serve as a consultant to the FDA and I was one of the primary clinical reviewers when the REMATCH study was brought to the FDA. I have no financial interests and I have not been contacted by anyone with financial interests.

Dr. Bergthold: I'm Linda Bergthold. I'm a senior consultant with Watson Wyatt Worldwide. We are consultants to Fortune 1000 companies about their health benefits. And I am also a researcher and participate in various research projects at UC San Francisco, and I have done so in the past at Stanford. I have no financial support from any of these folks, I do not currently serve on any other committees, although I have served on the MCAC in the past, and I have not been contacted by any members of the public, which actually is kind of a shame since I'm the consumer rep here, but that's the truth.

Dr. Helzner: I'm Eileen Helzner. I'm vice president of medical affairs at Johnson & Johnson for the medical devices and diagnostics group. I am here as the industry rep.

Dr. Slaughter: Mark Slaughter, a cardiac surgeon at Christ Hospital in Chicago. I have not received financial support from Thoratec or a competitor, have not previously served on any panels, nor have I been contacted by anybody prior to the meeting.

Dr. Aubry: I'm Wade Aubry, internist and endocrinologist. I have two major affiliations, University of California San Francisco, and the Institute for Health Policy Studies and the Health Technology Center in San Francisco. I have no financial conflict of interests. I did serve on an expert panel for a health technology center forecast on the future of organ assistance and substitution, and this was one of many topics that were covered during that panel.

Dr. Daniels: I'm Norman Daniels. I'm professor of ethics and population health at Harvard School of Public Health. I have no financial support or relationship to Thoratec, I have not been on any advisory committee that has addressed this issue, and I have not be contacted by anyone prior to this meeting concerning it.

Ms. Woerner: Good morning. I'm Louise Woerner. I have my own company headquartered in Rochester, New York. We do home health and public health work primarily. I am currently project director of a chronic disease management

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grant. I have not received any financial support from Thoratec or a competitor. I have not served on any panels that were related to this topic and I have not been contacted.

Dr. Goodman: I'm Cliff Goodman, from the Lewin Group, a healthcare policy and management consulting firm in Falls Church, Virginia. I have not received financial support from Thoratec or a competitor. I do not currently serve on related advisory committees on the subject, and I have not been contacted by any party prior to this meeting.

Dr. Garber: I'm Alan Garber. I am a staff physician with the Department of Veterans Affairs, a general internist and professor of medicine at Stanford, where I direct the Center for Health Policy. I have no direct financial interests in Thoratec or its competitors. I do serve on Blue Cross/Blue Shield Association's medical advisory panel, which has discussed and voted on LVAD, I believe as a bridge to transplantation.

Dr. Gordy: Good morning. I'm Tracy Gordy, a psychiatrist from Austin, Texas, and I'm also chair of the AMA CPT panel. I have not received any financial support from Thoratec or any of the competitors. I have served on the AMA CPT panel where the codes for this, for left ventricular assist devices have been considered, and I have not been contacted by any party.

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Dr. Sox: I am Hal Sox. I am a general internist and editor of the Annals of Internal Medicine, an internal medicine journal. I don't have any financial interest in Thoratec or any of its competitors. I have not served on a panel that has considered the left ventricular assist devices, and nobody has contacted me.

So, with those introductions, we're now going to hear from Perry Bridger, staff for the Medicare coverage, for CMS in the coverage group, and he's going to make the

presentation for CMS.
Mr. Bridger: Thank you. I just need to bring my presentation up. Good morning. I'm Perry Bridger, of the CMS coverage and analysis group. I am the lead analyst for this project. Chairman Sox, distinguished panelists, invited guests and members of the public, it's an honor to present to you today on behalf of the ventricular assist device analysis team at CMS.
For the next ten minutes or so I'm going to briefly describe the impact of congestive heart failure on the Medicare population, discuss with you the history and time line of Medicare coverage for ventricular assist devices, give a quick overview of the current coverage request, and present the voting and discussion questions that will be your focus today.
This is the rest of the CMS review team that has

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been working on this issue. Dr. Madeline Ulrich is an internist and our lead medical officer. Kim Long, our executive secretary of this panel, who you know so well. Dr. Steve Phurrough, Joanna Farrell, and Stuart Caplan.
Dr. Sox: Could I just interrupt for a second to remind the panelists that you have a copy of Perry's slides that you can use to take notes on. Thank you.
Mr. Bridger: Congestive heart failure is one of the most common medical problems facing Medicare beneficiaries. 80 percent of those diagnosed with new onset failure are over the age of 65 and it's the leading cause of hospitalization in Medicare. Prevalence of congestive heart failure in the Medicare population is estimated to be as high as 10 percent, and this diagnosis represents a significant portion of total Medicare expenditures.
Heart failure is a progressive disease with a spectrum ranging from few and mild symptoms to end stage failure. The New York Heart Association classification system is most commonly used to describe the stage of a particular patient's heart failure. The patients who participated in the study which we will be discussing today had progressed to the most severe form, Class IV failure end stage heart failure, and were not eligible for cardiac transplantation, which is the only cure for this condition.
Our next presentation will be from the

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co-investigators of the REMATCH trial, who have requested a change in Medicare policy to include Medicare coverage for left ventricular assist device for end-stage heart failure

patients who are ineligible for cardiac transplantation. Currently, Medicare coverage limits the use of these devices to post-cardiotomy support and bridge to transplant. The current policy is summarized in this slide and the full policy is available in your panel package and on the CMS web site.

CMS received a letter and supporting documents from the REMATCH investigators requesting expansion of the current Medicare policy. We formally accepted this request in August, pending final approval for this indication by the Food and Drug Administration. In anticipation of an FDA decision, we referred this issue to the Medicare Coverage Advisory Committee in October.

Although there are several ventricular assist devices that have previously been approved by the FDA for indications that Medicare already covers, it was not until September of 2002 that the Thoratec SNAP VE LVAS received additional approval for use as destination therapy. This specific FDA approval language is shown on is this slide. It states that this device is now also indicated for use in patients with New York Heart Association Class IV end-stage left ventricular failure who have received optimal medical

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therapy for at least 60 of the last 90 days and who have a life expectancy of less than two years and who are not eligible for cardiac transplantation.

The request to CMS for a coverage change was based on evidence presented in the REMATCH trial and asked that Medicare revise and update coverage policy for ventricular assist devices, to include destination therapy consistent with the current scientific and clinical literature. The requestors were Drs. Eric Rose, James Long and Leslie Miller, who you will be hearing from today, and Dr. Lynne Warner Stevenson.

CMS conducted a literature search for evidence related to use of ventricular assist devices for destination therapy. The only published peer reviewed report of a trial that specifically evaluated the use of a ventricular assist device for this purpose was REMATCH. Specific details of the search methodology can be found in the CMS summary of evidence in the panel package. We have also included in that packet several additional articles that provide information relevant to this topic and questions that we have posed to you today.

The REMATCH article was published in the New England Journal of Medicine, and updated data from that trial

is in your packet. The inclusion criteria for the REMATCH are described briefly on this slide and you will be hearing
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much more about this from the requestors. Also, the panel received the materials described on the slide, all of which are publicly available, many of them on the CMS web site. Although this is not the sum of all the material that CMS will evaluate in our review, these materials represent the data from the REMATCH study and the relevant background information for your discussion today.

You have had an opportunity to review the materials submitted to you in advance of this meeting and you will be hearing oral presentations from the requestors and other interested parties. Following these presentations and the discussion of the materials, we will ask that you vote on the following question: Is the quality of the evidence adequate to draw conclusions about the net health outcomes in Medicare beneficiaries meeting the REMATCH trial criteria who undergo LVAD implantation?

We ask that you consider the following questions when casting your vote. Are the study end points and patient selection criteria appropriate? Are the management and extent of complications adequately described? Do the follow-up survival data for the REMATCH trial suggest any meaningful difference in patient survival compared to data at the time the study reached its primary end point?

Additionally, the magnitude of net health outcomes should also be considered in reaching your discussions. We
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ask that you use the MCAC's own categories of effectiveness, which I will review for you next, as a guideline. They range from breakthrough technology to not effective, and are listed for you in greater detail in your packet and summarized on this slide.

We have also posed to you a number of issues which are not directly addressed in the REMATCH study but which are pertinent to a revision of Medicare coverage policy to include destination therapy. Your discussion of these issues will be helpful to CMS in developing appropriate national coverage policy. Please discuss the following, and I would like to read these into the record.

REMATCH showed increased survival in device recipients, but the survival advantage diminished over time and was associated with severe complications and increased hospitalization. Do the demonstrated extension of life and the limited improvement in the quality of life justify the

risks of LVAD implantation?
Number two. One REMATCH inclusion criteria was that candidates for LVAD implantation for destination therapy could not be a heart transplant candidate. Should the evaluation to determine transplant candidacy be performed only by a heart transplant center that has been approved for Medicare reimbursement?
Discussion question three. Initially, should there
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be specific facility and personnel requirements that must be met to provide the patient with an optimal chance of successful LVAD implantation?
Discussion question four. REMATCH results are based on LVAD implantation in 68 patients. Complete, timely, and accurate LVAD implant and outcomes data for destination therapy patients is critical for future Medicare coverage review and policy refinements. Should mandatory data reporting be required as a condition for Medicare reimbursement?
And finally, there have been improvements in both LVAD design and medicine management of end-stage heart failure patients since the start of the REMATCH trial. Have these improvements affected the applicability of the REMATCH results?
I would like to thank in advance all of the panel, the participants in today's meeting for devoting their time and effort to this very important topic. Thank you.
Dr. Sox: Thank you very much. So just to remind us of what our job is today, we're supposed to vote on one question, and just so that everybody understands, the only people who will be voting will be the people who have a voting member under their names here on the podium. Everybody else will participate in the discussion, but only this group can actually vote on the main question. And it's
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important to understand that the question is advice to CMS about the quality of the evidence, that's what our job is. Our job is not to recommend to CMS that they cover this device, it's to recommend to them or to characterize for them the strength of the evidence for the effectiveness of the device.
We're then to discuss five questions and we won't be taking a vote on those questions, but a transcript of this meeting, which is painfully accurate for those of you who have ever read a transcript, it will have all the uhs and so forth in there, and CMS will read this transcript very

carefully during their deliberations about coverage policy so that what we say in that discussion will be valuable input to CMS even though we're not going to vote on any of those questions. So now you have your charge.

Next we're going to be hearing from the requestors. Dr. Rose, are you going to be the lead speaker here?

Dr. Rose: Yes.

Dr. Sox: Please proceed. And Dr. Rose, I would just remind you that the requestors, as well as everybody else, are subject to the same rules about stating your conflicts of interest and so forth.

Dr. Rose: All right. I'm Eric Rose. I am one of the four requestors for this change in policy. I am the chairman of the department of surgery at Columbia University

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in New York, and surgeon in chief at Columbia Presbyterian Medical Center. I am speaking on behalf of the REMATCH investigators as well as my university and hospital. I have received financial support of our research from Thoratec Corporation, as well as MicroMed and Arrow International. My expenses for coming here today were borne by Thoratec. I have not served on any advisory committee, and I would say that I feel like I have been contacted by everybody with regard to today's proceedings. I don't have a list, but I think just about every constituency I have heard from with regard to today's discussion. So let me launch into my remarks.

I'm going to be, in addition to speaking to the evidence, I will be the emcee, if you will, for our combined presentations. The objectives of our presentations today -- I don't know if this is working. Do you have one?

First, we want to show you the evidence essentially with regard to the net health benefits of left ventricular assist devices for destination therapy in patients with end-stage heart failure. We also want to elucidate the ongoing improvements to enhance outcomes with LVAD therapy as a destination. Jim Long will be doing that. And Les Miller will conclude our presentation, outlining guidelines for responsible dissemination of this new technology, following which I will offer some concluding remarks.

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The treatment options for end-stage heart failure that are based on firm evidence now are three: Medical management with a variety of drugs, diet restrictions, fluid restriction, physical therapy. Unfortunately for end-stage heart failure, outcomes are limited and survival is poor.

Cardiac transplantation has an enormous impact on individual patients who are lucky enough to get a donor heart, but the applicability of this approach is clearly limited by the availability of donors, which is approximately 2,000 per year. We would state essentially that while the benefit of transplantation is huge to the individual patient, it's an epidemiologically trivial operation. And what we're addressing today, the use of left ventricular assist devices.

The device in particular that we're talking about here is the Thoratec HeartMate device, which restores the circulation in patients. After implantation in the abdomen, it derives its inflow from the apex of the left ventricle and ejects into the ascending aorta. A single drive line comes out through the right upper quadrant of the abdomen and the prosthetic ventricle has it's own mitral and aortic valves to insure unidirectionality of flow.

There has been extensive experience and incremental improvement in this device, which has happened in the scenario of bridging to transplantation, which has been done in more than 3,000 patients worldwide since 1986. This

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bridging experience raised this critical clinical issue, which REMATCH is designed to address. That is, can VADs improve net health outcomes of patients when used as a long-term destination therapy?

REMATCH is an ongoing trial. The primary end point was reached in June of 2001 and formed the basis of our New England Journal report in November of 2001. We also presented this data simultaneously to its publication at a plenary session of the American Heart Association. The objectives of REMATCH were to evaluate the efficacy and safety of VADs for destination therapy. We looked at quality of life as well as survival, in patients who were ineligible for cardiac transplantation. And we also documented and analyzed the frequency and nature of adverse events and the instance of device malfunction and failure in patients receiving them.

The primary hypothesis of the REMATCH trial, which was formulated by investigators from the more than 20 centers involved, representing I think the top leadership in management of end-stage heart failure in the world, was a 33 percent reduction in mortality with equal or improved quality of life for VAD patients, versus optimal medical management patients over two years. 33 percent.

The trial was a joint effort of investigators at Columbia, the National Institutes of Health, and Thoratec.

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It was a multicenter randomized trial at 21 centers. Investigators, both cardiologists and surgeons, were credentialed. There was a trial gatekeeper that reviewed each patient's eligibility to insure the patients that were enrolled in this trial were appropriate. The analysis was by intent to treat, using Kaplan-Meier actual survival analysis. I mention that Paul Meier of Kaplan-Meier was one of our lead statisticians for this trial. And a total of 129 patients were randomized to the point where the trial reached its primary end point with the death of a total of 92 patients enrolled. 68 patients were randomized to receive the device and 61 patients received optimal medical management.

These were the findings. The primary hypothesis was exceeded, there was a 48 percent reduction in mortality over the two-year observation program compared to optimal medical management. Our expectations with regard to quality of life were also exceeded. We hypothesized that quality of life would be no worse and instead, it was clearly better in the VAD patients compared to the control.

This is our most recent intent to treat analysis. The curves are obviously quite statistically significantly different. The one-year survival with the VAD patients is 51 percent, compared to 28 percent in the controls, and at two years, there is a 29 percent survival in the VAD patients compared to 13 percent of the controls. The one-year and

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two-years differences, as well as the entire curve, are statistically significantly different. And in addition, the deceleration in mortality of the control groups compared to previous times reflects the crossover of three of the control patients to the VAD arm.

This table summarizes a series of survival analyses that we've done over time, and we reported in the New England journal based on the cutoff at the time that we ended enrollment in the trial, we reported a 52 percent one-year and 25 percent survival, which was statistically significant, as well as the 48 percent reduction over the entire two-year observation period. But at that time the 23 percent versus 8 percent two-year survival had not reached statistical significance.

At the FDA panel, the two-year data had just reached the point of significance, and now with extended observation, it's clear that this two-year difference is robust.

I should point as out as well the slight

improvement in the control group; because it was an intention to treat analysis, there are three crossover patients, and only one medically managed patient that remains alive in this cohort, with 14 patients now still alive on devices.

When we look at an as treated analysis, in which we censored the patients in the control group at the time that

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they receive the device, they are not added to the device group. The two-year survival rate of control patients is 8 percent, which corresponds to the earlier reports.

We thought at this point that it would be interesting and reasonable to offer a perspective from the patients's side. This is a patient who has actually seen REMATCH from both sides of the fence. He was enrolled and randomized to the medical management group. Just a little bit shy of five months prior to completion of enrollment, everyone was offered a device when the trial results were over, he was allowed to cross over.

(Video played.)

I think where the tape hiccupped is that he said he'd driven 350 miles in the last two days prior to this tape.

This slide I think may be the best graphic representation of the net survival benefit. It's a cumulative compilation of days alive of the control group in blue and the VAD group in yellow, and you can see that the control group days alive essentially reached an xenotope at approximately 540 days or about a year and a half, and you can see that the cumulative days alive for the VAD group continues to grow.

With regard to quality of life, we looked at several prespecified measurements. We used the SF-36,

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particularly looking at physical function and raw emotional scores, disease specific, a Minnesota Living with Heart Failure questionnaire, the Beck depression inventory, and the benchmark New York Heart Association functional status. I want to show you data essentially that are cumulative across the entire trial. The VAD patients are in yellow, OMM in blue. At different time intervals, these are the scores on the SF-36 physical functioning score. At the bottom of the panel, and these are in your packets as well, is the total number of patients responding. And here, the cumulative difference across the entire two years of observation, is highly statistically significant, that the VAD patients physically function better.

The same holds true -- I'm sorry, that was general health, this is physical functioning, with the same p value of point .01. The Minnesota Living with Heart Failure score, a highly validated disease specific metric, here lower scores reflect better health, better quality of life. Yellow bars across the board with the exception of the early time points, but the entire experience is highly significantly better in the VAD patients.

The Beck depression inventory, patients enrolled in this trial uniformly met the clinical criteria for depression and you can see Beck scores are highly significantly lower, and here a lower score is also better.

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When you look at the percentage of patients who were NYHA Class I or II in the two groups, less than 20 percent of the medically managed patients by a year after randomization were NYHA Class I or II, compared to more than 75 percent of the VAD patients.

So to summarize the quality of life findings, the quality of life was significantly better for the VAD patients compared to the OMM patients, measured with every prespecified instrument. And in addition, VAD scores were never worse than the OMM group, except for short-term postoperative pain in the first 30 days.

Now all this was achieved at a cost of an incidence of adverse events that we reported were 2.35 times more common in the device patients compared to the medically managed patients. Now this is a graphic representation of those events occurring at 30 days or less after surgery and events 30 days or more. While there is a higher incidence depicted in red, particularly early after the surgery, the frequency of those adverse events diminishes markedly after the early perioperative period, and begins to virtually equalize with the frequency of the adverse events of the control patients late.

What's particularly interesting as well is even in spite of all these adverse events in the device patients, the mortality rate of the device patients, even early, was lower

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than the mortality rate for the medically managed patients even in this early 30-day period. This has particular import with regard to the question as to transplantation evaluation because any delay in the process of evaluation of these patients can result in the incurring of the high mortality rate during even that early 30 days.

The other thing that's important to point out is

that we did not prespecify worsening heart failure as an adverse event. If we had, I think it's fair to say, especially in light of this high mortality, almost all of which was due to heart failure, that the incidence of adverse events early would be closer.

So the voting question that you're asked to respond to, is the quality of evidence adequate to draw conclusions about net health outcomes in patients meeting the REMATCH criteria? We think this is a well designed trial that does provide high quality of evidence to answer these questions. With regard to what the evidence shows itself, we have documented what we feel is a clinically meaningful and statistically significant survival benefit over a two-year observation period, which also holds up with both one and two years after randomization. We've shown improved quality of life in VAD patients in multiple prespecified functional and subjective domains. The incidence of adverse events we believe is reasonable, given the patient's terminal condition

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and the magnitude of the benefit that we've demonstrated. And in summary, we think that the net health outcome here is that this is substantially more effective therapy than medical management.

Our second objective is to elucidate the ongoing improvements to enhance outcomes with VAD therapy, and Jim Long will address those improvements.

Dr. Long: Good morning, I'm Jim Long. I am a cardiovascular surgeon, was a participator as an investigator in the REMATCH trial, and I am here to represent fellow investigators in the field as well as patients with end-stage heart failure that I work with on a regular basis. I have received material support from Thoratec for research and for travel and arrangements, but I have no financial interest or disinterest directly in Thoratec. I have been a discussant on panels but not dealing with the subject specifically as we have it this morning. I too have been contacted by people, but nobody on the panel directly about this discussion this morning.

Eric has given you an excellent overview of the facts as they speak for themselves from this REMATCH trial, which in fact was a landmark in the field of circulatory support. And it will be my objective to think beyond the REMATCH trial and how that sets the stage for where we go next. We would be loathe to do this if we didn't walk the

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fine balance between the realities we face, the facts that we

need to know, and the hope that we must have for the patients that we serve.

Let me illustrate that with some words from Jim Kastner, a 70-year old patient.

(Video played.)

In addition to Jim Kastner, who you've heard from, these are two of my patients, Bernie Calderwith on the left in these three panels, a 78 year old gentleman whose quality of life has been immeasurably improved over two years of experience with assist therapy. On the right is Carl Grover, a 73-year old gentleman who has traveled extensively, including an Alaska cruise, and who has returned to work actually. While these voices are not true science, they are indeed real experiences and they represent real hope in this field, an area where we do not otherwise have hope for these patients, and we'd be irresponsible if we didn't bear that in mind.

The REMATCH experience formed a basis for improving outcomes. This was a pioneering trial, first ever with destination therapy. Through the REMATCH trial, destination therapy was demonstrated to be an expanded indication for an assist pump, the HeartMate ventricular assist device that's a very good pump, and a pump that continues to undergo instrumental improvements. It's not perfected technology,

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but it is indeed outstanding and was good enough to allow us to improve the efficacy and safety of this therapy.

The HeartMate LVAD started out as an electric pump with a VE as a double lead system. You can see the pump here, inflow conduit and outflow conduit; this takes blood from the ventricle, returns it to the ascending aorta. There's a percutaneous lead here. When this originally started, it was a double lead system; it evolved to a single lead system, and then changed the location of where the single lead went to improve our outcomes, reduce our exit site infection problems, and the REMATCH trial began in this era right here. Late in the REMATCH trial we found some things that could be done to improve the technology, outflow graft relief so that we would not have tainting of this outflow graft, which was causing increased pressures transmitted into the pump causing failures of the inflow valve. We found ways to couple it better and make some improvements.

Beyond the REMATCH trial there are further improvements that will reduce device related complications. Particularly notable are those that change the way the pump

drives so that inflow valve failure is reduced, and I will address that in a minute, and also an important topic and that is the change in the percutaneous lead to make it more flexible and less prone to infection.

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I want to give you a sense of what happened during the REMATCH trial with the technology and with management, and talk to you about things that are changing based on this improvement in the technology as well as improvements in our overall management. And those are very important topics. The two that we'll focus on are with the left ventricular assist device failures, which represented about 15 percent of our causes of death in the REMATCH trial, and infection, the second or the largest cause of death at 40 percent. Those are the two single greatest complications that occurred during the REMATCH trial, 40 percent infection related death and 15 percent LVAD related death.

LVAD failures are most commonly associated with this problem right here, the inflow valve. The inflow valve, as I showed you, is in a conduit placed between the left ventricle and the pump itself. And during the trial, we experienced as the highest cause of LVAD failure dysfunction of this inflow valve as a result of a flexible suspension conduit here buckling on itself and causing this valve to distort and causing it to fail. Prior to the REMATCH trial we had rarely seen this problem. About the same time the REMATCH trial began, there was a change in the design of this to accommodate a better design, less abrasion on the graft so that we would have less incidents of graft related separation and failure, and less bleeding, and that certainly prevailed,

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but as a consequence, there was increased problems with the inflow valve, and that as I said was the single most significant cause of LVAD failure, which was responsible for 15 percent LVAD failure, responsible for 15 percent of the deaths in the trial.

To correct that, and this is work that's coming down the pike, there will be a change in the way this inflow valve is structured. At present there is no external support on this flexible conduit, and under pressures generated from the pump pushing backwards toward the left ventricle, this graft distorts itself, buckles and then the valve is exposed to distortion and as a result of that, the valve fails, and these valves can fail as early on average as about five to six months. You can live with them for another six months or so but it eventually leads to device replacement. A new

design is coming down the pike and hopefully will be available to us shortly. It will be an externally reinforced configuration that will prevent this buckling, prevent migration of this valve, undergoing bench testing presently, and there appears to be somewhere between a four and six-fold increase in durability of this valve, so that we will expect to see based on improvements in that less incidents of inflow valve failure, one of the modifications that is coming out of our learning from the REMATCH trial.

The device itself was good enough in its present

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state to get the results that you have already seen, but coming down the pike are further improvements and enhancements. Destination therapy is an extended indication for an LVAD that's already good but improving.

Secondarily, where the REMATCH formed a launching pad basis for us to improve our outcomes is in our clinical understanding and management. This is the first time we had ever dealt with this patient population, and we learned a great deal. Some of us who felt we were well experienced in the bridge to transplant community learned some new lessons with this patient population and we're continuing to evolve those lessons and learn and apply them to the field.

I told you about the problem of infection and I will get to that in just a second, but our patient management improved during the course of the study. As a result of that, we are now -- we have been and are continuing to share those outcomes with others. We saw center to center variations in our outcomes with the same patients, same technologies, leading us to believe there were changes in management that we could learn from, and we found best practices that could be modified and transferred to others to make our outcomes even better than what you see in the REMATCH trial.

Let me focus on infection, again, a serious problem. 40 percent of the deaths in the REMATCH trial were

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related to infection, not all those device related, but nevertheless a significant problem. To illustrate that in fact changes in management can have an impact on that, we looked at two centers who took a very aggressive approach to infection prevention and management, and we isolated those two centers and looked at the data. If we look at all the other centers and taking 52 patients total, we found an infection rate of 0.72 serious septic episodes per patient year. When we looked at 16 patients done in these two

centers, accounting for 24 percent of the patients who were enrolled, we saw a zero percent serious infection rate. And it's noteworthy that the median duration of use in these two centers was higher, longer term implants than all other centers combined, meaning a greater exposure of risk to infection, higher with these same patients, same technology in two different centers could lead to an improved outcome like that. That led us to believe there were differences in management that we could exploit and learn from.

And in fact, something as simple as this was a very key part of that aggressive management. The percutaneous lead, where it comes out of the right upper quadrant, must be immobilized. That lead must be immobilized so that you don't get exit site problems, exit site problems that propagate into full fledged infections, deeper infections. And the two centers that were using this aggressively, using a simple

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binder, a flexible binder that found a way to properly immobilize this were the two centers that had the lowest rate of infection, and this was a significant factor.

There were other factors that went into this and as part of our learning and transmission of that learning, we created some infection control guidelines. These guidelines have now actually been transmitted into a booklet, the booklet that you see here with our guidelines that we can now disseminate to the field. This is learning that came out of the REMATCH trial that had a significant impact.

What kind of impact did it have within the REMATCH trial? Well, if you look at effects before we introduced guidelines when we came together as a group and formed consensus on this, and after, we found that there was a reduction in serious infection rates from 68 percent to 41 percent. The average duration of support was no different, the risk of these patients to infection was no different, but with the introduction of infection control guidelines, we saw a reduction in serious infection rate.

So indeed, you have seen that there are improvements that can be made in our technology, improvements that can be made in our management, and that REMATCH formed the basis, a springboard on which we can further improve our outcomes.

Do we have any reason to believe that this is a

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reality? This slide indicates that. Here are survival statistics in various areas throughout the REMATCH trial and before, looking at survival with an assist device and

survival in the medical group. The data that you have been exposed as a composite in the REMATCH trial is here in the center. This was the data that Eric presented in the original New England Journal of Medicine article. It was presented initially at the American Heart Association. This is the total REMATCH data looking it as of the beginning of this year, 23 percent survival at two years, 29 percent in the LVAD arm compared to 8 and 13 percent. But if you divide that into early REMATCH data and late REMATCH data, what you see is 21 percent survival in the early experience through '99, compared to 9 percent on the medical arm, versus 37 percent on the LVAD arm compared to 12 percent.

And if you go one step further back in history and look at a warm-up trial for the REMATCH, the PREMATCH, we had zero percent survival at two years in that patient population. So there is a significant trend to improvement over time with the patients who are receiving assist pumps, but no significant change in the outcomes with patients who are receiving optimum medical management. Setting the stage for us, we believe, to move beyond this curve and move further with changes in their technology as it continues to evolve, it's good to start with, it will get better, and

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changes in our management, which was pioneering initially but has progressively improved based on the experiences that we have learned.

So, our management and extent of complications adequately described, we believe we understand the issues and the significant cost of morbidity and mortality for this therapy. We believe that from our experiences we can have ongoing learning and we can disseminate that learning with sharing of our information we've learned. We believe that extension of life has been demonstrated and the improvement in quality of life justifies the risk of LVAD implantation for patients who don't have hope otherwise, and as the improvements in LVAD therapy for end-stage heart failure since the REMATCH occurred, we believe that they are, the REMATCH results are applicable. We believe based on what we've seen, they actually underestimate the potential for what we can achieve with LVAD benefits based on ongoing and progressive improvements and while we don't expect to see a concomitant improvement in patients with overall medical management.

So the data we have at present, the strength of the evidence that has been compiled at present, allows us to believe unequivocably that LVADs are effective therapy for

destination therapy. The REMATCH trial set the stage for that, set the stage for device improvement, set the stage for

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improving patient management, and as a result enhancing our patient outcomes. And we believe that what we have learned from the REMATCH trial provides a basis now for responsible dissemination, transferring the knowledge that we have learned, making sure that there is adequate expertise and proper resources to take care of this labor intensive group, and we believe that it will be important to track their outcomes for further refinement of the best practices so we can continue to learn as we continue to see this field evolve providing a promising therapy.

Dr. Miller: Good morning. I'm Dr. Leslie Miller. I'm the director of the cardiovascular division at the University of Minnesota and also the director of the heart failure and transplant programs there. I do not own any stock or have financial interests in Thoratec. I have received support for research and travel to meetings to prepare this presentation. I do not currently serve on any panels relevant to this topic and have not had any conversations with any of the voting members of this panel.

You have heard the compelling body of evidence that the REMATCH data has put forth to support the superiority of mechanical devices over medical therapy for this population, and I think Dr. Long has clearly articulated the progress that has been made, particularly on the surgical side, supporting and leading to improved outcomes in this area.

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I would like to address the remaining questions that have been posed by CMS to this panel, which are really relevant to the issue of how do we now responsibly disseminate this important technology.

I would like to begin by drawing your attention to an important document that has been included in your packet, and this is a document that leads to the guidelines that a task force of two of the leading societies in the field of cardiovascular medicine, namely the American College of Cardiology and the American Heart Association have put forward to guide the current treatment. This evidence based document importantly calls our attention to the early phases of heart failure in which we need to focus on prevention, to prevent this extraordinary prevalence that was referred to in the original presentation.

It describes in an algorithmic fashion an escalation of medical therapy for patients as they progress

through the various stages of this disease, until they get to Stage D, the most advanced form of this condition, which describes patients who have marked symptoms at rest despite maximum medical therapy, which includes ace inhibitors, beta blockers, diuretics, et cetera. But importantly in this Stage D, this task force has clearly recommended that those patients who are refractory to all medical therapy, that mechanical circulatory support is clearly an approved and

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evidence based recommendation.

Those guidelines were actually in focus with the designers of the REMATCH trial. In their eligibility criteria, it clearly states that patients should have been managed with ace inhibitors, beta blockers, digitalis and diuretics for a substantial period of time, and are refractory to those agents to be eligible, have a reduced ejection fraction describing poor systolic function, but importantly, have a low peak oxygen consumption. The importance of that is that it's been shown in comparison to other variables to be the most important prognosticator of outcome in patients with heart failure and is importantly a functional limitation beyond just limitation of symptoms, and helps us differentiate patients who might have symptoms because of deconditioning or a concomitant pulmonary disease, and clearly defines their exertional difficulties to be cardiogenic and in general, for a variety of topics, are considered ineligible for transplantation.

There were few exclusion criteria, primarily because of the size of device, body surface area less than 1.5 meters squared, and those with active systemic infections.

But the third point on this, I think is really a very interpretive criteria, and that is patients who have irreversible end organ dysfunction that would otherwise

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independently limit their expectation for survival, or have a coexisting terminal condition such as a malignancy that would similarly limit their outcome beyond living with heart failure.

An important consideration is how many people would be served by this technology, and REMATCH I think gives us a window into that. There were 20 centers that participated in the REMATCH trial, all of which were transplant centers with experts not only in implantation and management of the devices, but cardiologists experienced in the management of advanced heart failure and all the options that are

available. Of that group, nearly a thousand patients were referred for consideration for enrollment in this trial. As it's depicted here, we only actually enrolled 129, or approximately 1 in 7, or 15 percent of that initial referred population.

As this slide describes, many of them because these were experts in management of heart failure, had escalation of their medical therapy, improved, were referred for conventional modalities such as bypass surgery or in fact were shown to have irreversible end organ dysfunction, and therefore, not considered to be candidates for this technology. So we ended up with 129 patients who were eventually randomized into the trial.

I think an important question that has been posed

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to this panel is should the evaluation to determine candidacy be performed only in a transplant center. I think the experience with triaging patients and looking at other options is an important consideration, but clearly that resource and experience is not confined to transplant centers. But we do believe that the non-transplant centers who will begin to employ this technology should have an affiliation and working relationship with a transplant center to take advantage of this experience in triaging and evaluating options, so that we can get the best outcomes for the patients considered for this therapy.

The importance of this prospective randomized controlled nature of the REMATCH trial is shown in this slide and it points out that we ended up with absolutely identical populations in both the medical arm and the LVAD arm, so a very legitimate comparison. Many of the parameters were literally identical. But the second thing that this slide points out is that this was an extraordinarily ill population with very advanced heart failure.

Pictured here is an ejection fraction, very limited, cardiac index reduced, serum creatinine very high, and many patients requiring intravenous medical support with inotropic drugs. This table, which was developed by Lynne Stevenson, I think gives you a very good look at the current status of this population in comparison to other recent

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trials in the heart failure population. Pictured on the top is the REMATCH compared to a trial with the First trial, intravenous inotropic drugs with a (inaudible), Promise, a recent trial with a new beta blocker drug in Class III to IV heart failure patients, RALES, with (inaudible), and

Consensus, an early ace inhibitor trial. When you compare the ejection fraction was the lowest in these comparative trials, the heart association class was the lowest, the systolic blood pressure the lowest, the serum sodium the lowest, serum creatinine the highest, and importantly when you look at the control mortality in this population, it was clearly a sicker group of patients than had ever been studied.

A good way to summarize the REMATCH population is a new subset of patients with advanced heart failure that probably are applicable to approximately 15 percent of patients with end-stage heart failure. The severity of illness far exceeded all previous heart failure trials and the mortalities was four times that witnessed in recent beta blocker trials, and outcomes that clearly are worse than currently expected and seen with diseases such as AIDS, breast, colon or lung cancer.

Dr. Long has just shown you this slide, and I think it's an incredibly important body of data, and I guess I just said something important. The improvement in progress shown

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with surgical therapy has been noticed over each escalation and era of the application of this technology. In contrast, the medical therapy pictured in blue and the outcomes associated with medical therapy have remained extremely disappointing and very poor.

I remind you that the medical therapy that was utilized by the cardiologists who were very experienced in the management of end-stage heart failure is depicted here, and consisted of all the conventionally approved agents for heart failure, but importantly, despite angiotensin inhibitors and ARB inhibitors, 29 percent of the patients were too ill to tolerate that form of therapy. Similarly, beta blockers were only utilized in approximately a fourth of the patients because of intolerance of these medications.

This data, which has not been shown previously, is a Kaplan-Meier curve depicting survival over the course of time. In the red is the patients who were in fact enrolled in the trial in the latter half of the trial in comparison to medical management of those patients enrolled early in the trial, and I think it's very evident that there has been no improvement in the medical management of advanced heart failure as witnessed in this trial, whether early or late. And unfortunately, there have been approximately ten trials that have had very tantalizing hypotheses because they're addressing and trying to reduce substances such as

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endothelium or vasoconstrictors, or important planetary cytokines like (inaudible), which have failed to demonstrate a survival advantage and therefore, there are not a lot of new technologies or drugs that we think are going to be readily available to alter this unfortunate prognosis for these patients.

An important panel question, therefore, is, have improvements in medical management in end-stage heart failure since REMATCH affected the applicability of results? I think the REMATCH results and conclusions in comparison to what I have just shown you are clearly still applicable.

A second important question is, should there be specific facility and personnel requirements, and we believe there are. I believe that you will hear a consensus amongst the societies involved in this field of cardiovascular medicine that beyond simply going to a training course, it's important that both the cardiologists and the cardiovascular surgeon have documented experience in this field to bring to the assessment of patient selection and the management of these patients. The cardiologists should clearly have a great deal of experience in the management and the options available for end-stage heart failure, as well as clear training and experience in the management of mechanical devices. And similarly, the surgeon should be involved in the assessment of these patients and the therapeutic options,
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and clear documented experience as well as recently trained in the management of this technology.

Similarly, the facility criteria should include a team of advanced and trained experts with the management of end-stage heart failure and these devices. It should include a facility that has clear capability of managing post-operative cardiovascular surgical patients and patients with advanced heart failure and as I mentioned previously, an arrangement and coordination with a Medicare approved transplant center.

The facility should include an array of experts and people focused in the knowledge of infectious diseases in many of the medical disciplines, but importantly include resource personnel in social services to provide patient education and psychological support for decisions about options in advanced and end-stage disease, as well as nutrition, radiology, and of course nursing.

And finally, should data reporting be required? We think that is definitely an important aspect to advance our

understanding of the success of this field, and we fully support a registry to document the outcomes with this technology.

I'll turn the podium back to Dr. Rose for our conclusions.

Dr. Rose: We want to express our gratitude to the

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panelists, to CMS for working with us actually for quite a long time to refine our request and to bring it to this decisive day.

We would summarize by saying that there is clear strong evidence supporting the use of VADs in patients that meet the REMATCH criteria. The clinical data from REMATCH clearly established that VADs provide a substantial survival and quality of life benefit with patients with Class IV end-stage heart failure. And in addition, the decade of data from the use of VADs as a bridge to transplant offers further documentation with regard to the strength of the evidence and the direction of the improvement in the technology.

We would say that the magnitude of the net health benefit is substantially more effective and that the progress in reducing adverse events, that this technology has the potential, I believe in the near future, to achieve breakthrough impact. The destination therapy now clearly should be responsibly disseminated. The bottom line is quite simple. Patients live longer and feel better for a substantial period of time with left ventricular assist devices, and the evidence clearly supports a Medicare coverage decision for these patients.

On behalf of the patients, on behalf of my fellow investigators, we thank you for the opportunity to present this material.

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Dr. Sox: Well, thank you very much, Dr. Rose, Dr. Long, Dr. Miller, for a lovely presentation. We're going to move on now without time for questions to scheduled public comments. These are people who have contacted CMS in advance of the meeting to get permission to address the panel. And we've got about 40 minutes for that part of the meeting, we have five scheduled presenters, so that's about eight minutes each, and that should be plenty of time so that I won't have to use a hook to get you off the podium. And I just want to remind you that you should state any financial conflict that you have, including relationships with the companies that make these devices, and also tell us who paid for your travel to speak at this meeting.

Our first speaker is going to be Dr. Mario Deng, and Dr. Deng, why don't you introduce yourself?

Dr. Deng: Thank you very much, chairman, panel and public guests. My name is Dr. Mario Deng. I'm a cardiologist specialized in the care of patients with advanced heart failure and I am the director of cardiac implantation research at Columbia University in New York City, and I also serve as the medical director of the mechanical circulatory support database of the International Society for Heart and Lung Transplantation. With respect to disclosure, I receive research support from World Heart Incorporated, as well as serve on an international cardiology

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advisory board to World Heart.

The ISHLT appreciates the opportunity to testify with regard to this important question of left ventricular assist devices as destination therapy.

Dr. Sox: Excuse me. Dr. Deng. Who paid your way here?

Dr. Deng: The ISHLT.

Doctors Rose, Long and Miller have just made the compelling case for the extension of Medicare coverage for reimbursement of left ventricular assist devices for destination therapy. The four speakers scheduled after my presentation will focus on clinical requirements and the condition to what Dr. Miller has expanded on, for centers wishing to perform destination implantation. My presentation will focus on discussion question number four, with respect to the mandatory reporting in centers wishing to embark on this new mode of therapy.

REMATCH has provided the proof of principle for the benefit of MCSD therapy, but translation of REMATCH result into clinical practice will be challenging. Based on previous experience, post-approval trends will be following: Like the first centers will begin to place these devices into patients with a less dismal prognosis than those randomized in REMATCH. And secondly, the expansion of centers will lead to the establishment of start-up MCC programs having less

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experience than established centers and providing no on-site heart transplantation capabilities.

These trends may decrease the survival benefit from destination MCC therapy. There may be in the worse case scenario no detectable survival benefit anymore and thus, we will only witness a switch of the mode of death. Thus, a major concern at this time is the inappropriate application

of MCSD for patients who are either too ill or too well. This concern must be addressed for a collaborative strategy focusing on safety and effectiveness, which would then be option five that the International Society for Heart and Lung Transplantation board of directors has outlined, which was part of the written background material for this testimony, where an option five should include a mandatory database committed to outcomes research.

Why is a database necessary? Although the observations in 129 patients in REMATCH provide definitive evidence for the benefit in this specific patient population, they can neither adequately identify subsequent target populations nor can they define in which centers this next stage of implementation of this new mode of therapy should occur. For this, the continued collection and analysis of the ongoing clinical practice is crucial. Randomized clinical trials, which are the gold standard generally of evidence are time consuming, resource intense, and restricted

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in their applicability. Current industry based registries are insufficient to generate this evidence. The consensus conference on MCSD future trial design in June 2000 has recommended a mandatory database reporting mechanism. The International Society for Heart and Lung Transplantation, known for its heart and lung transplantation registry for 20 years, has therefore created an international mechanical circulatory support database with the goals that are threefold.

First, enabling evaluation of the safety of all current and future mechanical circulatory support devices, not only the one in question here, by applying the same uniform consensus definitions of complications to all devices and thus providing a framework for measuring every device along the same lines.

Two, potentially evaluating MCSD effectiveness by integrating validated heart failure risk stratification parameters at the time of implantation.

And three, capturing overall current practice patterns, not just the practice of selected centers of excellence.

Quoting the summary of evidence which you have in front of yourself as a compilation of CMS in preparation for this meeting, the European registry demonstrates the value of registry data in preventing unrestrained use with regard to

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applications and patient selection in the post-approval era.

Why should the participation in a database be mandatory? A voluntary database is not able of generating either the financial support or the institutional participation necessary to insure long-term viability of a database mechanism. In addition, the advantages of a mandatory database include participation of all MCSD centers, complete data entry because personnel for data entry will be provided, is crucial, and three, increased credibility and usefulness of the resulting analyses.

Dr. Sox: Dr. Deng, we want you to wrap up in the next minute or so, please.

Dr. Deng: Yes. You will hear from the four next speakers that every single constituency will endorse the mandatory reporting mechanism, and I would like to conclude by saying this database mechanism does fit into the development framework of the U.S. healthcare system in the following way. The Institute of Medicine's report in 2001 characterized the U.S. healthcare system as being unable to translate knowledge into practice consistently and apply new technology safely and appropriately. Recommendations of the IOM include performance and outcomes measurements, ongoing analysis and synthesis of evidence, and payment and synthesizing quality enhancements in pending reimbursement decisions on destination MCSD provides a unique opportunity

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to create a model along the lines of this national agenda by mandating participation in the ISHLT MCSD database, which is ongoing since one year. Thank you very much for your attention.

Dr. Sox: Thank you, Dr. Deng. Our next speaker will be James Kirklin, from the University of Alabama in Birmingham.

Dr. Kirklin: Thank you very much. My name is Dr. James Kirklin, and I am a professor of surgery and director of cardiothoracic transplantation at the University of Alabama at Birmingham. I am a member of the ACC committee on advanced heart failure heart transplantation. I also serve as the editor of the Journal of Heart and Lung Transplantation, which is the official publication of the International Society for Heart and Lung Transplantation, or ISHLT. I have no financial interests in nor financial support from Thoratec or its competitors, and my travel was paid for by the ACC.

My comments reflect the responses of our committee to voting and discussion questions for the Medicare Coverage Advisory Committee on destination therapy for mechanical

circulatory support devices or MCSDs, also called LVADs. My complete testimony has been forwarded to the committee.

As has been discussed, REMATCH was a landmark randomized multicenter trial of one of the highest risk

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groups of advanced heart failure patients. They were not eligible for heart transplantation, they were of advanced age, mean of 66 years in the LVAD group, and a majority required continuous inotropic support.

One of the discussion questions focused on whether the limited extension of quality and duration of life justifies the risks of MCSD therapy. The major causes of death in the device arm of REMATCH are shown here. As Jim Long emphasized, infection, most often device related, and device failure accounted for nearly 60 percent of the MCSD group mortalities. Despite the frequency of device related causes of death resulting in a two-year MCSD survival of only 23 percent, MCSD survival as shown in the upper curve was more than twice that of the medical group at one year, shown in the lower curve, and nearly three times the medical survival at two years.

With technological improvements and developments of methods to neutralize or prevent these potentially lethal events, the survival advantage should increase in the future. This notion of continuing improvements is supported by the finding of a 25 percent decrease in the relative risk of MCSD death per year when survival is adjusted for the date of entry into the trial.

Furthermore, Jim Long noted that infection was significantly reduced at two REMATCH centers that routinely

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utilized a patient device harness designed to minimize movement of drive line at the skin exit site.

Other questions related to the selection of patients and qualifications of centers for this therapy. In suggesting policies for identification of centers to perform chronic MCSD implantation, our overriding commitment is to the protection and benefit of the individual patient. In this regard, the patient could most obviously receive harm if the medical and surgical personnel did not have sufficient expertise. But perhaps equally important is prevention of the premature application of this therapy, the patients who could more appropriately be treated with medical therapy, heart transplantation or other surgical treatments.

Thus, a major concern is the inappropriate selection of MCSD for patients who are either too well and

therefore subjected needlessly to an expensive and incompletely studied long-term therapy, or too ill, with multisystem dysfunction and a low probability of successful outcome, if decisions for implantation are made by individuals or institutions not truly experienced and expert in the allocation of therapies for advanced heart failure.

A proposal for a minimum set of requirements for MCSD centers has been endorsed by the ISHLT and the ACC heart failure and heart transplant committee is in agreement with its principles. We believe that an MCSD center should have

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an established heart failure program directed by a specialized heart failure cardiologist who has extensive experience in caring for patients with advanced heart failure, heart transplantation and bridging with potentially long-term mechanical devices. The qualifications could, for example, include documented experience at a transplant bridging center in caring for ten or more MCSD patients. An MCSD center must also have a cardiac surgeon with established expertise in MCSD bridging therapy. This minimal experience could, for example, include implantation and management of at least ten MCSDs as the primary implanting surgeon in a heart transplant center.

There should be required center reporting of chronic MCSD implant volumes and outcomes in order to evaluate the ongoing efficacy of this therapy. Participation in a national or international database on MCSD therapy is critically important for a proper identification of risk factors for adverse events and for predictors of favorable outcome.

Based on the above criteria, we envision that centers currently performing bridge to transplant MCSD implantation as part of an established advanced heart failure and heart transplant program would likely meet these requirements immediately. If MCSD destination therapy is deemed efficacious for a sufficiently large subset of

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advanced heart failure patients, additional centers wishing to provide this therapy could qualify by fulfilling the above requirements through the acquisition of appropriate surgical and cardiologic personnel, or through appropriate training.

The ACC appreciates the opportunity to testify before this CMS panel. Thank you.

Dr. Sox: Thank you very much, Dr. Kirklin. We will now go on to hear from Dr. William Baumgartner, from Johns Hopkins.

Dr. Baumgartner: Thank you very much, Chairman Sox. Good morning. I am Dr. Bill Baumgartner, a cardiac surgeon in charge at the Johns Hopkins medical institutions, and immediate past president of the Society of Thoracic Surgeons. I am speaking here on behalf of both the Society of Thoracic Surgeons and the American Association for Thoracic Surgery. We sincerely appreciate your invitation to testify at today's hearing regarding left ventricular assist devices for destination therapy. I have no financial interests in the companies presenting here today nor in any of their competitors. My transportation here today was fairly inexpensive and on my own. I have not participated in any other advisory committees or panels, and I have not been contacted by any panel members.

The last 30 years have seen remarkable advances in the diagnosis and treatment of heart disease. There remains,

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however, a devastating heart disorder that shortens the lives of millions more. Congestive heart failure, which now accounts for more than a quarter million deaths a year, remains one of our most difficult challenges.

We have carefully studied the results of the REMATCH trial. We believe the evidence clearly supports the use of left ventricular assist devices for the treatment of heart failure in patients meeting the selection criteria outlined in the trial. Challenging issues remain, particularly in the medical management of patients after implantation of a VAD.

I do not want to repeat the discussion of REMATCH data, which have been so eloquently presented. Let me discuss other issues such as dissemination of this technology, the criteria for qualifying centers and physicians, and the development of a database for quality improvement.

First, we support the recommendations of the International Society of Heart and Lung Transplantation summarized by the American College of Cariology by Dr. Kirklin regarding criteria. We agree that dissemination of this technology should be controlled. The patient selection criteria for the REMATCH trial should be followed. This technology should be reserved for patients for whom a transplant is not appropriate, but who have a sufficient life

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expectancy that they will benefit from the ventricular assist device, both in duration and quality of life. We in the medical community must insure that this technology be applied

only to these those patients for whom significant benefit is likely to be achieved. We suggest that Medicare approval of centers for implantation of LVADs be phased in an ISHLT and ACC have recommended. Although dissemination of this technology will inevitably occur slowly, such systematic and deliberate efforts will be essential to insure appropriate patient selection and the highest quality patient care.

Second, we believe that there should be established criteria for the experience and qualifications thoracic surgeons and other medical staff must meet before institutions beyond the REMATCH participants and transplant centers qualify to offer this technology. Our organizations have had experience in assisting practitioners in implementing new surgical technology in the past. In the late 1980s, video thorascopy emerged as a new technology for treating intrathoracic disease. The STS in 1990 convened a task force to evaluate this new technology and to find a scope of practice, develop a methodology to train thoracic surgeons who were already in practice, and establish criteria by which this technology could be successfully introduced into hospitals.

The STS sponsored wet-laboratory courses throughout

the United States and supervised procedures performed at the attending institutions before VADs could be added to the arm of that hospital. We in the thoracic surgical community recognize our responsibility and are ready to offer our resources to CMS in the development of standards for training and in facilitating the certification of surgeons who wish to embrace this new technology. We have already established work forces on the treatment of end-stage congestive heart failure and on clinical education. These work forces were designed specifically to facilitate such training and certification processes and can provide immediate input from experts in the ventricular assist utilization.

Finally, we believe that ongoing participation in a centralized clinical database is an important criteria, and therefore any surgeon wishing certification for VAD implantation must participate in a centralized clinical database. In accordance with HEPA regulations, patient confidentiality will need to be protected. Such information would allow for continuous quality improvement and further refinement of eligibility requirements. The adult cardiac surgical database of the Society of Thoracic Surgeons provides a model for clinical database development. This database now includes over two million patients who have

received coronary artery bypass surgery in the last 13 years, including comorbid conditions, disease history and other

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relevant factors. This database is used to review individual programs for quality improvement.

Despite the fact that we are now operating on older patients with comorbidities that make good outcomes more difficult, the mortality for this procedure has been reduced 23 percent in the last 10 years. Similar criteria for reporting patient conditions and outcomes developed from the REMATCH patient selection criteria will enable us to improve upon the already impressive results of the REMATCH trial. A VAD database would require longer-term follow-up, adverse events, and quality of life measures. The STS is now consulting with the ISHLT on further development of this database, which would be an extension of the patient registry already established by ISHLT.

In summary, we believe that the REMATCH trial has conclusively demonstrated that LVADs are reasonable and effective in prolonging life with satisfactory quality of life for a small cohort of properly selected patients. This criteria utilized in the REMATCH trial should be utilized for Medicare coverage. Coverage should be limited to institutions who have staff with demonstrated competence in selection and management of these patients, beginning with REMATCH participants and established heart transplant centers. Training for individuals must be provided and must be required for further dissemination to other centers so

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that appropriate patients are not denied treatment by geography or personal limitations. And finally, complete patient follow-up must be required through a thorough well managed database, so that effective efforts at refinement and quality improvement can be undertaken.

The Society of Thoracic Surgeons and American Association for Thoracic Surgery stand ready to assist CMS and the medical community as we move forward with a successful innovation in the medical and surgical management of advanced heart disease for our patients. I would like to thank, on behalf of the STS and the ATS, thank the committee for allowing us to testify today.

Dr. Sox: Thank you very much, Dr. Baumgartner. Our next speaker will be Dr. Robert Kormos, from the cardiac surgical transplant community.

Dr. Kormos: Thank you, Mr. Chairman and members of the panel. Good morning. My name is Dr. Robert Kormos. I'm

a professor of surgery at the University of Pittsburgh Medical Center and director of its artifical heart program and thoracic transplant program. Our program has had over 50 patient years of experience with the use of left ventricular assist devices, and were in fact the first center to manage patients with these devices as outpatients.

As past president of the International Society for Heart and Lung Transplantation and chairman of the work force on end-stage heart failure for the Society of Thoracic Surgeons, I have served on a number of panels and committees discussing the use of left ventricular assist devices, but none of these have addressed the question as specific to the one this morning. I do not own stock or have any financial interest in Thoratec or any of its competitors. I am on the medical advisory board, however, of Thoratec, World Heart, Cardiac Assist Technologies, VasCor, et cetera, and I have been supported financially for educational and some research grants from both World Heart and Thoratec. My travel expenses are covered by the American Society for Transplant Surgeons. I have not served on any specific panels other than today and have not been contacted by members here of the committee.

The American Society of Transplant Surgeons strongly supports Medicare coverage for the services associated with the implantation of ventricular assist devices as destination therapy, including the appropriate post-operative and outpatient care. We believe that the results of REMATCH clearly and unequivocally support extension of Medicare coverage for ventricular assist devices as destination therapy for those patients who are not eligible for transplantation and who meet the entry criteria for REMATCH.

We wish to emphasize, however, that these criteria are specifically employed and applied to patients who are not eligible for transplantation, and while REMATCH trials clearly established that these therapies work, a number of issues have to be resolved with respect to center criteria and the criteria of eligibility with respect to qualification of the surgeons and cardiologists who see these patients.

We believe that a number of the data that you've seen today show that there are complications and problems with these devices, and that the improvements in these outcomes can only occur by utilizing a controlled dissemination of the technology in centers experienced with

the use of these devices as either bridge to transplantation or destination therapy. An assessment of the severity of a patient's end-stage congestive heart failure is most appropriately made by a multidisciplinary team of cardiologists and surgeons who can make discriminating distinctions regarding extended medical or surgical therapy in lieu of a ventricular assist device or a transplant.

Likewise, an assessment of whether a particular patient is eligible for a heart transplant is dependent on clinical judgment and experience of the cardiac transplant team that does this assessment. We urge CMS to require that a patient be evaluated by a qualified cardiac transplant program to determine whether in fact the patient is ineligible for transplantation, and this determination should

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be a condition of coverage initially for implantation of the VAD as destination therapy.

We also wish to emphasize that the successful implantation of a ventricular assist device as destination therapy depends to a great extent on the experience and expertise of the team of healthcare professionals involved and on the institutional capabilities of the center where this procedure is performed. Currently ventricular assist devices are generally implanted in Medicare certified transplantation centers, and all of the institutions that participated in the REMATCH trial were in fact certified cardiac transplant centers. We caution that under these circumstances, if the Medicare program determines that these procedures are eligible for coverage in institutions that are not Medicare certified transplant centers, that CMS should require that criteria be met both by the surgical team and the institution to insure the quality of care provided. To that end, we do support the recommendations that you just saw by the STS and the ATS for qualification of the cardiologist, the team and the center.

We also believe that with the initial deployment of this therapy in REMATCH centers and those centers that do bridge to cardiac transplantation, that the lessons learned in patient selection, control of infection, post-operative and outpatient management, will be most reliably applied in

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the most efficient and rapid manner. This can only result in outcomes as have already been alluded to, that will be better than those already seen in REMATCH.

Finally, we agree with the principle that future evidence for further improvement can only come through

purposeful and mandatory reporting of outcomes. To that end, we support the mechanical circulatory support database registry as defined through the ISHLT and that you saw presented here by Dr. Deng, and we believe that this will be the most reliable way of analyzing that data.

I would like to stress that this statement was prepared by the board and the president and the directors of the American Society of Transplant Surgeons, and I think it's important to understand that this is a body that's dedicated to the other side of the coin, that is, the biological replacement and treatment of end-stage heart failure. And thus, it's extremely important that you recognize that their support of mechanical circulatory support and LVADs as destination therapy carries a significant amount of weight in that framework.

I would like to thank the panel, the ASTS would like to specifically thank them for the opportunity of giving their thoughts on this field and again, we strongly support the coverage of this therapy. Thank you.

Dr. Sox: Thank you very much, Dr. Kormos. We will

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now hear from Dr. Clyde W. Yancy, who is going to represent the American Heart Association.

Dr. Yancy: Thank you and good morning. My name is Clyde Yancy. I'm an associate professor of internal medicine and cardiology at UT Southwestern Medical Center in Dallas, a member of the national board of directors of the American Heart Association, and chair of the heart failure transplant subcommittee of the Council on Clinical Cardiology. I have no financial disclosures to report. My expenses were covered by the American Heart Association. I have not been contacted by any stakeholders with a commercial interest, and you should have received full testimony from us previously.

The American Heart Association is a voluntary health organization whose mission is to reduce death and disability from cardiovascular disease and stroke. With over 22 million supporters nationwide, our impact goal is to reduce events of and risks for coronary disease by 25 percent by 2010, in keeping with the goals of the Healthy People 2010 program. The American Heart Association is acutely aware of the well over 5 million individuals in this country who currently suffer from heart failure and the corresponding disability that that condition produces. With effective medical therapy for heart failure, the risk of death due to heart failure can be reduced by nearly 50 percent in the majority of affected individuals.

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We support the widespread use of these truly powerful medical treatment options and believe that this will substantially reduce the risk of death due to heart failure in our population. However, for the patient with fully advanced heart failure that you heard described this morning, the therapeutic options beyond comprehensive medical therapy have traditionally been limited to cardiac transplantation. The wait for transplant can be precarious and it is largely ameliorated with the use of left ventricular assist devices or VADs as a bridge for transplantation, a technique which allows greater than 60 percent of affected individuals to move forward with successful transplantation.

This success has now been extrapolated to an equally ill patient population that has been described this morning in whom cardiac transplantation is not an option. Application of left ventricular support systems could be hypothesized to prolong life, improve its quality, with no anticipation for removal. It is this use of the left ventricular assist device that constitutes destination therapy and for which this testimony is directed.

The support for the use of VADs as destination therapy is based on the REMATCH trial, the results of which you have heard extensively reviewed this morning. We believe the data are sound. Importantly, the REMATCH data identified the striking mortality risk for advanced heart failure,

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especially when treatment is limited to currently available pharmacological choices; this is a very real concern. However, the complication rate associated with VAD implantation was not trivial, even in the carefully selected and highly skilled REMATCH centers, one of which was my own. There is concern that the morbidity and perioperative mortality risk might be much higher in centers that are less specialized and/or have limited infrastructure for long-term follow-up and support. Nevertheless, there is a demonstrated benefit for an increasingly needy patient population with advanced heart failure. The highly selected patients cared for in experienced medical centers with appropriate multidisciplinary teams in place, the use of VADs as destination therapy appears worthwhile and we would support that.

It is our position that several caveats should be considered. The first is that these devices should only be implanted at centers with an established record of proficiency with VAD technology. Candidate selection should

be rigorously monitored and guidelines should be established with close adherence to the same in keeping with the patient population studied in REMATCH. Multidisciplinary teams are required to support the patient long term and these teams need to include expert nursing support and where needed, family support services.

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A registry should be established as has been proposed, and followed carefully for the discovery of new issues. An ongoing cost analysis is likewise desirable. New centers will likewise need to undergo careful scrutiny before being approved for implantation. The AHA has carefully reviewed the benchmarks recommended by the ISHLT for the approval of a center as a VAD implantation site, and we concur with those recommendations and support them.

As well, you have posed two voting questions and four discussion questions that have been addressed by the American College of Cardiology. We support the presentation by Dr. Kirklin. The AHA would like to make the case for ongoing research in this field. The public health implications of this technology are substantial, and adequate support for well designed clinical investigation is an inviolate requirement if this technology is to become entrenched in the cardiovascular alimentarium of the treatment of advanced heart failure. The same can be said for the medical therapy of far advanced heart failure. The very broad approach outlined in this testimony would allow for the provision of this beneficial treatment strategy to those patients who meet the REMATCH criteria while providing a platform that will move this technology forward, promote future investigation, and bring relief to more patients with advanced end-stage heart failure.

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On behalf of the Heart Association, I would like to thank you for the invitation and the opportunity to share our testimony with you.

Dr. Sox: Thank you very much, Dr. Yancy.

We have now earned ourselves a 15-minute break and we will reconvene about 20 minutes after the hour.

(Recess.)

Dr. Sox: Let's come back to order. Before we move on, I wanted to acquaint everybody in the room with something that we hadn't realized, and that was that Dr. Slaughter serves on the medical advisory board of Thoratec Laboratories Corporation. Sean and I talked with Mark during the break, and Mark, why don't you just describe what the nature of that

relationship is.
Dr. Slaughter: This had been revealed months ago, and they wanted additional clarification. Twice I have served on a medical advisory panel for Thoratec, I have not for the past two years. I have never used the device in question nor been a participant in the REMATCH trial, and have never received any money in any form, whether grant support, education, literally zero from the company.
Dr. Sox: So, Sean and I talked it over and we felt that this relationship did not constitute a significant enough conflict to ask Mark to recuse himself from the voting, so I just wanted all that to be out on the public

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record, and I guess if anybody feels that we're off base in making this document, now is the time to raise that issue. Otherwise, we will proceed.
We're now going to turn to open panel deliberation, which will give us a chance to start to talk amongst ourselves and with the presenters. We're going to start off by having a presentation from the two lead reviewers for the panel. Wade Aubry will lead off as our methodologic reviewer, and Mark Slaughter will follow him as the clinical reviewer. At that point I'm going to say a few introductory remarks before we get into the question period and then we will have an opportunity to ask anybody questions about their presentation as it pertains to our charge.
So, Wade, please.
Dr. Aubry: Thank you, Mr. Chairman. I'm going to talk a little about the REMATCH trial as well as react to some of the presentations we've had by our panelists up here in the front, and also by the invited public comments. And some of this will be repetitive but I wanted to highlight some of the areas.
Basically the evidence for LVAD as destination therapy is primarily the REMATCH trial. There were a number of supporting articles and guidelines that were provided to members of the panel and the public, but in terms of a rigorous trial that provides solid evidence, it's primarily

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the REMATCH trial with the January 2003 update that was provided to the FDA.
This is, as you've heard, a randomized clinical trial which was rigorously conducted in 20 experienced transplantation centers. Inclusion criteria of end-stage heart failure and contraindications to transplantation. A very long list of exclusion criteria, notably including the

body surface area of less than 1.5 square meters, and five patients who were added to the trial to increase accrual after 18 months. And also importantly, since complications were significant in the LVAD group, an independent committee reviewed the deaths and adverse events.

The key outcome measures, survival, function, quality of life, need for hospitalization, and adverse events. One of the questions for the panel is whether these are appropriate outcome measures, and I feel that they are.

Also, the appropriate question for the panel is whether the population studied in the trial was comparable to Medicare beneficiaries and it was, with LVAD average age of 66.

The only deficiency there is the under-representation of female patients. Approximately 80 percent of these patients were male.

The results showed median survival improved by approximately 8.5 months, Kaplan-Meier survival at one and

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two years, 52 percent and 23 percent in the LVAD group, versus 25 and 8 percent in the optimal medical management group. Notably, and this was brought up in Dr. Rose's presentation, that the two-year data was not statistically significant with a P value of .09; at two years, however, the follow-up data presented to the FDA in January 2003 was significant with a P value of .02 at 29 percent and 13 percent.

The New York Heart Association function was improved in the LVAD group and the quality of life data shows an advantage to the LVAD group despite adverse events, although sample size for the optimal medical management group was low. This is a point that I think the panel might want to explore further, and that is the patient-based assessments, only 6 of 11 in the optimal medical management group, which is a relatively low sample size and difficult to draw conclusions. The sample size was higher in the LVAD group.

Another significant issue for panel discussion is adverse events. With the LVAD group, more than twice as likely to experience adverse events compared to optimal medical management. The probability of infection in the LVAD group is 28 percent within three months of implantation and the probability of bleeding with LVAD was 42 percent within six months. As mentioned also, 41 percent of the patients in

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the LVAD group died of sepsis or infectional related

complications and 17 percent of device failure. So the probability of device failure was 35 percent at two years, which is significant. Also, as reported to the FDA, it is difficult to determine the optimal life of the device, which may be difficult to know when the device failure might occur. The LVAD was replaced in 10 patients.

LVAD patients spent more days in the hospital, but the longer survival translated to a greater absolute number of days outside of the hospital, which I think is important.

So in terms of the results and adverse events, I think the key issue was the significance of improved median survival and overall survival with a statistically significant at two years, but some issues relating to quality of life data which we may want to further explore. And in terms of the adverse events, the significance of infection and device failure, and this was partially addressed by Dr. Rose in terms of the adverse events being more likely to occur within the 30 days after device implantation, and having resulting in a better safety profile as time goes on.

So key issues, the evidence for LVADs as destination therapy in end-stage heart failure patients ineligible for transplant, I think the evidence is fairly good in terms of the randomized controlled trial and the evaluation of that and the follow-up data for that. The

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patient selection criteria for a recommendation for Medicare coverage will be important. The transplant evaluation to make certain that patients are not eligible for transplants. The question of facility and personnel criteria and requirements for outcome data for certification. Frequency of serious adverse events, especially as the technology is disseminated. Impact of advances of LVADs and optimal medical management; as mentioned, the drug trials for optimal medical management have not been promising to date. Mandatory data reporting.

And perhaps the most important questions that the panel will deal with, I think, is the impact of Medicare coverage on quality of care, impact on medical programs and quality of care as the dissemination of the technology will be very much influenced by Medicare coverage guidelines, and more flexible coverage guidelines do have the potential for adversely impacting quality if inappropriate patient selection occurs.

Some comments on the presentations. I think the REMATCH trial evidence level of evidence is an A, using the ABC rating, but the question is, will improved net outcomes

persist as LVADs for destination therapy disseminate to other centers. LVAD technology and optimal medical management will continue to improve and although drug therapy has not been promising to date, the implementation of guidelines more
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widely in Medicare population, the establishment of end-stage heart failure centers and quality improvement programs based on results in experienced centers will continue to improve.

There are concerns regarding liberalizing patient selection criteria to patients eligible for heart transplantation, and the recommendation has been made to have patients undergo a heart transplantation evaluation prior to determining whether they are eligible for LVAD for destination therapy.

There doesn't appear to be any controversy over the suggestion for mandatory reporting through registry as a requirement for coverage. Nearly all of the speakers spoke in favor of that. I didn't hear any negative recommendations for mandatory reporting. And facility certification should require a record of successful outcomes comparable to REMATCH, not just patient selection criteria but actual outcome data. And this would be consistent with Medicare heart transplantation coverage guidelines in which outcome data and volume is a requirement for certification, not just credentialing, appropriate background experience of the physicians and surgeons involved in the transplant center.

And one other consideration for dissemination, if the panel concurs that there is sufficient evidence to recommend Medicare coverage, and this would be a modified phase approach to the International Society for Heart and
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Lung Transplantation recommendations, a modification of number three, the first phase would restrict the coverage to REMATCH centers, second phase would restrict coverage to Medicare certified heart transplant centers -- and by the way on number one, I believe that all the REMATCH centers are Medicare certified heart transplant centers, but perhaps someone could verify that. The second phase would restrict coverage to Medicare certified heart transplant centers with LVAD experience in bridge to transplant therapy who demonstrate experience with minimum volume requirements and outcomes comparable to REMATCH. And then the third phase would open coverage more broadly to centers without heart transplant programs, but obviously coordinated with heart transplant programs for the initial evaluation, but who are able to demonstrate experience and outcomes comparable to

REMATCH.

So the key for this would be outcome data, volume and outcome data in addition to credentialing criteria for physicians, surgeons, basically experience of the center beyond credentialing of the individuals performing surgery. And then mandatory data reporting with recertification.

So, Mr. Chairman, that is a summary of some of the key aspects of the REMATCH study and a few recommendations for consideration by the panel for further discussion.

Dr. Sox: Thank you, Wade. Now we will hear from

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Mark Slaughter, who was our lead reviewer for the clinical aspects of the trial.

Dr. Slaughter: Thank you. I was asked to put a few comments on the evaluation of the HeartMate VAD as destination therapy. I tried to restrict my comments more towards the initial voting questions for today, and in particular those related to the adequacy of the evidence. When we look at the adequacy of the evidence as a clinician, there are certain issues that also become very important, the ideas, are these really statistically significant findings or are they somehow influenced by trial design and patient enrollment.

Two of the biggest issues that we need to look at are bias and external validity, which is also explained to us in our packet handed out to everyone today, and the other is the overall size of the health effect as it might affect Medicare.

When you look at adequacy of evidence, today the predominant discussion has been the REMATCH trial itself. There is some concern that in those patients randomized to surgical therapy, that there are only 68 patients and this is a relatively small group of patients, particularly when you look at the overall effect of heart failure in those patients that were theoretically candidates nationally. I think it's important, though, to note that provided to us in our packets

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is that there is other information out there available which is probably applicable. Certainly these devices are not new and have been used for a prolonged period of time.

One of the articles provided to us was certainly that published by, the primary author was Dr. Frazier, looking at the bridge to transplant experience. I think it's important because once again, it gives you a much greater cohort of surgical patients to evaluate and look at. Once begun, very similar to the destination therapy data, but in

many more patients, hundreds of patients, the survival to transplantation was approximately 70 percent versus 30 percent, and if you look at the average time on the device, it was 112 days. And there are 54 patients in this paper that were on a device for over 180 days. So the idea is that these patients had a significant survival, significant survival advantage, they did well, and their adverse events were very similar to the current study.

So, is there additional information that can be used and should be looked at, I think, in addition to the current REMATCH trial, and then I think the answer is yes, which gives us an additional body of evidence to evaluate.

Then the REMATCH trial itself, which has been the focus of most of the discussion today, certainly it is a very well designed trial and is a landmark trial as far as surgical trials go. It was multicenter, prospective

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randomized, and the two main important issues when we look at this patient population, because they have been able to define what appears to be sort of a terminal illness, it's not if they will die, it's when will they die, and that clearly has been the difficult part in all of this, is trying to clearly identify that patient group. So survival is a very important end point.

But in addition is the quality of life, and this is very important because it's one thing to say you have a few more survivors, but if they're all bed ridden, on tracheostomy in a nursing home, the answer is it's not really a benefit. So quality of life was also evaluated and I think with appropriate depth.

When you talk about multicenter trials, though, I think it's very important and it raises several issues, I think for the panel and worthy of discussion. The purpose of a multicenter trial for the most part is, it should be reproducible at each center. So the idea is, is this really a treatment option that is going to be available and reproducible at many institutions, not even maybe just the 20 centers, but other centers, because there are many more transplant centers in the United States and other centers of excellence that do a significant amount of heart surgery, but maybe at the moment do not participate in heart transplantation.

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So the issue comes up then, and the first question was that of bias within the evidence, and I think this becomes very important when you look at patient selection. I

think one issue, and to some degree it has been addressed, is why did it take three years to complete. If we look at our data that has been given to us, and there is 5 million patients with heart failure, half a million new cases per year, and somewhere around a quarter million deaths per year from heart failure, and the majority of these patients are all over the age of 65, why would it take three years to complete this study?

Partially this was answered, and the issue is how many patients were screened. The idea is, were these patients then truly directed towards these centers, is it really a viable option that can be used nationally, regionally, or at least in dedicated centers of excellence, and I think this needs a little more explanation.

The next issue was then, why was the criteria broadened? After 18 months the criteria was broadened to basically include less sick patients. Despite that fact, then only five new patients were enrolled over the next 18 months that met this less sick criteria, so what it sort of implies was that even though the criteria was broadened, the centers followed the old criteria and somehow got better at identifying very sick patients that were probably terminally

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ill but yet could tolerate an operation.

The other issue is women. The 20 percent is very consistent, essentially with transplant center data as well as just general cardiac surgery, but in this patient population in particular, I think it's very important, although it wasn't powered to evaluate them as a subset, it probably warrants a little more discussion. The women per se represented only 20 percent of the population. The issue, though, is did they have increased mortality and were they selectively not chosen. Just as an example, a woman at 64 years of age that weighs approximately 110 pounds and has a BSA of 1.5, 1.6, and creatinine of 1.8 certainly might meet the entry criteria, but certainly you would predict her morbidity and mortality would be significantly greater than a male that 64 years of age that has a BSA of 1.7 and creatinine of 1.8, because in general his creatinine has to be higher and subsequently he would be in a lower risk category.

The other issue is along the way, were these centers able to become better identifiers of survivors, i.e., using the women as example, is in the last 18 months, how many women were enrolled. If in the first 18 months the 12 women were enrolled and they all died, and subsequently in

the last 18 months no women were enrolled, then this would certainly induce some selection bias and affect the outcome.

The other is patient selection itself we were talking about, and that is age. Once again, the idea that the average age certainly is 68 years of age, but there were approximately 22 patients less than 60 years of age. Of those 22 patients, the one-year survival was 74 percent, which appears to be significantly better than the remainder of the population. So I think it would be worthwhile to discuss in general the overall age distribution and range, and once again, over the time of enrollment in that last 18 months, was there a trend towards younger patients being enrolled as opposed to still the 68, 70-year old patients.

The next issue that we ought to address as a panel is that of adequacy of evidence for external validity. And by external validity, what they're sort of implying is, does this apply in general to the Medicare population? Once again, there's the idea that this was a multicenter trial with 20 sites. Well, if there are only 68 VADs implanted at 20 sites, and it was evenly distributed, that means each center did 3 devices. This wouldn't give any center great experience, unfortunately. So the issue is, how many VADs were implanted at each site, were there differences between the sites? We've already talked about, there clearly was a glaring difference in the infection rate between institutions, and at two of the 20 sites, they had a significantly reduced infection rate, so this raises the

issue, does the overall improvement in benefit reflect just the results from these two institutions, or was this truly a global improvement in patient outcome compared to medical therapy?

Once again, the issue of age, the idea is, is this truly a Medicare patient population? There were a fair number of patients that were less than 60 years of age. So the issue is how many really were Medicare patients versus was this at least partially a younger population and not a Medicare population. And the other is women, the idea is, is this representative of the population in general and Medicare population, or was this trial really sort of the equivalent to the old VA trial where it represents surgical results in 60-year old men.

And lastly, the issue that we have to address as a voting question is the size of the health effect. There is no question that the study was very well designed and

statistically worked out ahead of time, so the issue is, is it statistically significant, and the answer is yes. But I think what becomes an equal or perhaps even more important question as a clinician now, is it clinically relevant? An example being I was recently reviewing a paper where there was a 30 percent improvement in exercise activity. Well, this sounds fantastic. If you look at the baseline distance the patient walked, it was approximately 20 feet. So that

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means now the patient can walk 25 feet. So they still can't go from their kitchen to the bathroom without being short of breath. So there is a difference between something that is statistically significant versus something that is clinically relevant.

Certainly the mortality was less in the device group and there are more survivors. The other issue, though, which I think we need to spend a little bit of time on and have discussion is the quality of life. Because once again, the quality of life becomes very important. And certainly I think to some degree they have done an exceptional job, and that is particularly looking at functional quality of life and the SF-36 in particular. As they pointed out, most of these patients are depressed. It's very hard to ask a depressed patient how you're feeling today and would you be happier if you had a different outcome, because the answer is usually going to be the same and they're glad they're alive and they will take the pills. So this quality of life becomes very important and probably warrants a little more discussion.

And I think the other issue that comes up which was not discussed today, for which there is some data available, though, is what is the cost per year of life. As was told to us today in our little premeeting, the CMS administrative staff has recently gotten a pay raise. However, this meant

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they couldn't afford to travel, so we couldn't have our orientation meeting yesterday. So we may be able to save some lives, but if the cost is so astronomical that it reduces services within the hospital or other services available to the patient population in general, this does become I think a relevant issue.

And I think I will stop there and leave it open to the rest of our panel.

Dr. Sox: Thank you very much, Mark. We have to be sure we can get those slides back at some point.

What we're going to do now is to have a discussion

that will focus on a number of things, but I want to start off the discussion by focusing on the quality of the evidence, because that's the voting question that we have to deal with. So let me just remind you what the voting question is:

Is the quality of evidence adequate to draw conclusions about the net health outcomes in Medicare beneficiaries meeting the REMATCH trial criteria who undergo LVAD implantation? So, is the evidence adequate to draw conclusions, those are the operative words.

Now what I would like to try to do is organize this discussion in a systematic way so that we kind of go through the various aspects of the trial and ask questions about one aspect, try to finish the discussion of that and then move on

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to the next, so we're not jumping around too much.

And so, the areas that I thought we would want to cover would be cohort assembly, how they assembled the study group; allocation, in other words, the randomization procedures; issues that have to do with comparability of the groups both at baseline and then as the study proceeded, dealing with issues of crossover and the like; deal with the ascertainment of outcomes, how that was done; and then finally, wrap up by getting into some of the issues that Mark raised at the end, namely, what are the meaning of the outcomes that we saw.

So what I would like to do now is start the question period by asking us to focus on how they put together this study population. And we heard, me for the first time, that they actually screened 968 patients in order to find 129 patients that were randomized. So, maybe I could ask you just to describe, what were the screening procedures you did? How did you identify patients to start asking the questions about whether they met the inclusion criteria or the exclusion criteria?

Dr. Miller: Patients in general were referred to each of the enrolling sites as a candidate for this potential therapy. They were treated for end-stage stage heart failure and I think the importance of this broad enrollment, there was no age discrimination, they were considered for

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transplantation at each site and found to not be candidates, and then a very important review for the adequacy of their medical therapy. And I think that was the importance of that slide, to say that many of those patients could have an escalation of current therapy and were not completely

transplant candidates or considered candidates for destination therapy. So, it was an open enrollment that referring physicians would refer patients to our centers for management of end-stage heart failure, and this was considered as one of the options for that patient.

Dr. Sox: Yes, Linda.

Dr. Bergthold: I'm curious as to what proportion of that original population were female or even minorities, because we haven't talked about the fact that most of these are older white men and that's certainly not typical of the Medicare population. So, I was wondering if there were women referred and obviously there may be other sort of barriers in society to getting women referred in the first place but what was the proportion in that 900?

Dr. Miller: I don't know that I have that right in front of me, but I think there has clearly been a lot of commentary about the access of women to cardiovascular care in general, but there was clearly not bias of trying to specifically see male patients or Caucasian patients. The referral base at that time probably reflects the demographics

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of cardiovascular care in each of these facilities.

Dr. Rose: The size criterion creates a differential selection just because of the higher prevalence of lower body size in women and just not being able to fit these devices. We do have data with regard to black and Hispanic patient enrollments. The black patient enrollment I believe was in single digits, and Hispanic in the teens.

Dr. Bergthold: Is there any consideration to a more proactive approach instead of sort of waiting for people to be referred, more of an outreach?

Dr. Miller: Well, we certainly have reached out to the regional centers and tried to, you know, get patients referred at an earlier stage in their disease. But I would remind you that these demographics are almost identical to what we see for heart transplantation today, even though this procedure has been done for 20 years in thousands of patients across the United States, it's still 80 percent male, largely Caucasian, and I don't support that as a good outcome, but that has been the referral practice, and again, the population of perhaps the greatest density of disease of this nature. There was no bias in trying to get patients of a certain demographic population.

Dr. Sox: I just remind panelists, if you want to be recognized, just put your hand up and I will put you on the list, and I think Cliff is next.

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Dr. Goodman: It seems that only 13 percent of patients referred actually chose to enroll, and how much of this drop-off was due to an informed consent process, which I assume may have discussed some aspects of anticipated morbidity and risks associated with being randomized to the LVAD side. And I'm asking that question now because we want to understand how the allocation took place and I may want to follow up later, wondering to what extent that similar kind of process, ala informed consent, might be used in the field should this procedure be used more widely.

Dr. Rose: First, with regard to the randomization process or the screening process, rather, the predominant reason that patients were not eligible for this trial were not because they refused to be randomized but because they didn't meet entry criteria, either because they were too well or too sick. There was a small number of patients who did refuse randomization, and they were about equally distributed between people who either definitively wanted a device or definitively did not want a device and therefore did not want to enter the randomization process, but the number of such patients was small.

Certainly one of the things that defines this population is that they were patients that were willing to be randomized, and I'm not sure that that necessarily introduces a particular set of identifiers to prospectively generalize

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this to a larger population, but that's true of any randomized trial.

Dr. Goodman: The informed consent process took place when, and did it include just briefly some description of the morbidity risks associated with the LVAD?

Dr. Rose: The informed consent process occurred obviously prior to the patient's decision to participate in the trial, but it was a remarkably straightforward process. I have a copy of the consent form here. Contrary to rumor, this was a very simple informed consent, it was six pages long, it was designed to be about eighth grade reading level, and it enumerates the purpose of the study, which was essential to identify whether or not there was a survival and quality of life benefit to the intervention or not. And it in detail enumerates the adverse events that were possible for both forms of therapy, for both the device and for the medical management.

There has been some discussion as to whether or not we ought to use this as a template going forward for informed

consent, and this is clearly an outdated document. It was based at that point from the position of whether or not the two interventions were different or not. That question we think has been answered. So the REMATCH data essentially we think, ought to be part of an informed consent process going forward, where patients would be informed of the magnitude of

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the benefit that has been observed, as well as the frequency and nature of the adverse events that they can suffer, but it then becomes their choice to make in the face of that information.

Dr. Goodman: Thank you.

Dr. Sox: Alan.

Dr. Garber: I think every one of the speakers addressed the issue of patient selection for the trial and it's spelled out very nicely in the REMATCH publication. What I am curious about is, there have also been the statements about how this should be done in highly qualified centers. What I'm curious about is how difficult is it for another institution to follow the inclusion and exclusion criteria the way they were followed in the context of the trial? Were there very extensive ongoing discussions to insure that in each center that the inclusion and exclusion criteria were applied in a consistent way? Several of these criteria seem to be very objective, like I presume an ejection fraction or a radionuclide scan, and others somewhat more subjective. How difficult is it to insure matching locations and other settings to the REMATCH criteria?

Dr. Miller: I think it would be fairly reasonable to expect that those, as you said, many of these criteria are objective. For example, listing for heart transplantation, the oxygen consumption has to meet a qualifying level, and

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inclusions are described as they're on X medicines and so forth. Perhaps the nuance that's most difficult is judging the irreversibility of end organ function, and that is a complex issue even in transplant centers, but much of the criteria are fairly well defined and quite objective.

Dr. Rose: I think if you asked that question ten years ago, it would be hard to answer it in the affirmative. With the proliferation of interest and information and the treatment guidelines for heart failure, I think this is information that is being disseminated and being followed by a professional community that would want to get the best outcomes, and that these selection criteria can be put into protocol.

Dr. Sox: Dr. Miller.

Dr. Miller: I just wanted to come back on Dr. Goodman's comment or question regarding the consent process. In each center, it was probably at least four different individuals that reviewed the potential risk-benefit ratio, including the cardiologist, independently the surgeon, independently the nurse coordinator, and in almost all circumstances because they were done in centers that had patients with the devices in, they would talk with families and really get a true portrayal of seeing the device, what would it look like, what would it seem like to the patient and so forth. So I think that there was an extensive

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opportunity for them to truly understand what they were beginning to be involved in.

Dr. Sox: I think that the thrust of Dr. Garber's question was the degree to which there was standardization across centers about how to frame the questions that dealt with inclusion and exclusion, how to interpret the results and the process that led to deciding that somebody should be asked do participate. Can you just say a little bit more for that for the record?

Dr. Long: There were two levels of control, if you will. One was the use of guidelines and protocols, and the other was a gatekeeper, which Eric and I referred to. Clearly the guidelines and protocols would exist in the dissemination process. In the dissemination process you wouldn't have that same gatekeeper role per se, although as part of the dissemination process that's been discussed here today, you would have some analogy to that with a relationship with a center of experience, so that if there were a new center to come on board, it would have an existing relationship with a center with experience that would help act in a guiding role and to some degree simulate what was available in that gatekeeper role.

You know, the final check remains one of monitoring and making sure that in fact you are meeting performance specifications, are enrolling according to guidelines, and

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are getting outcomes that you are. I think in summary, we would think that the guidelines are applicable broadly; however, in the early phases of dissemination, there would be the loss of some of those controlling elements that were present in this trial, and some effort ought to be introduced to maintain a degree of control until this is responsibly disseminated.

Dr. Sox: Just so everybody knows where we are, we are going to continue to work away at questions related to cohort assembly and how that might be generalized in the dissemination period. When we've exhausted those questions, then we will move on to another aspect of trial design. I think Norman Daniels is next.

Dr. Daniels: Yes. Is there any accessible data that explains a little more clearly in the sorting out process from the 968 who were screened down to the 129 who were randomized? For example, I'm interested to know what role in particular the body size criteria played in exclusion, whether that for example worked more heavily against women than men and so on. So that's one piece of it. And if one were to try to disentangle any information about bias in the cohort assembly, then it would have to come out of looking at that data more carefully rather than just having the gross numbers having to pare down. What were the reasons and were there differences across subgroups, for

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example by patient age, by gender and so on?

Dr. Rose: Well, we do not have an extensive data set with regard to all the patients that were screened. It was outside the purview and funding, frankly, of the trial to gather extensive data on everyone who was screened, and it would have required an informed consent process to gather the kind of data ultimately, that we'd all like to estimate to look at the way these populations did.

With regard to the issue of bias, what Paul Meier instilled in all of us who participated in this trial was that the great overcomer of bias in this trial, this is a randomized trial, so whatever biases you may say were brought to the selection over time, it was a randomized trial.

The other thing is, with regard to the patient characteristics and outcomes of the trial, there was a blinding process. Neither I as the principal investigator, nor the investigators in this trial during the course of our doing it, at any time were aware in the aggregate other than our own patient experiences, what was happening with the overall cohort. So while it's possible, I don't think there was any systematic generation of knowledge that could have influenced the patient selection as time passed. And again, if it did, it simply brought a different type of patient to the randomization.

With regard to the selection of women versus men,

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there is no question I think in anybody's mind doing this

that the size criterion is a bias in terms of selection against women. There are just more women candidates that don't meet the body surface area criterion.

The other question, I'm not sure this specifically fits, but is has already been raised as to whether or not this loosening of criteria reflected some injection of bias. I think it's important to point out that we didn't view this as a loosening, but rather a refinement of criteria. The patients who entered this alternative group were quite sick. What we had noticed is that one of our initial criteria required three months of Class IV heart failure symptoms and we were seeing a cohort of patients that we thought would have been good REMATCH candidates who had Class IV symptoms for somewhat less than four months but who were spending weeks to months in intensive care units trying to get to that 90 days of symptoms criterion, and what was happening is that they were all dying before they could become candidates. So the judgment was made that we could extend that criteria to patients who had 60 days of Class IV symptoms, or if they in addition had been in intensive care unit on inotropic support for at least a month, and five people met that criterion. I think you would be hard pressed to say necessarily that these people were any less sick, you know, perhaps a little bit more acutely ill, but in terms of prognosis, our anecdotal

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experience had been that by excluding them, we were just letting them all die.

Dr. Miller: The other variable criteria that was altered at the same time was this peak oxygen consumption performance, and the original goal was to be less than 12. It was increased to up to 14, which is still below the current recommendations for heart transplantation, but I would remind you that the average in this study was a PPO-2 of 8. So these patients, 12 to 14 didn't make any difference in enrollment, they were still critically ill, and all of them were well below current transplant guidelines.

Dr. Long: I might add one feature about the issue of bias that's important for me. This was the first trial in the circulatory support field where we had the entry of cardiologists in a formal way. At each center there were co-equal cardiologist and surgeon investigators, insuring that there was best therapy on the medical side, insuring there was best therapy on the surgical side, and bringing the biases in perspective that might come from each of their dimensions together and meeting them head on.

Dr. Sox: Just a comment, that randomization deals

with the problem of internal consistency, but it doesn't deal with the problem of generalizability. For example, if surgeons believe that older patients aren't likely to be accepted as transplant candidates then you're not going to see them and it's going to be a relatively small representation of Medicare aged patients.

So, I think unless you want to respond to that, I will move on. I think the next person is Ileana.

Dr. Pina: I have three questions, but I think to clarify for the panel, what percentage of patients that ever get referred to a transplant center for transplant actually get transplanted may help sort out this large number of 900 to a number of 129, so do you want to comment on that first, and then I'll ask you the other two?

Dr. Miller: I think that's a moving target, Ileana. The average, I think over the last decade has been somewhere around a third. We have been happy when we have better educated our referring physicians and it has gone up towards 50 percent, but we've seen it frequently go back down to 30 or below that actually get on there. I think when it's lower it's saying that we're doing our job and these people are well treated.

Dr. Pina: I just thought that that might clarify, you know, the big pool to the small pool. Now, knowing how many transplant centers have different characteristics for acceptance, and that some transplant centers have been moving to transplant the older individual more and more, and you know who these individuals are, and the fact that in your paper it talks about the patients that were not transplant candidates was more likely to be because of age. We're talking about a Medicare population, so in transplant centers that would accept patients up to the age of 70, which has been done quite extensively, how many of those centers were in here? Because this is a very critical part of this decision, who is the transplant candidate and who isn't? And somebody may be deemed not a transplant candidate because they are 65 in Center A, but if they moved over to Center B, they'd be transplanted. And I think that's a very important point for this population.

Dr. Miller: Another moving target has been the evolution of age in the assessment of transplant candidates, and clearly it's drifting because of the age and the amount of hemodisease. The average recipient is now in their mid-50s for transplant, but I think a number of reports have

documented that advancing age represents an independent risk factor for transplant success and outcomes, whether it's renal insufficiency or other things that would be complicated or further worsened by immunosuppressive drugs, the older they are, the more adverse risk factors they bring and perhaps the less well they do.

Conversely, you look at patients individually. There may be someone who is incredibly viable and well preserved and had an acute ischemic event, and that is the reason we said they should be deemed by a transplant center

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who has experience in evaluating those patients, that regardless of the age or the overall circumstance, they are considered to be or not to be a transplant candidate, where a transplantation may be appropriate in someone 68 who has no comorbidities. Someone else who might be 67 may have a composite that says that we would not undergo transplantation as a very good option, and refer them for mechanical support.

Dr. Pina: Do you have any information in the 20 centers that were involved in REMATCH how many had strict criteria for age? Because I know those centers too, that they would not have transplanted anybody over the age of 65 no matter how viable, and from our CTRD data you know that they also do well if they get through the perioperative period, they reject less. So Eric, you may want to respond to that.

Dr. Rose: When we started enrollment in the trial, all the centers had a policy with regard to not transplanting patients over the age of 65. I'd say by the time that we finished the trial, virtually none of the centers had a policy with regard to restricting transplantation to patients younger than 65. That notwithstanding, I think the patients who do get transplanted over age 65 are usually -- while they are in the older group, they have nothing else wrong, and the universe of patients older than 65 typically usually does have some other comorbidity that would preclude

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transplantation.

Dr. Miller: I think that also is what brought this same review in the study, that you saw 68-year old patients that were, many of them were turned down because they had the same kinds of collective comorbidities that would have turned them down for a heart transplant, and I think that's part of this process, is looking at them in the same context and having that experience of reviewing that they are in fact too sick for any type of advanced therapy.

Dr. Pina: And my last question on this group, we talked about a gatekeeper. How many patients do you know that were referred to the gatekeeper, did the gatekeeper say no, these are not good candidates for the REMATCH trial?

Dr. Rose: It was, I would say an active process. There was gatekeeper input into inclusion, or at least the evaluations obviously, of every patient that was enrolled, but they were not -- of the screening from 968 down to 129, the overwhelming majority were not because of the gatekeeper intervention. The judgments were made at the centers.

In terms of the gatekeeper function, I think to generalize the gatekeeper function, the reason that we're advocating that there be a -- first of all, the gatekeeper was a cardiologist. I think it's very important that that be recognized, and it was someone who was identified to have expertise in state of the art medical therapy. In order to

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generalize this, we're recommending that centers and programs that do this have a cardiologist that has essentially the skills and knowledge set of the gatekeeper in REMATCH, which I think is a generalizable skill set, and that this not be simply done as surgical programs and institutions, that there needs to be that function of someone with expertise and knowledge of what's available to treat end stage heart failure as part and parcel of the program.

Dr. Sox: Steve Gottlieb.

Dr. Gottlieb: A number of the public speakers suggested that the REMATCH criteria should be the criteria for the future, but it's obviously clear that the criteria are very different than what the patient population was. You already mentioned peak VO-2 of 14 as the entry requirement, but an 8 as the mean. Clearly just looking at the study and comparing it to other studies which had similar entry criteria, it was clearly a very different population, I mean the placebo mortality rate is obviously different, so I think that it's important, and while we're talking about 68 people in REMATCH and clearly if we start going into subgroups, this is a potential problem. But I think that we have to figure out who those patients are and I guess my first specific question is, we had two-thirds of the patients were inotrope dependent, a third weren't. What was the placebo mortality rate in that third?

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Dr. Miller: It has been an issue that caught a lot of people's attention, that two-thirds of the patients were on inotropes, and some early suggestion that in fact they

were the population that were the sickest and would have the best potential gain from this procedure, but in longer-term follow-up, when you look at the patients who were pulled off inotropes and consider them to those who remain inotrope dependent, there was no difference in the outcome and benefit in the medically managed patients or the LVAD patients, so we can't use inotropes alone as an indication of the population for whom this therapy should be applied. I think that if you stay within the guidelines, we found many patients who were not on the brink, or they had PCO-2s of 15, they were often very advanced heart failure. But I think that we're able to use these criteria and derive a population who should see a substantial benefit from this therapy. Does that answer your question, Steve?

Dr. Gottlieb: Well, I have a problem because with these criteria -- I mean, you know, the next study was the prostacyclin study, which had really very similar severely ill patients and you have a 50 percent mortality in there instead of your 75 percent, and you lose the benefit if you end up with a placebo. Even in your study with a gatekeeper and everything, you have 20 percent of the people who somehow have reversibility, and you weren't able to identify those

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patients. This is a very sick population, this isn't a population that meets criteria of a peak VO-2 of less than 14 and Class IV heart failure. I mean, there is something about that them that may be very subjective and I'm certain it was in the way that the investigators enrolled people, but when you broaden this, I'm just -- I don't know how to define that.

Dr. Miller: One shot at that. Donna Mancini has looked at some of the factors that have influenced outcome, regardless of the assignment but particularly in the medical group. And the inability to take an ace inhibitor was a tremendous adverse population, and that's a third of the people that were in the study. And we somewhat had that inference, but it may identify that cohort you're following that identified the group for whom this therapy are not inotrope dependent but already have identified a very high risk population. Similarly, all of the cardiologists in the program are tremendous supporters of beta block, you had to be on a beta blocker or been through that trial to get enrolled in the study. And so, I think if you say inability to tolerate a beta blocker and/or an inability to tolerate an ace inhibitor identifies a population who will probably get closer to this peak VO-2 criteria and therefore, derive what

we think is a benefit. But I think we're getting a lot closer to identifying a risk population not necessarily at

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the end stage of inotrope dependence, but for whom this therapy would perhaps provide a substantial benefit over what their medical outcome might be.

DR. GOTTLIEB: How about renal function? Because I mean --

DR. MILLER: Creatinine was 1.8. Again, every time we looked at that data, it was really nicely shown that that is a tremendous risk factor to escalating mortality. So the composite, if you look at the outcome in bridge to transplant, patient selection is unequivocally the most important determinant of outcome and we're beginning to identify a consistent story of creatinine and renal function as being one of the variables that identifies the poor outcomes. So again, when you look at a composite of no ace, no beta blocker, poor creatinine, that population may be the ones who will benefit the very most.

Dr. Sox: Joanne.

Dr. Lynn: I have a few questions trying to understand this. First with regard to the 90 days which got, even during the study, shortened to 60 days, that seems a remarkable period of time to stay in bad Class IV failure. I'm not at all surprised that you had a lot of deaths in it. That seems to be the group that, the criterion that is most obviously going to be difficult to sustain. It would seem that in real practice we would go to -- pretty quickly we'd

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be down to 15 or 20 days. What was that like? Were most of these people in ICU or were they on palliative care throughout trying to reduce their symptoms? I mean, what is it like to keep a person in Class IV failure for 90 days?

Dr. Miller: It's pretty horrific. I think that I'm impressed that the quality of life estimates in these patients were as good as they were, because I think it is one of the most limiting morbidity associated conditions and has been shown in this, if you look at the mortalities within 30 days, there were a number of the patients who were lost that might have been credible candidates for the study, that during the evaluation process, were really unable to be supported and sustained to be enrolled in the study. It is remarkable that -- I don't know whether the panel appreciates that many of the patients were self affirmed, for whom physicians felt nothing could be done and were languishing in very advanced, very high limitation in their day-to-day

functional life style, and even in the hospital in ICUs with multiple interventions.

Dr. Lynn: Was it a piece of the protocol to provide for preparations for death, advance care planning, do not resuscitate orders, so forth, during that period of time?

Dr. Rose: Yes, for both arms of the trial, and there were patients --

Dr. Lynn: Even before entry, in the 90 days ahead?

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Dr. Rose: No, it was not protocolized to state that they had to have end of life counseling.

Dr. Lynn: Once in the study, thought, you did have advance care planning?

Dr. Rose: We did, absolutely.

Dr. Lynn: What sorts of rates did you get?

Dr. Rose: Excuse me?

Dr. Lynn: What sort of rates? Did all 129 have plans for what to do for a stroke or what to do for a cardiac arrest?

Dr. Rose: I don't know the answer to that. Certainly this was something that was, I would say -- I'm not sure we have documentation around it, but I think there were the questions that were asked by patients appropriately and was brought to patients' attention appropriately, and most importantly, a lot of people acted upon it in both groups. In both groups, there were patients that chose essentially to stop either support with the device or to terminate their medications or inotropic support and to let their disease take its course.

Dr. Lynn: I will have a question on that one later.

In the construction of the cohort, a couple other questions. One is, Dr. Slaughter mentioned earlier with the split at age 60, which of course is not a relevant split for

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Medicare, if his data are correct that 74 percent of the people survived who were under 60, then 39 percent survived past 60, so what is -- the relevant piece, it seems, is how many people were over 65, and especially how many were even a little older, because the peak age of death of heart failure is 70 to 80. Do you have substantial numbers of people in that age range?

Dr. Rose: Only approximately 20 of the entire 129 were patients that were less than 60, and they were patients who had a contraindication for transplantation, for example a previous malignancy, reasons that they -- or complications of

diabetes, which rendered them transplant ineligible. Of that cohort, only half got a device.

Dr. Lynn: How many at 65 or 70? What does this curve look like.

Dr. Rose: There are three specified age strata that were evaluated as part of the analysis, the less than 60 age group as you've heard, which had a 74 percent one-year survival, which we were absolutely quite thrilled by, and almost a 40 percent two-year survival. But that difference was not statistically significant, it was not powered to look at that. The largest cohort was between ages 60 to 69, and there the survival benefit was, even within the substratum, the survival benefit was statistically significant. And the final stratum, which also showed a trend but not statistical

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significance, was in patients older than 70. That was the smallest cohort.

Dr. Lynn: How many people?

Dr. Rose: I believe it was about 70 patients, 70 or 80 patients in the 60 to 69 age group; it was by far the largest of the three strata.

Dr. Lynn: So something on the order of 29 people were over 70?

Dr. Rose: I just don't have the age stratification.

Dr. Lynn: Do you remember what the --

Dr. Rose: The average age, the mean age was 68, as I remember on the device, and 66 in the medical managed cohort.

Dr. Pina: I just calculated 57 were over 70.

Dr. Lynn: Well, we can come back later to what the rate of their survival was.

Dr. Rose: And all three -- there was not an age stratum, unlike other trials which for example, the shock trial found that patients older than 75 were actually done harm by revascularization in the face of shock. There was no age stratum either prespecified or not prespecified that we could identify that would show that you shouldn't, you know, that there was not a survival benefit to having a VAD.

Dr. Lynn: Yeah, but it would turn somewhat on how

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big a survival benefit, Medicare's decision will turn somewhat on how big the survival benefit, so it isn't just that there is one.

Dr. Rose: No argument.

Dr. Lynn: The last couple of things I was

concerned with, there are always in these trials, it seems effective exclusions that aren't necessarily in the list. Obviously one of these is the person has to survive the 60 or 90 days, but in addition they had to actually get to a center and they had to be able to be supported at the center. These are very sick people. Did they all come by ambulance, or were there provisions for their families? How strong a selection bias is it that you had to be able to get to one of these centers? You know, people who were old, poor or frail, poorly connected weren't showing up?

Dr. Rose: I think it is a selection bias but many of our centers, like ours, are in neighborhoods filled with old, poor, frail people that get taken care of by a heart failure service.

Dr. Long: And some of our centers that are very remote or sparsely populated, where we have a great number of outlying centers, we worked as a very important part of the trial to make sure that we had people working with us in cooperation. We even had cardiologists who would be partners with us identifying these patients out there and giving us

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access to those patients. We wanted to make sure there was not a limitation on the front end. We also didn't want a limitation on the back end, returning these people back to their communities, we did not want that to be a selection bias either. We were able to effectively achieve that in the vast majority of these patients.

Dr. Lynn: That's reassuring. What would you say about personality disorders, mental illness, difficult family situations, is it important that these patients have a demonstrated evidence of compliance in their setting?

Dr. Miller: They were all formally evaluated as part of the panel, much as we would with, again, heart transplant patients, to look at psychosocial support, compliance profiles, and other things that would distinguish them as being high or low risk for successful outcome of the procedure. But it was a very thorough evaluation by healthcare professionals to ascertain that on a formal basis.

Dr. Long: That's why we've identified the input of people with psychosocial capacities expertise to help assess these patients. We believe that's an area of critical and important concern, that these people have the capacity to function well, have the support that they need from their families, and we felt that was a very important selection factor, that we wanted to make sure there was an adequate support structure for them.

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Dr. Lynn: My last question has to do with clarifying something that Dr. Rose was saying earlier about this 986 down to 129. You were implying I think, although you didn't quite say this as clearly as I'm sure I'm understanding, that most of the patients improved with optimal therapy and --

Dr. Rose: No, we don't know that. We don't know the outcomes in the patients that were screened but not enrolled in the trial. I think some of them were judged that they were too well; our prediction would be that their outcomes would not be as bad as the OMM group in REMATCH, but we just don't know the answer to that. And others were even sicker where you know, we had many patients actually that, you know, part of the logistics of REMATCH was to get the screening process to be short enough so that patients did not die in the process of the screen. You saw what the mortality was even in the first 30 days for patients randomized to the OMM group, so --

Dr. Lynn: But you did say something about a large number of them, when you got them on optimum therapy, they improved enough.

Dr. Rose: Any coronary service that's seeing this type of referral patients, there are many patients who come who are not being treated according to guidelines that -- you know, just the fact that we had somebody show up at our
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doorstep who was in pulmonary edema basically at the time he arrived for the evaluation who was not on enough diuretic, he was not on an ace inhibitor, he was not on a beta blocker and he was put on these, and as you would expect --

Dr. Lynn: Do you have any rough estimate of the portion of that --

Dr. Rose: Again, this was not a study of the nonrandomized patients. I mean, it was just outside our purview.

Dr. Miller: I think again, you can go back to my response to Dr. Pina's question, that it may be somewhere between 20 or 30 percent, or conversely, 70 to 80 percent of the people that we see sent in for transplantation actually get on a list, there's that much response. We were a high enrolling center, had a lot of referrals, and I would say that it was about 50-50 of patients that we felt we could definitely improve their medical regimen and they would do well, and a substantial percentage that came to us very very late and their disease had advanced.

But the proportion of patients, I don't know what the total number were that declined enrollment in the study, it was by virtue of the request to not go into a randomized trial. They had already failed every medical regimen we had available, and that was a small percentage, but it was much more of that than refusing to get into the device arm. They were looking for the device.

Dr. Sox: We'll have a couple more questions on the issue of cohort assembly.

Dr. Rose: I think it is a paradoxical effect of creating programs of high intervention like this, that part of the unexpected dividend is you get patients identified who were just not being treated according to medical protocols in the first place. It would seem almost counterintuitive that the less ill patients would get better care because of such a complex intervention, but it forces a discipline on the evaluation because of the rigor of selection criteria, that patients who could get better treated with other methods, by coming into a programmatic approach to the end stage of disease often have the dividend of being identified as candidates for what's already out there as medical therapy.

Dr. Sox: Louise?

Ms. Woerner: Yes, thank you. You've talked about this in a variety of ways but I just wanted to ask if you would report your experience a little bit differently. Your original goal was to have, I believe 140 people or maybe some more, than you selected. What was it that caused you to decide that you were not going to be able to achieve that goal and what were the primary barriers on the enrollment?

Dr. Rose: The power calculation as that we needed 140 patients to have a 90 percent power to document the benefit we had hypothesized, but the primary end point of the trial was a fixed number of deaths, and when those were reached, enrollment was stopped, it was not stopped by a DSMB or was not a willful -- this was a protocolized decision, that when we reached a given number of outcomes, that was when we stopped enrollment. That's why we did 129.

Ms. Woerner: Did it have to do with the speed of the enrollment against the speed of the deaths?

Dr. Rose: That's correct, and the speed of the deaths actually was faster than enrollment.

Ms. Woerner: So, what was -- when you started, you thought you would get the enrollments before you would get the deaths, I assume?

Dr. Rose: We thought we would get a reasonable enrollment; we did not know whether or not we would exactly get up to the 140 or not. We certainly thought it was a possibility that we would reach our end point before we enrolled all 140. It was also possible that the DSMB would have stopped the trial earlier. As it turns out, there were four prespecified DSMB reviews of the outcomes, and the survival benefit actually in retrospect was apparent at the time of the next to last DSMB review when three-quarters of enrollment was completed. And I think wisely, the DSMB chose not to stop the study at this point in order to allow the gathering of a complete set of quality of life data and not

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raise the issue of a controversy that a premature stopping of such a controversial trial would have generated.

But this trial was not stopped prematurely, I think that's a commonly held misbelief.

Dr. Sox: Ileana, last question on this topic.

Dr. Pina: I just want to clarify for the panel that even though the entry criteria was a little bit more than the VO-2 of 14, VO-2 of 14 is more for the broad population of transplant patients. In this population, of the 60s and 70s, a VO-2 of 14 may be normal and adequate for a small woman, for example. And therefore, I am not at all surprised that they ended up with 8, because that's more appropriate as a sick population. So as part of the entry criteria, it's understandable.

Dr. Long: Let me just add one thing to put in perspective this issue of meeting the original criteria. While in some cases, for instance VO-2 max, you ended up with a worse population than originally specified in the criteria. On the other hand, with renal dysfunction, creatinine up to 3.5 were allowed and the average, as you saw, was 1.8. so there is a condition where you have gone the other way and you had a less ill patient population than the criteria might have originally specified.

Dr. Sox: Well, let's move on --

Dr. Gottlieb: Wait. Can I clarify that? I think

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that's misleading. I mean, that was an absolute high point of the 3.5 that you had. A 1.8 mean creatinine is probably why you got the high mortality that you did. I mean, that is a sick population. To say that this was a less sick population because the mean creatinine was not 3.5 --

Dr. Long: My point simply was that while on one hand the criteria were more liberal, or the experience was

more liberal than the criteria, it went the other way as well, where the criteria were also more conservative than the actual experience.

Dr. Sox: Well, let's move on. We took quite a long time on that, but I think it reflects the importance of the subject, and I can't resist the temptation to say that I wish that you had been funded to do a more careful data set on the process by which you assembled the cohort, because it would help to decide issues of generalizability.

Let's move on to the allocation procedures. This was a randomized study using a block design, stratifying by centers so that roughly the same number of patients in the two groups ended up, the proportion of patients ended up in the same center.

I wanted to ask a question about allocation concealment. What steps were taken to be sure that somebody who was enrolling a patient wasn't aware that the next person was going to be an LVAD patient or a control patient?

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Dr. Rose: The randomization was done, the envelopes were pulled at the data coordinating center. There was a Chinese wall between the data coordinating center and the clinical coordinating center, and there was no communication that I'm aware of either that had happened or even could have happened to allow centers to gain essentially what their next chip would be.

Dr. Sox: So basically a patient's assignment was in a sealed opaque envelope?

Dr. Rose: Absolutely.

Dr. Sox: A detail that wasn't mentioned in the New England Journal paper and is often omitted.

Dr. Rose: We can provide you with the protocol information that outlines that precise process, but we were sensitive to that.

Dr. Sox: So, other questions about how patients were allocated to the control group and the intervention group? Mark?

Dr. Slaughter: I just want to follow a similar concern number wise. If you say, though, each center, the idea is it's going to end up being 50-50, and you're anticipating that center is only going to enroll six patients, then theoretically the block wall, their group of envelopes, they have six envelopes assigned to that center, they can't have 50 because otherwise that center, many

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centers may end up with only VADs or only medical therapy.

So the idea is if you're an implanting center and you have just enrolled three patients that were medical therapy, in the back of your mind when you see the next patient, you realize that you've got an awfully good chance of putting a VAD in this next one. Is that not true?

If each center is its own randomization site essentially, they are not pulling the envelope, but if I know I'm only enrolling eight -- we are currently participating in a trial that's very similar, and I can tell you after two patients, I know what the next one is going to be, and I will be right 90 percent of the time.

Dr. Rose: We don't have our statistician with us. Exactly this whole issue around, you know, can someone gain this based on what's happened with the last three patients resolved the issue. I can't explain necessarily the details around how the blocks were specifically done, but that methodology is available.

Dr. Long: The way it worked out in almost, in the vast majority, especially the high enrolling centers, there was about a 50-50 distribution between OMM and LVAD in the final analysis.

Dr. Rose: And the blocks were not exactly 50-50. As you saw, we ended up enrolling 68 VAD patients versus 61, so there was some variability.

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Dr. Miller: And there was no finite number of enrollees per site, so you didn't know that you were going to have seven or five, and so where you were at any specified time did not indicate how many more you could enroll or what that outcome might look like.

Dr. Sox: Other questions about allocation procedures? Cliff.

Dr. Goodman: Just a point of clarification. I think we understand this. First of all, with regard to what you knew was coming from the next envelope, you probably didn't because you didn't know if you were at a center and you had six envelopes, you didn't know the distribution of less or what the allocations were among the six, so you couldn't know -- if you knew what the answer was for the first envelope, that didn't tell you anything about your second envelope.

Dr. Garber: You could get six that were all one kind.

Dr. Goodman: And that center, right, that's possible, so that probably wasn't a problem. But just to clarify, you were shooting for a one-to-one ratio and in this

block design you did end up with 68 versus 61. Can we just say that that was the luck of the draw basically?

Dr. Miller: Absolutely. I mean, I think if we got to 140, it would have been 70-70.

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Dr. Goodman: So this 10 percent difference is reasonable to expect, given this kind of allocation?

Dr. Miller: Right.

Dr. Goodman: Thank you.

Dr. Lynn: What then does the report in the New England Journal mean when it says something like block randomization by center, block design to insure continued equivalence of group size. What does -- it sounds like an utterly random design. What you said sounds like an utterly random -- you know, you would have ended up even, but in the report it says a block design to insure continued equivalence and stratified according to center, just the words of the report, I'm trying to make them come together.

Dr. Rose: We can furnish you with the specifics. The New England Journal, you know, if you're writing to a 2,700 word limit, and I can't tell you that we specified in precise detail everything that is in our protocol, but we're happy to share that.

Dr. Lynn: No. I'm just saying that the answer to the question, to Alan Garber's question was that you could have had six LVADs at one site, but the report says that it was a block design stratified by center. And I can't readily make them come together. I suppose I can a lot --

Dr. Rose: The size of the blocks, though, was not so small that a center --

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Dr. Lynn: So the blocks were not the center?

Dr. Rose: The block is the center, but the size of the block is not so small that you can gain that.

Dr. Lynn: Okay. That's making it clear.

Dr. Rose: If the block is four, then obviously it's the third one, but the block may be larger than that.

Dr. Long: I think what's important here is what, as Mark alluded to, what did the centers actually believe was coming down the pike next. Having been through that process some 18 times, I can tell you it was with a great deal of uncertainty that we made the call to the center about what was going to come out of that final disposition.

Dr. Sox: Having a statistician with you at a time like this is like having a lawyer with you when you go up in -- well, let's move on then. Sorry, Wade?

Dr. Aubry: Just a brief question. What was the range of patients treated? You have a total of 20 centers, a total of 68 patients, so what was the range in number of patients treated from the lowest volume center to the highest volume center?

Dr. Rose: It ranged from one to 18.

Dr. Aubry: So, my point is that there were some very low volume centers?

Dr. Gottlieb: This will come up later but I wonder actually, how many low volume -- I mean, we heard that

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REMATCH centers should automatically get it. I mean, how many REMATCH centers did one patient and have no more experience than anybody else?

Dr. Long: I think that's a fair question, and I think it reflects drug trials today that with some enrolling sites, some of them think they're going to get the same enrollment and they simply don't.

Dr. Rose: We initially thought we would get this trial done with three centers. Then we went to six centers.

Dr. Lynn: Four centers had more than 50 people.

Dr. Long: The largest number there is 18, so that gives you an idea. You also see the relative distribution between the LVAD arm and the medical management arm.

Dr. Sox: Norman.

Dr. Daniels: I have a question, but I'm not sure which of your categories it fits in.

Dr. Sox: Take a chance.

Dr. Daniels: You showed data that among the LVAD patients at two centers, they had a much better result because of low infection rates versus other centers, and you used that to improve the management of those patients in other centers in the later stages. Were there variations among the medically managed patients by center, and were any of those built on in a comparable way?

Dr. Rose: It's a good question. I don't know that

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I can quantitatively answer it. Part of the structure of the trial is that there was a medical management committee and there was a surgical management committee that met at intervals essentially to compare notes on what it was that they were doing, and I think as time progressed there was a uniformity of approach that developed over time. The infection guidelines were a reflection of that consensus development and uniformity. I can't say that there is a comparable document that emerged compared to the infectious

guidelines, but I do think there was a consensus.
Dr. Miller: I think as close as possible there was a lot of discussion with the cardiologists that were participating in the trial, and I think fairly standard algorithms of approaches to drug treatment and maximizing doses and those things, as witnessed by the number of people who were felt to be too well, that they could in fact escalate and improve their medical regimen, I think is a reflection that everything that could be tried was tried, and they were deemed refractory at that point.
Dr. Daniels: But there was no mortality variation among centers among medically managed patients?
Dr. Rose: There was no outcome that we could identify for which, you know, given the size of this that we could say that a single center had better outcomes with regard to anything, including infection. What was
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statistically significant is that we could reject a null hypothesis that there was not a difference between centers with regard to infection, but we could not say on the basis of this data that a specific center had a lower incidence of infection.
Dr. Daniels: Thank you.
Dr. Sox: Well, let's go on. I would like now to talk about issues relating to trying to keep the two groups as similar as possible, except for the single intervention variable of LVAD. So, are there questions about how they were able to maintain essentially the same intervention and basically comparable study groups as they proceeded though the study except for the intervention and death? Thoughts about that? Joanne.
Dr. Lynn: You have already spoken to the couple of people who really deliberately crossed over at the end, but in one of the documents, there was mention of 15 people who deliberately stopped on LVAD. What was the story with that, what was happening there? Did they just stop it and di, or was it a refusal to continue?
Dr. Rose: Well, in both groups there were patients who elected end of life care. Obviously it was their decision along with their families, and those decisions occurred in both groups. Device patients who ended up in a state of what I think you could describe as medical futility,
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that there was no meaningful chance of their recovering enough function to survive desirably, the care was stopped. That option was taken advantage of in both groups.

Dr. Lynn: Was this mainly neurologic injury, or was it --

Dr. Rose: No, not necessarily. In some instances in the device patients, if the patient had a device infection that could not be eradicated with antibiotics, or had had supervening renal failure requiring dialysis, essentially as the cascade of multisystem organ failure became apparent, then the decision would be made that ongoing aggressive management would be futile and would be prolonging death.

The whole issue around the issue as to whether or not these devices were prolonging life or prolonging death is something that we were very sensitive to, and it's the underlying reason for the quality of life criterion being part of the primary hypothesis. We did not want to show that patients would survive longer on these devices and feel worse.

Dr. Sox: Just a follow-up on that question. I gather there were 15 LVAD patients who either had the thing basically removed or elected not to replace it when it broke. Is that correct?

Dr. Rose: I think it was a little bit higher in terms of patients that we replaced devices in, I thought it

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was --

Speaker: He's saying that chose end of life.

Dr. Rose: Oh, that chose end of life, yeah, I think it was 15 total, including both groups.

Dr. Sox: Pardon?

Dr. Rose: I think that includes both the medically managed patients and the --

Dr. Sox: To a total of 15. So in some sense they were crossovers to medical therapy but since you had an intention to treat, it was not pertinent.

Dr. Rose: Absolutely.

Dr. Sox: Other questions about the parallels? Julie.

Dr. Swain: I guess I have a question about that number, Eric, because at the FDA, the public meeting, it was presented that of the device patients, seven had it turned off or didn't want it replaced when it was recommended, and six additional ones chose DNR, so that's 13 out of 68.

Dr. Miller: That's a correct number.

Dr. Swain: And so no more since that date, what, February '02, so no further patients chose that.

Dr. Rose: I don't know the answer to that.

Dr. Swain: So it's at least 13 out of 68.

Dr. Lynn: In the booklet we were sent from Thoratec, it says 15 out of 68.

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Dr. Swain: And the other point of withdrawal is that you know, this really hard randomization scheme where they had to be treated and they finally, you know, got into the study and agreed to it, and then essentially loss the coin flip, they lost the lottery, that four of the medical patients chose to go DNR within one month of randomization, which really front loads these curves when you look at the differences in the curves, so I think that's something that we also need to keep in mind, because the problem is any device study is unblinded, and the effect of that is considerable.

Dr. Rose: It's not unblinded if you put it in and don't turn it on, but we rejected that at face value as a design for the trial.

Dr. Sox: Linda, you're next.

Dr. Bergthold: I'm curious about the quality of life assessment of the patients who had infections and so forth, how their scores -- and when did you give these tests, were they at the beginning?

Dr. Rose: They were at prespecified intervals and the data that I showed you were across the entire study, so if you were infected and you were scheduled to have a quality of life measurement, and you were not on a ventilator and could answer the questions and were willing to, then we collected the data.

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Dr. Bergthold: And there were no significant differences among those groups, because you would think that those folks who had the most problems with the device would be the most dissatisfied or feel it wasn't worth it.

Dr. Rose: They would, but again, this is a comparison to people that are also short of breath at rest, and one of the things that was particularly interesting when we started doing this is the optimism that these patients can show in terms of their absolute rating of their quality of life is pretty amazing. A patient's in an intensive care unit on a balloon pump and inotropic support, on a scale of zero to one where zero is death and one is perfect health, the scores we were getting for patients was like .7, that's what they would rate their quality of life, which from my perspective is extraordinarily optimistic, but still remarkably high, but I think entirely valid. It's their life.

Dr. Sox: Ileana, you're next.
Dr. Pina: There is a table that has been submitted here as additional data that shows that, who the patients in the LVAD arm were transplanted. I thought you couldn't do that once the patients enter the trial, or is that after the trial stopped?
Dr. Rose: After the primary end point was reached, this occurred. But actually in the design of the trial, we
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budgeted, the power analysis included potential crossover rates as high as 10 percent as part of the power calculation. As it turns out during the period of enrollment, before we reached the primary outcomes, none of the patients crossed over. But we could not ethically say that if a patient on a device after a year, you know, for any reason becomes a transplant candidate, or if the centers change their entrance criteria for transplantation, being in this trial should not preclude their getting treated the way they wanted to.
Dr. Pina: Do you know the age group of those two patients? One died after transplant and one is still surviving but in your intention to treat arm shows as alive, so I'm asking what age group was that, do we know?
Dr. Miller: One of them at least was over 70.
Dr. Pina: One of them was over 70. And is it okay to ask now how many patients are actually alive, because I'm having a hard time figuring it out, how many patients today are still alive with the device, and of those that are alive, how many are in the over 65 age group that would be the Medicare beneficiaries that we're talking about today?
Dr. Rose: I think it's 11 and 2, 11 from the -- 14 patients alive -- is it 2 that are crossovers, or 3? 3 that are crossovers that are alive and 11 from the original group. One of the three crossovers that you saw was 70 years old. I don't have an age breakdown of those patients.
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Dr. Pina: So we don't know the age breakdown of the 11 that are still alive that were in the original cohort?
Speaker: I can get that to you in a couple minutes.
Dr. Pina: I think that's important for the Medicare folks to hear.
Dr. Sox: So the question is, what's the age distribution of those still alive on the device, and we're going to try to get that data. Steve, I think you're next.
Dr. Gottlieb: I just wanted to follow up on the quality of life issue and make sure that we don't

over-interpret that. Since it is -- and you kind of started pointing this out, but when you have an unblinded study, which by definition this has to be, there is a lot that goes into people's assessment of quality of life and depression, and I think the optimism is true, and it looks like you actually lost people to follow-up once they were in medical care, because they didn't care anymore. So, it's comforting that these people didn't feel absolutely terrible, I think you can get that from the information, but I think to kind of say that their quality of like is really improved based upon these scales, I don't know what quality of life means, it's such a subjective sort of thing, and how much the scales really reflect.

Dr. Rose: I think the counter argument to that is

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I do think the quality of life is still legitimately a subjective observation, and for whatever reason, the process, if you look at this intervention as a process as opposed to a device, for whatever reason, the patients who went through this process this way, on multiple scales and in terms of multiple measures of functional capacity, did better.

There is -- the issue that has been raised which is important is the issue of missing data in the OMM group, and I think that that --

Dr. Lynn: Actually in both groups, because other people --

Dr. Rose: Actually, it was a problem. This was a first foray really, for a trial like this to include a rigorous assessment of quality of life. The original batteries that were used in the PREMATCH experience took about two hours to administer, so essentially you now had an instrument that was wrecking the quality of life itself by forcing them to do it, so we had to edit that down to something that was doable in a short enough period of time, and particularly for the medically managed patients, it had to be easy enough that they could do it without exhausting themselves. Most of the patients in the OMM group that did not do the whole battery of quality of life testing, the reason for it predominantly was that they were too sick to feel they could even answer the questionnaires.

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That having been said, we did not impute any values to those, so that there is a subselection in the OMM patients to those who could at least complete these batteries of tests. Certainly in the device patients, a much higher percentage of them would complete the battery of tests.

Dr. Miller: And perhaps the Minnesota Heart Failure Disease Specific Questionnaire may be one of the more objective looks, and sorts out some of those issues you're looking at, and that was again statistically significant and relates to a broader, and incidentally is a greater reduction than any medical trial has shown in terms of the change in the absolute score of the Minnesota questionnaire.

Dr. Rose: And again, our hypothesis was not, we weren't looking to prove nor were we stating robustly that the quality of life is so dramatically improved in device patients that that alone carries the day here. On the other hand, we were looking to show that their quality of life was not worse, that we were not prolonging death. I would say that the counterveilling analysis to Julie Swain's comments about the four patients who chose end of life, what's even mor amazing perhaps, is the 57 even feeling like that, did not choose end of life care, and that quality of life even at that level in patients this sick, I think you could still argue, most patients who have that quality of life still want to be alive. That being the case, I think we more than meet

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the bar of, you know, do we prolong life that people think is worth living.

Dr. Sox: Okay, Joanne. We're starting to get into the lunch hour now, so we will try to make things as short as possible.

Dr. Lynn: Two quick follow-ons. I'm not 100 percent sure they fit the category as laid out, but they seem to follow on what was just being discussed. One is, what was the pattern of use of ICDs in this group?

Dr. Miller: That's a very good question and it was in the range of, ICD use was about 20 percent.

Dr. Lynn: In both groups?

Dr. Miller: Yeah.

Dr. Lynn: And among the people who chose not to continue, do you have any sense of how many happened in the first year, so that they are effectively part of the nonresponse for quality of life at the end of the first year?

Dr. Miller: I don't have that data, but I would say from our own center experience that it was a self selection that the people who really, particularly in medical therapy, were so discouraged by being left to no change in their outcome that they opted early to do that, not after a year. And conversely in the VAD, we showed you a couple of examples of people that had gotten that far and were incredibly rehabilitated and were not a part of that.

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Dr. Lynn: I'm just trying to answer the technical sort of question of the non, what would you count as nonresponse? If the LVAD patient decides to stop, they're dead, or on the whole there are not very many of them who live very long. So if 15 of them stop in the first year, at the end of the first year one could, one could argue about this, I'm sure, but one could say that effectively the quality of life of 15 people was shown to be less good than continuing to survive because they chose to stop, so they were effectively nonresponsive at one year. If on the other hand, you know, 15 of them the second year, then that doesn't affect your major end point at one year. I still agree with Dr. Rose, I think he's shown that this is not miserable, and if that's the claim, that's fine. It's just, I was trying to understand what the distribution at the time was.

Dr. Rose: That's the claim. I think that the data suggests that it does more than that and certainly -- I mean, we've shown you some vignettes today that are obviously anecdotal, but there are no OMM patients that have gone out and fished or gone back to work or you know, mow their lawns, or the things the patients were able to do with devices in this trial. But we're not representing to you that that's at all expected.

Dr. Miller: Just in response to clarify Ileana's question, they tell me that now 12 of the 14 survivors are

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over 65, so a substantial percentage are clearly in the Medicare realm.

Dr. Sox: Tracy, you're next.

Dr. Gordy: My question comes, we've been focusing on 65 being the Medicare population. Do you have any data to support the fact that you had some of the patients on disability who were receiving Medicare benefits who were younger than 65?

Dr. Rose: That is a great question and it's interesting that it's hard to qualify for Medicare benefits if you're less than 65 with this degree of heart failure because you have to be disabled for two years, unlike the end state renal disease benefit where you know, just having renal failure regardless of your age qualifies you. This severity of illness does not qualify you for Medicare benefits, so the frequency of that, as is the frequency in the heart transplant population of Medicare beneficiaries younger than 65 is very low, because it's hard to live this sick for two years.

Dr. Sox: The penultimate question to Norman.
Dr. Daniels: I wonder, this again is on the quality of life issue, I'm still puzzled at the lack of correction between the adverse events and the seriousness of them and the quality of life reporting. But also, I wonder whether any of the instruments you used got at issues about
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cognitive deficit that was induced by the procedure.
Dr. Rose: We did not do formal neurocognitive testing as part of the follow-up for this. I want to put the quality of life in perspective. The quality of life, you know, the differences are differences between groups. To say that the quality of life of the device patients was normal or was absolutely perfect would be also a gross overestimate. The SF-36 physical functioning scores that we record are essentially about the same as patients on dialysis, who also have plenty of adverse events even though they can be sustained for long periods of time. So I don't think it's completely surprising that patients rate their quality of life in those ranges, I think they are comparable to other patients that have chronic disease states that still cause hardship.
Dr. Daniels: I was raising the question because if you look at your table of LVAD versus others and the types of events, there is such a huge discrepancy between categories like psychiatric episode and neurological dysfunction and so on in the medically managed groups and yet, there isn't any reflection of any of that in quality of life.
Dr. Rose: But the AEs also, are front loaded. As with a heart transplant, there are lots of complications to heart transplantation, but most ever them occur early in the going and as you saw in that plot that broke out adverse
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event incidents over time from the first 30 days compared to the later 30 days, the absolute incidence of adverse events after the first 30 days diminishes considerably. So the fact that it doesn't reflect in the later quality of life measures, which is where most of them were, I don't think is that surprising.
Dr. Sox: Julie.
Dr. Swain: I think the neuro is very interesting, you know, 49 percent of the device had neurocomplications and I think two things you mentioned, psychiatric problems and delirium, and Dr. Baumgartner's group at Hopkins, and the neuro group there has shown a very distinct correlation of people with delirium and then subsequent cognitive

dysfunction, quality of life. It's conceivable that these patients didn't know they had the deficits and that very much affected the scores. But Dr. Ron Lazar just presented an abstract at AHA showing that the neuro events continue, it's sort of the gift that keeps on giving on neuro events, so that that is a continuing problem with neuro deficits. So I think that lack of --

Dr. Rose: You're saying they didn't know how bad off they were?

Dr. Swain: Right. So the lack of cognitive function, I think if the study were redesigned now, that would be included as a very important part of societal

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functioning. And I think later we're going to have more quality of life discussions, so I'll hold some other comments for later.

Dr. Sox: I have one question before we break and it has to do with maintaining parallelism so that the only variable that distinguishes these is the device itself, and that has to do with the intensity of care for optimally medically managed patients. The New England Journal article is really kind of silent on the issue I'm concerned about, and that is, did they get sort of the full court press of the best heart failure centers in the country with all the nursing support, home visits and everything that can be done to try to sustain them medically?

Dr. Rose: That was certainly the goal and that's what was represented to patients to get them to participate to begin with. The consent form, you know, describes just that. But a lot of patients also didn't -- you know, chose -- though it was certainly desirable from our point of view to have them followed at the expert center to have their continuing medical management, some chose not to do that.

Dr. Lynn: Were they put in heart failure management programs?

Dr. Rose: Well, before they could be a candidate, essentially they had to prove that they had been in a heart failure management program and 90 days on optimal medical

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management. So you know, a patient that we did not think was treated optimally, the 90 days doesn't start to be measured until you're on digidiuretics and ace inhibitors that you could tolerate.

Dr. Lynn: And after randomization that was continued? Or is what you're saying after randomization, that may or may not have been continued?

Dr. Rose: If they became ace intolerant, then they were dropped from --

Dr. Lynn: I'm more concerned about whether if they start feeling even worse one day, do they have a nurse to call, do they get all the interventions?

Dr. Rose: Absolutely.

Dr. Miller: They were bonded to the nurse coordinator in the study, and the study specified that they should be seen back at the center monthly or if it were logistically impossible for whatever reason, there was direct phone contact, contact with the referring physician who helped us evaluate and guide therapy, but there was very close follow-up in the medical group.

Dr. Sox: Just so I'm clear, it sounds like there may be some departure from parallel treatment in that the LVAD patients were all watched like a hawk, perhaps because of the fact that they had a device that you put in there, but that the optimal medical management patients, some of them

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elected to go back to community care that probably wasn't as intense as if they had gotten heart failure center care. Is that fair?

Dr. Miller: I would refute that statement. I think that we absolutely followed these patients as closely as has ever been described, and directed their care and their drug therapy on a weekly, daily basis. So there's no question that the continuity of care was there in the medically managed patients.

Dr. Sox: For both groups?

Dr. Miller: Yes.

Dr. Sox: So you feel it was parallel.

Dr. Miller: No question.

Dr. Long: And let me make a point about it possibly going the other way. We are in a sparsely populated area and we return people back to their communities, and we generally tried to work with a cardiologist, if not a well experienced primary care physician, we tried to identify cardiologists in the region that we could be assured would provide ongoing care and support, not only of the medical patients but the LVAD patients. And I have a great deal more confidence at the beginning of our experience that we could expect compliance with good medical care more so than we could compliance with good LVAD care in these communities. This was an area where we had to educate. We had to go out

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and educate these people as to how to care for these patients

in the community. So our experience was, you know, clearly that we had, even in the periphery, excellent follow-up for those patients, and clear communication with the central coordinating group.

Dr. Rose: We were one-eyed hawks for both groups.

Dr. Sox: So, this is absolutely the last question before we take a break. George. Sorry, Julie, did I miss you? Two more.

Dr. Swain: The only thing is, if there was a metric to determine face-to-face physician-patient visits. Do you have metric and data to show equivalence, because there's impressions, but are there metrics?

Dr. Miller: I'm sure we can go back to that, but I can only say, there were very few patients that missed follow-ups on either arm in our follow-up.

Dr. Agich: This has already been answered.

Dr. Sox: Okay. In that case we're going to take a break. We will reconvene at 1:15. Thank you.

(Luncheon recess.)

Dr. Sox: Well, before we get into the afternoon's agenda, we wanted to make one other statement that related to potential conflict of interest, just to be sure that it's on the record. Cliff?

Dr. Goodman: Yes. Thank you, Dr. Sox. This is

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Cliff Goodman, from the Lewin Group. It is true that I have no financial interests with Thoratec or a competitor. However, in the past, within the last two years, two years ago, my company did some work for a company other than Thoratec that makes a VAD-type device. That work is no longer ongoing and I still have no financial interests in Thoratec or competitors now. I just wanted to state that for the record.

Ms. Long: And I just want to state for the record that we did speak prior to the meeting and we had our ethics department look into it, and it does not pose a conflict for him to serve at this meeting.

Dr. Sox: The next part of our agenda is devoted to comments from members of the audience that haven't signed up way in advance, and my understanding is that there are two of them. And I see an opportunity to catch up with our time, so I'm going to rule that we will allow them three minutes each.

Speaker: You know what, the requestors have been doing such a great job in presenting all the information and facts to the panel that I was actually going to present on behalf of the LVAD patients, and we are going to push the

time back to the panel to further their discussion.
Speaker: And I would yield my time back to the chairman as well.
Dr. Sox: Thank you very much. In that case, we
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will continue our period of questioning and discussions, and I just have a couple more sort of topic areas that I would like us to cover. One has to do with the ascertainment of outcomes and here we should be concerned about, I think, differential ascertainment of outcomes and whether there was bias in the way it was done. And perhaps you could just recount for us in a little bit more detail to start the discussion about how you actually collected the data that went into the measures of patient status and so forth, and then also go over how you decided exactly what the cause of death was, the degree to which the people who decided on cause of death were blinded to the person's treatment allocation and so forth.
Dr. Rose: Well, with regard to gathering the data, the date actually were gathered entirely electronically by coordinators at the individual center who had been trained in its gathering, and also allowed essentially performance management of the completeness of reporting and the correctness of the reporting right at the site of entry. So the design essentially eliminated the occurrence of errors of transcription or nonsense data. Nonsense dates, nonsense laboratory values could not be entered, so there was immediate feedback. It was a pre-Internet design. The coordinators would download their data by modem daily to the data coordinating center.
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Dr. Sox: As I understand, you were supposed to see every patient once a month?
Dr. Rose: Yes.
Dr. Sox: So that's how you kind of kept in touch with what was happening?
Dr. Rose: Yeah.
Dr. Sox. What was the compliance with those visits?
Dr. Rose: Pretty high.
Dr. Sox: I mean what, 90 percent, '95 percent?
Dr. Rose: In that range, and maybe higher. There was some deviation where if there was a snow storm and a patient got there four days later, that was considered to be a deviation, and there were queries made. The centers that participated got constantly hounded by the study coordinators

to be sure that the visits were being done and that the data was being reported.

Dr. Sox: And the last question I have, which I think you've answered but I didn't find it in the New England Journal article, was how you adjudicated the cause of death.

Dr. Rose: There was a morbidity and mortality committee comprised of individuals who were experts but not investigators in the trial. They could not be blinded; it's impossible to adjudicate a cause of death. You know, where device failure can be a cause of death, you obviously need to

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know that the patient had a device. So they were not blinded but they met -- actually, they still meet to adjudicate adverse events, as well as causes of death.

The quality of life instruments were also administered by trained people to do that and were recorded electronically as well. We were able to get the entire data set into a reportable form for the New England Journal submission within two months of the last enrollment. That was enabled by this data acquisition method which, I think there were more than 100,000 report forms that were part of the database and the fact that they were all electronically entered to begin with allowed for fairly rapid real-time cleanup of the data, just in the sense that it was in order.

Dr. Sox: I'll yield the floor to anybody else who would like to ask questions that have to do with outcomes ascertainment. Joanne.

Dr. Lynn: Has there been any follow-up with the families after the death and how they -- you were talking earlier how it seemed sort of counterintuitive that people are reporting such a wonderful quality of life while they lead it, and I think those of us who work with very sick people are impressed at how often they see themselves in a better light than anybody else, but I'm wondering what meaning the family ascribes to this experience and whether on the whole the family sees it as having given up Uncle John

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for the good of science, or if they see that Uncle John's life was really wonderful, or how do they stack it up. Did you do any data afterwards?

Dr. Rose: It was not done systematically, and I think our lack of planning on these issues and others, frankly, is apparent in this regard. Anecdotally, I think all of us have had patients who ultimately have not survived and whom, there are expressions of gratitude for what most is a meaningful period of time.

Dr. Long: In every case for us, we approached this with patients and families as if they were getting access to the two best therapies available for them in the world and because we didn't know which of those two were the best, they would flip a coin and go one way or the other. And for us it was very important that they understood that this was an opportunity for them, but also a huge opportunity to make a contribution in a field where there is not yet an established therapy and in virtually all the cases, there was not an expression of resentment, nor an expression of long-term ill will, any of those things. None of these responses occurred.

Dr. Lynn: That latter, of course, would vanish in routine use.

Dr. Long: I'm sorry?

Dr. Lynn: That latter justification would not be present in routine use. That's okay. I'm just pointing out

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that if part of the reason they felt well about it was because it was breaking ground for other people, once it's a routine therapy, that part is gone.

Dr. Sox: Ileana.

Dr. Pina: Other than infection, which was the major cause of demise, the second one was neurological events, mostly central neurological events.

Dr. Rose: The second was device.

Dr. Pina: I'm sorry. After that, the CNS events, and some of them were bleeds that ended up in the patient's demise. Have you broken that down into ages and did you see the same improvement in the infection rate that you saw as the trial went through, did that also get better, because that's a very significant morbidity in a population whose neurocognitive impairment may already be there.

Dr. Rose: We haven't done an analysis of neurologic events over time. These are ongoing analyses but that's not one that we've done. I can't say also that -- unlike infection, there was no intervention over time that the group made to the management of adverse neurologic events. With regard to age stratification of any of the adverse events, to my knowledge there is no analysis that shows that any incident is more likely in any particular age group, but we're underpowered, I think, to answer that question.

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Dr. Pina: Do you think there were any modifications done in the device during the time period of the trial that would have decreased CNS events, or did more

investigators use, let's say plavics (phonetic)?
Dr. Rose: If you look at Ron Lazar's data that was mentioned earlier by Julie, it's interesting. The neurologic events cluster early and then there is a period where it's basically flat from like 3 to 18 months, with almost no incidents of stroke, and there was not routine use of anticoagulants. And then when you start seeing things like intro-valve regurgitation device failures, I think it's not surprising that you start seeing an incidence of thrombolic events again that are reflective of device malfunctions. To the extent that those were being corrected, I think that they will address issues of thromboembolism as well. With regard to anticoagulation, patients almost uniformly were not anticoagulated unless they had some other indication to have it done. Whether or not they should or should not was not a question that we asked, and we were completely underpowered to answer that kind of question.
Dr. Pina: I was just wondering if through the experience, you know, you pick up as you get together in committee, you pick up something that someone's doing that's a little bit different and maybe a little bit better.
Dr. Miller: The one thing that I think we've also

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noticed is the ability of the pump to restore normal blood pressure and have a substantial DPT in stroke volume is clearly a dramatic change and the augmentation from where they were, and for older people or you know, small infirm individuals, we've learned to cap that blood pressure, cap the flow of the device, and I think that's an attempt to mediate the difference in these neurological complications.
Dr. Pina: So that's an improvement.
Dr. Miller: No, it is. It's clearly an improvement that's a lesson learned from our experience.
Dr. Pina: Now going back over outcomes, after the first year, where now the infections have probably decreased and the early CNS events are not there, what would you say was the major cause of death in the LVAD group after that first year?
Dr. Rose: Infection is still common beyond the first year and in the later cohort it's clearly less frequent, as you saw, but still high in incidence.
Dr. Long: The curves for the two major causes of death, sepsis and the device replacement, are curves with the device replacement for example, that goes out to almost no deaths related to device failure, goes out to about 14 or 15 months, and then begins a progressive decline so that at

about two years, you're down in the 60 percent freedom from death due to device failure. Sepsis has a curve that starts earlier than that and begin seeing a freedom from sepsis related death earlier, it begins dropping off and plateaus a bit, and then continues to drop off further later in the course.

Dr. Sox: Wade.

Dr. Aubry: My question is a little bit related, but I'm interested in the high volume versus the low volume centers, and referring to page 12 of Dr. Rose's presentation, in which you identify adverse events within 30 days and then beyond 30 days, I'm curious as to whether the high volume centers like those who did 18 cases, or more than a smaller handful, whether there was a decrease in these adverse events over time, and was that analyzed at all in those high volume centers?

Dr. Rose: Like I said before, we could reject a null hypothesis with regard to infection, which is the most common fatal adverse event. We could reject the hypothesis that the center didn't make a difference, but we couldn't identify which centers, you know, were better in that regard. You know, a second look, you could look at who had a high instance of infection and the like, intuitively I think you could come to conclusions if that's true that they must be doing something different. But it's not a large enough data set for us to reach any definitive conclusions. I mean, even a high volume center has done 18 cases.

The flip side of that, though, is even doing 18 cases and even with this relative inexperience, we still achieved the outcomes relative to the control group that we did.

Dr. Sox: Joanne.

Dr. Lynn: In the usual medical care group, I think probably very few people return to fly fishing and golfing as the videos showed, but in either group, do you have accurate measures of how many people -- the handbook makes a big point of how you can return to sexual intimacy. How many people ever got well enough to either be going back to work, engaging in very active sports, or having sex?

Dr. Miller: It was probably age appropriate. I can't really speak to that.

Dr. Lynn: Oh, come on, I'm a geriatrician. Age appropriate is 102.

Dr. Miller: Well, there are two that I know have

asked for Viagra, so maybe that answers the question.
Dr. Lynn: That's an initial indication.
Dr. Rose: Certainly in the VAD population, both in bridging and in this population, there are -- you know, just the logistics of sexual intimacy is something that patients raise questions about, and they are, I think is indicative of their activity and their interest.
Dr. Long: Outside of the REMATCH trial, our
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experience has been that the vast majority of folks who are interested and wish to do so, do so.
Dr. Lynn: With the LVAD?
Dr. Long: That is correct. And we did take a psychosocial dynamic very seriously. I mean, what we're all about here is trying to normalize people's lives and return them to a state of well being that's far different than what they entered this process with.
Dr. Lynn: Is my guess in the control group right, that that's very uncommon in the control group?
Dr. Rose: Yes.
Dr. Sox: Ileana.
Dr. Pina: We talked about inotropic therapy killing people. How much of the enhanced mortality of the control group or medical therapy group do you think is heightened, understandably they are awfully awfully sick, is heightened by the use of the inotropes? You did have a small group who didn't have inotropes before, I don't know if they ended up on inotropes, but I think again, it's important for the panel to know that inotropic therapy is not benign, and can actually accelerate death.
Dr. Miller: I think what Ileana is alluding to is that there have been a number of trials trying to look at a very complex therapy of using intravenous inotropic drug therapy largely in an outpatient setting, and you would say
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that of all of the drugs that have been used that are shown to enhance cardiac performance short of ace inhibitors and beta blockers, they have all been associated with enhanced mortality, and largely sudden death. So it is a therapy that just represents the end of what medical intervention can bring put clearly is not a benign therapy.
Dr. Sox: George.
Dr. Agich: I want to go back to a point that we sort of ended with before the break, quality of life. If I understand correctly from what you said, the assessment of quality of life, there were places according to protocol

where those assessments weren't made because the patients weren't able to complete the assessment. Do you have any data or breakdown in terms of would that fall more in terms of the medical arm or the VAD arm.

Dr. Rose: There are many more missing data in the medical group, which is further compounded by the high mortality in the group. So when you're making comparisons, you're going to a very small end on the OMM side.

Dr. Agich: Right. That's very helpful, thank you.

Dr. Sox: Linda.

Dr. Bergthold: I would just like some clarification of the ability of the folks in the VAD group to move around. Now I can imagine that you could make an eight-foot putt with one of these devices without moving too

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much. It's really hard for me to imagine you could actually drive a golf ball.

Dr. Rose: That's the video that we showed you.

Dr. Bergthold: I saw it, but I wonder, if you said that immobilization helps to control infection. And so I'm just wondering, is that a one-on example and how many guys, and they were guys were out there, were out there driving golf balls?

Dr. Miller: We had a golf tournament, so it's not a unique experience. I think the belt immobilizes the drive line so well that they really have fairly free range of their upper torso and have been quite active. I think it would surprise you how much they are able to do.

Dr. Long: Laying bricks to put a building up for the second pizza shop that a 73-year old gentleman has opened, skiing, in and out of airports, travel cross country.

Dr. Bergthold: And that's common?

Dr. Long: Yes.

Dr. Sox: Other questions? Yes, Steve.

Dr. Gottlieb: I want to get back to the inotope for a second, and I think it would be useful to see those data. I mean, if you have a third of the patients who weren't on inotrope, two-thirds that were, just kind of whether there were differences.

Dr. Miller: Yes. We actually looked at that,

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Steve, a comparison of the people that were considered on inotropes or not on inotropes and their overall demographics at the baseline and as you might guess, on inotropes, their hemodynamics were worse than the cohort that were not on inotropes at all and just medical therapy. So they were a

little bit sicker, which might fulfill the natural history that they would not do as well. We don't have it broken out by how many could not take ace inhibitors. The dominant inotrope use at that time was dobutamine rather than milrinone, and so they probably were not exposed to beta blockers as much. But the group is clearly a very advanced failure group, and in centers where that's not preferential therapy, it's really the last resort type of intervention.

Dr. Gottlieb: But what were the mortality rates for the two groups?

Dr. Miller: When we separated out the patients that had no inotrope dependence in terms of documented attempt to withdraw from the others, they had a worse prognosis, but there was no difference in the outcome using medical therapy or VAD therapy in terms of those who were inotrope dependent or not inotrope dependent. So it does not independently identify a selected cohort for whom therapy should be reserved. Does that answer your question, Steve?

Dr. Gottlieb: Not totally. I mean, just the one-year mortality of people not on inotropes at entry, or

both, do you know?

Dr. Miller: It was slightly worse on the inotrope patients.

Dr. Rose: But still high, in the 60 percent range, something like 60 versus 80.

Dr. Sox: Other questions relating to outcome ascertainment?

Since there aren't any, I have kind of gone over my mantra of evaluating the conduct of the trial and I wonder if there are other questions that, people have other questions for our presenters, before we start our discussion. Yes, Cliff?

Dr. Goodman: I'm seeking some clarification regarding the big picture concerning patient populations. I understand that your original early literature review indicated, and the study was designed based on the assumption that there would be a two-year mortality of 75 percent, and in fact the trial found a one-year mortality of 75 percent. So clearly as we've been discussing, your trial ended up treating a much sicker patient population than planned. And so you'll forgive me for pushing on this, but in your estimation, is the population that you enrolled in REMATCH different from the population you had in mind or is it at the far end of the distribution of the population that you originally anticipated for this study? And in either case,

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does that raise your curiosity about the need to do subgroup analysis?

I ask this because it's pretty clear -- I'm not a clinician, but listening to the clinicians and looking at your data, you planned the trial anticipating a certain set of characteristics for population, and these people look different to me than what it sounded like you said you were going to be enrolling. And it has implications for how the results of this trial would be carried forward. It seems to me like you must have been pretty surprised.

Dr. Rose: I guess we were a little surprised. I mean, typically in randomized trials the group does better than anybody expected. In this randomized trial the control group did even worse than we expected.

Dr. Goodman: And I might add, by the way, they did worse recently versus a literature review which is a couple years old, based on literature data that were gathered --

Dr. Rose: And I think we're finding out the weakness of the literature. There is not much written. It was amazing to us that we had to convince people that people with end stage heart disease actually die and that they die quickly. This is a terminal illness, and I think the descriptors in REMATCH describe an illness that's even more terminal than we would have given it credit.

Dr. Goodman: But you're implying that the
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population that you treated was the same one you thought you were going to treat, except it was really sicker than we thought, as opposed to you treating a population that was truly different than the one you thought you were going to treat.

Dr. Rose: I don't think we treated a patient population that was different from the one that we anticipated treating with this trial. And the outcomes, as I said, were worse than we had expected but in retrospect, I think we had defined, and the whole focus of the description of Stage D heart failure, which was not even a description that was available when we began this, I think that there is an emerging consensus about what terminal heart failure looks like, and it's worse than we thought.

Dr. Sox: Norman, and then Alan.

Dr. Daniels: Alan, is your question a follow-up on this?

Dr. Garber: It's closely related.

Dr. Daniels: Go ahead.

Dr. Garber: Well, it's actually independently, Cliff and I were thinking about the same thing, about the subgroup analysis, and Dr. Rose, I think you make a good point, a very valid point that it's hard to do much in the way of subgroup analyses with an N this small. Nevertheless, there are simple things you could do, and this one I'm very

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serious about. First, let me just say it's clear that although this is a very sick population, it is not a homogeneous one, and you had a good distribution on many of the variables. And there are CHF prognostic models out there and you could do a prognostic model based on a control group in your trial.

The question is, have you looked at a prognostic model and say, compared the relative risk reduction in the top half of risk group to the bottom half, in other words, is the benefit from LVAD pretty much uniform? And I think this gets back to Steve's earlier question which was talking about individual variables and Dr. Miller, you did refer to this. I'm more interested in the question, if you did such a prognostic model and took the highest risk group, would they have a greater benefit, same benefit or lesser benefit than the group that's lower risk?

Dr. Miller: Let me try to come at that from two ways. One is that we looked at a number of variables, one of which was the heart failure survival score, which has been very well validated as a very good prognostic composite index of that, and it fell out as I think number two or three in the ranking of correlation with poor outcomes. So that composite score could be fairly predictive. I don't know that I've seen it tiered by high, medium and low, and then substratified, because again, we get down into smaller and

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smaller numbers. But we do have some inference that the high and middle range scores of that had a very substantial benefit from that, but it's not completed, this is really based on functional capacity, but I don't think I can answer your question more on what we've looked at so far. We've just begun to stratify the data by simply the single parameter and that was the composite score.

Dr. Sox: Steve's got some data.

Dr. Phurrough: Unfortunately I can't identify the source, but I have a couple Kaplan-Meier charts here on the benefit of LVAD in patients without baseline inotropic therapy and with baseline inotropic therapy.

Dr. Rose: This may be part of -- there was an

earlier analysis that had been reported to the American College of Cardiology that suggested that most of the benefits in this trial came from the inotrope dependent group. It's untrue. When you look at that analysis and you do it in detail and you sort out inotrope dependent patients versus patients that are on inotopes, and there is a difference, because inotrope dependent patients, you've made weaning attempts to show that they're not. None of this sorts out as a predictor of outcome.

Dr. Sox: Well, the curves look different, so what explains away the difference? What variables are there?

Dr. Miller: It's worth perhaps pursing this.

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There were nine patients that were able to be weaned from inotropic therapy at the time, and when you take them out as not being inotrope dependent and fold those patients in as you did the other general medical group and analyze that data now two years further into follow-up, there is no difference in the benefit of the VAD whether they are inotrope dependent or not inotrope dependent.

So, a subsequent analysis and reanalyzing the data by truly being shown to be inotrope dependent by an overt volitional attempt to wean them off, and if they were off, they stayed off for a period of time, they were considered with the general medical group, or conversely, they were inotrope dependent and then analyzed on that strata.

Dr. Gottlieb: Excuse me, when you wean them off when?

Dr. Miller: At the time of randomization, they were attempted to be weaned off so that they could be analyzed potentially with exercise or whatever, as noninotrope dependent. So there was a clear initiative from the steering committee and others to try to get any patient on inotropes off inotropes, and prove by clinical or objective criteria that they had failed an attempt to wean. Nine patients were able to be successfully weaned by all criteria and to the principal investigator's satisfaction that they were no longer inotrope dependent.

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Dr. Gottlieb: And this is prior to randomization?

Dr. Miller: Prior to randomization.

Dr. Gottlieb: So in that analysis, are you saying that they were put in the wrong group?

Dr. Miller: Looking at that analysis, that they were at all on inotropes anytime in the immediate period prior to randomization, they were counted as inotrope

dependent.
Dr. Sox: Okay. I think the next question is for Norman Daniels.
Dr. Daniels: I'm not sure if this is out of place again, but it connects to the previous set of questions. I'm trying to get some sense of the magnitude of the population group that you're trying to reach with this protocol, and the degree to which the REMATCH criteria for isolating a particular definable group or one that readily blends into a much larger population of heart failure patients and if so, if it's an isolatable group, what's the size of it in the national Medicare population?
Dr. Rose: Our estimate would be somewhere between 5 and 10,000 patients a year. It's a low prevalence group.
Dr. Lynn: In Medicare?
Dr. Rose: Yes, most of them will be in Medicare. It's a low prevalence group because they die so fast, so at any one point in time, you take a snapshot, how many are out

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there that have this problem, it's relatively low because they don't have particularly long incidents.
Dr. Sox: Incidents higher than -- I mean, you said prevalence is 5 to 10,000.
Dr. Rose: What I'm saying is if you started doing it now, there is no reservoir of pent up patients because they don't live long enough. Our estimate or guesstimate over time would be that there would be 5 to 10,000 patients annually in the United States that would meet this set of criteria that could benefit from this kind of treatment.
Dr. Sox: Julie.
Dr. Swain: This is sort of to address both Dr. Goodman and Dr. Garber's comments, who had asked the sponsor Eric about the Kaplan-Meier curve's confidence limits and they have not brought those, so I wonder if we could show the confidence limit slide from the January '02 data presented at the FDA meeting?
Dr. Rose: I think it's worth pointing out that these data now are a year old, and the confidence limits have changed.
Dr. Swain: Well, we would love to see them.
Dr. Rose: Well, we can give them to you.
Dr. Swain: Okay. I just have a hard time interpreting graphs without error bars, confidence limits, things of that sort. But that's the February '02 data and

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when we look at the very good point about the prediction of

what these patients were like, and clearly they weren't anywhere near what the prediction was, because if this hadn't been a randomized study, the differences would have been, would have not been in favor of the device. So when you take into account the unblinding aspects of patients dropping out early because they lost the coin flip and if you then wish to include a less sick group, if you could identify that, I think there would be a hard time looking at a statistically different set of curves here.

So the challenge that I think the Medicare people have to do is to figure out how that group was defined, and I think it's very difficult. And the gatekeeper, I think is probably one of the key aspects of this, and that some patients were referred from the 20 centers, included centers, and the investigators have told me that their cardiologists, who are the best cardiologists around in these centers, referred them to the gatekeeper and the patient was disallowed because they didn't fit the criteria. And we had asked, I think Ileana asked how many patients that was and there were some number. So I think defining these patient populations so that you get the patients represented in the black curve is absolutely the key here.

Dr. Sox: Alan, I'm just wondering if you want to make a comment about that curve and about if you're trying to

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make an assessment of the effect of an intervention, whether you should be paying attention to the confidence intervals on individual points in the curve or the overall curve. We need our lawyer, but Alan will suffice.

Dr. Garber: Well, you know, there's a long answer and a short answer to your question, and it really depends on, being someone who really believes in cumulative effect, my answer would be neither. I would rather look at something like what happens to overall life expectancy, which is closer to looking at the overall curve, but it doesn't weigh the points equally. So none of this perfectly fits.

But I what Julie has mentioned is very important, and there is several issues here about the definition of patient population that are key. The point of my earlier question about stratifying by the subgroups according to predicted outcome, even if prognostic models don't apply perfectly here, we know they don't, but they may be pretty good at ranking patients in their study. And the issue is well, if most of the benefit is in the sickest ones, that leads you one direction; if most of the benefit is in the less sick ones, it leads you in an entirely different

direction.
Dr. Rose: And we don't have enough data.
Dr. Garber: You do have enough data to at least give a suggestion here, because this is not a complicated
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thing. I'm not talking about doing ten different subgroup analyses. You can do a simple prognostic model, plugging in variables used in one (inaudible) externally, for example, and just divide up your sample according to whether they were in the top 50 percent or bottom 50 percent, and ask the question, is the relative risk reduction equal in those two groups, and if not, in which direction does it go. We know, we don't expect --
Dr. Rose: But the confidence intervals around that are slice and dice there.
Dr. Garber: No, this is basically two predicted -- it is only defining a subgroup and its binary comparison. It's arguing in the low and the high risk group and what was the relative risk reduction. That is not the same as asking about subgroups defined by ten different variables. You're going to have a prognostic score as a single variable, even though it's constructed from the characteristics of the patients and there could be a number of variables. The inotropic support is one of them, creatinine might be another, age might be another, and so on and so forth. One summary score dividing top and bottom group.
And obviously, if you're seeing most of the benefit is in the lower risk half, then we should talk about looking at a broader population that might benefit. If most of the benefit is in the higher risk set, we're talking about
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presumably a narrower population.
Dr. Miller: I think whenever we look at survival as the only surrogate end point, I think we go back and we ignore quality of life, and I think for these patients that survival in Class IV-B heart failure may not seem to show the exact end point you want by that analysis, but I think it really ignores the incredibly poor quality of life they have and how much better the survivors of this technology have shown.
Dr. Garber: Well, yeah, I think quality of life is extremely important and I'm not saying that. I'm just trying to suggest an analysis.
Dr. Miller: I think your point is well made. It's just that in that variable, it's hard to fold in quality of life into that equation, but it's really an important

variable for the patient.
Dr. Sox: Yeah, trying to help CMS formulate policy with these types of analyses might be important to do.
Dr. Rose: I'm concerned, though, that creating a post hoc scoring system on the basis of this data to make clinical decisions about this patient population using the stick, essentially, of reimbursement, in a field that is still moving with outcomes that are changing quickly towards the better in the groups that's treated when there is no subgroup analysis that we have shown that shows inferiority

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in outcome in those that get a device, is I think a dangerous place to go.
Dr. Miller: I think one thing that hasn't been said that's probably worth mentioning is that as CMS has to approach this, you can appreciate that in the realm of transplantation, which is another therapy for end stage disease, there is no data, there has never been data to document that that therapy was superior in any aspect to general medical therapy, but was adopted. Here we have a randomized controlled trial to form the basis of this analysis and I think that's a distinguishing point that we can go back and try to look at that data, but it's amazing in the area of heart, lung, liver, kidney transplantation, we've had no body of data to suggest that that was favorable and yet, because of the weight of the evidence that was put forth subsequently, it has been adopted now.
Dr. Sox: Well, the standard of proof is going up and that's wonderful, and I guess we're just asking whether it's possible to push a little harder and you're basically saying no, I think.
Dr. Garber: Can I just make a quick?
Dr. Sox: Yes, Alan.
Dr. Garber: I don't think that any of the panelists are questioning whether this works. I don't think that's what this discussion is about. This discussion is

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about in whom does it work, what can we infer from the trial. I haven't heard any comment suggesting that we're questioning the results of the REMATCH trial and whether this is effective in a group of patients. Our big question is well, who should we say these results apply to.
Dr. Long: It's important to everybody at this table, responsible dissemination is often critical from lots of points of view, economic as well as well being for our patients, and irresponsible application of this beyond an

appropriately proven population set would be inappropriate. A starting, point, however, here today, is the REMATCH population, and that population is characterized, that population has gone through pretty impressive scrutiny from a statistical analysis point of view, and gives us that starting point. That's why we would argue that the importance of acquisition of data subsequent to this process is critical.

We believe we have to collect that data and look at this moving target. Right now if you were to ask those of us who have been involved in this, which way is the target moving, you'd hear what we said earlier this morning, the target is moving in the direction of improved outcomes for LVAD patients and static progress or no progress for medical patients. Is that proven yet? No. That's a trend and it will have to be analyzed by subsequent data collection. So

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it's important as part of the responsible dissemination of this that, A, start with what we have and what we know. I think we feel it unconscionable to do that. But secondly, make sure that we don't broaden beyond what we have studied and make sure that we do collect the data long term to further focus it.

Dr. Daniels: But Alan's point is slightly different, it seems to me. I thought what he was really pushing you to answer was this: Can we figure out more from what you've got there than what we now know about which group is the, in a sense targeted population for this therapy. Because if we're going only for the sickest part of that population rather than the broader base of it, it makes a big difference in how one thinks about what you've learned from this particular --

Dr. Rose: I think that point is very well taken, but I guess we're feeling chagrined at this point because we've jumped out of the box and said that inotrope dependency is a major predictor here, and when we put that to further tests, just looking at our own data, it just didn't hold up. So before we make policy, which is what our concern here would be, that we would see policy emerge on the basis of secondary analyses of a small data set that would generate decisions about patient selection. We don't want to represent that this data is good enough to do that. I think

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over time we will get that information, but to think that it's necessarily here in this data set, I think overestimates its utility. It's too fine a hair to split, I think, with

this data set. We have been burned already with this inotrope issue.

Dr. Sox: Mark.

Dr. Slaughter: I think the big concern, I mean, you all are the experts in the field and assuming that the evidence is adequate, the next issue then is how do you disseminate it. And if the issue is that there is very little guidance other than REMATCH entry criteria for who should get them, then the question is well, can you really sort of open it up to other centers to try to expand the field to the Medicare population in general. And the concern then would be well, it should stay in the hands of 10 or 20 people, and it will take another three to five years to get 60 people, and these people are sort of looking for some additional information, guidelines, prognosticators, such that if it is adequate and if there is some mode of dissemination, then there is reassurance that these guidelines will ultimately lead to improved patient outcomes and truly identifying a patient base.

Dr. Miller: I think that's well phrased. I think that what we're trying to identify is similar to your previous comment. We have now understood that inotropic

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therapy and waiting until someone now becomes inotropic dependent to get them there is a 60 to 80 percent one-year mortality. We're really getting closer to inability to tolerate ace inhibitor and ARB, inability to tolerate a beta blocker. So I think we're describing more clearly a population that if we wait until they pass that threshold, we will have such a high mortality we really won't benefit this population. So, I think we can really pretty well describe in a very short publication the things that we have learned from the INOVA, that we have learned from really looking at risk factors for outcomes that better defines the broader population that may well eventually exceed the 5,000 who could benefit from this, because I think we will always be able to show that the improvements that have been demonstrated with device technology will always exceed the prognosis for the patient with end stage heart failure.

Dr. Sox: Now, I put the voting question up there as sort of a warning to the panel that we're starting to get to the point of taking a vote on this so we can move on to the other issues. So with that, Steve and then Linda.

Dr. Gottlieb: You know, I think it's wonderful that REMATCH was done, and I wish that we would have more randomized studies in this field, and somehow they're not

being done. So what we have are 68 patients and the question is where do we go, and there are two conflicting things here,

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because you can look at REMATCH and say you had a 75 percent one-year mortality, and that's what drove your benefits and that you're going to get benefits just in sick people. And then what I hear you arguing is you know, the healthier people obviously do better and have better outcomes, and the device is getting better, and it's the healthier people who are going to benefit.

I think you would totally agree that, you know, it's one thing if these 20 centers, to say ace intolerance, beta blocker intolerance is a predictor, which I'm sure it is. On the other hand, you and I and plenty of people know that 90 percent of the people who come to you ace intolerant and beta blocker intolerant are not ace intolerant and beta blocker intolerant. So I'm wrestling with the question of how are we really going to define this so both appropriate people whom your paper will describe as the ace intolerant, beta blocker intolerant, are really the ones who will get it and who will benefit.

Dr. Miller: That's our hope, that having the connection to a transplant center in one way or another, having it vetted through them will go to define and push that definition, like inotrope dependent, like ace intolerant, like all those things will be able to define a patient who's had a really aggressive go, and would therefore fit into that category.

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Dr. Gottlieb: Along related lines, and this may be tough for you to answer, but we're talking about what sites this should be at. Do you have any insight just based upon your 20 sites of characteristics that might predict a better outcome among the sites?

Dr. Miller: Between the sites?

Dr. Gottlieb: Yeah, you know, there were some sites that presumably were better than other sites.

Dr. Miller: I don't think on that aspect, Steve. I think everybody would say, I think, we're respected people in the field and have pushed that envelope as far as I think we can, that they clearly all met with similar review and aggressive therapy.

Dr. Sox: Linda and Cliff, and then I am going to kind of press to a vote.

Dr. Bergthold: I'm going to hold it until after we vote on this.

Dr. Sox: Okay. Steve, did you want to say something?

Dr. Phurrough: I just had one final question. The voting question says conclusions about Medicare beneficiaries meeting the REMATCH trial criteria. Now the REMATCH trial criteria included an EF of 25 or less, and a peak VO-2 that started out as 12 and then went to 14. However, the patients were much sicker than that. The average EF was 17 and the

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standard deviations didn't make it up to 25. The peak VO-2s, you said were 8, and the standard deviations I assume didn't make it up to 12 or 14. So, is the evidence adequate to conclude that this is beneficial to patients who meet the REMATCH trial criteria or the average values for patients that were treated?

Dr. Rose: I think with regard to the confidence limits around the criteria, there are lots of patients who were this sick for this long that are inotrope dependent who can have an EF as high as 25 percent. If you look two standard deviations around --

Dr. Phurrough: Well, the two standards were 4.5, I think, 17 plus or minus 4.5, so that's 22.

Dr. Rose: I think that those who are knowledgeable in this field would say that to parse candidacy or not on the basis of 3 ejection fraction points, and someone --

Dr. Phurrough: Is 20 a better number than 25?

Dr. Rose: That's exactly what I'm trying to answer. We debated this and I think the sense is certainly 20 is too low, 22 is --

Dr. Phurrough: No one measures at 22, they measure at 20 or 25.

Dr. Rose: Yeah, it's either going to be 20 or 25, and that's I think why we came down on 25. With regard to the VO-2 max, I think 12 would be a reasonable upper limit

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versus 14, I don't think there is strong feeling on that either, but lower than 12, again, you may have someone that but for that criterion is being denied access to this who on a clinical basis when for every other reason looks like they should be a candidate. So, to build in some flexibility --

Dr. Phurrough: I guess the underlying --

Dr. Rose: I'm looking, and the VO-2 max I thought was 9, not 8.

Dr. Phurrough: I guess the underlying issue is, when we do decisions and set policy, we want to include the right groups of patients, and if we're putting in criteria

which don't make a difference, why put the criteria in? If in fact you're going to base it on Class IV symptoms despite optimal medical therapy, or ineligibility for cardiac transplant or other issues, and everyone is going to be below 25 who meets that and everyone is going to be below 12 who meet the other criteria, do there need to be this criteria at all? And patients are sicker than that, if you're going to use the criteria, why use criteria that the patients in the trial didn't meet?

Dr. Miller: Well, I think one important criteria would be the functional assessment. Cardiopulmonary exercise test has been clearly shown, a number of patients are breathless on moderate exertion or breathless at rest, who's not really limited by cardiac dysfunction. So I think

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proving that that's cardiogenic with the exercise test, I think is a critical part of that differentiation. It's clear from a lot of data that the worse your ejection fraction, the worse the prognosis, so it begins to identify a cohort that fits into that that defines it as not diastolic dysfunction, it's systolic dysfunction, so forth. I think what we put is a pretty simplistic list that most people will qualify and will fit within that criteria.

Dr. Sox: You certainly don't want to pick the middle of the distribution as your cutoff.

Dr. Rose: That's exactly our reasoning.

Dr. Sox: And so something at the upper bound of the 95 percent confidence interval ought to be a reasonable expression that would cover most of the patients in the study, not half of them, or the median. Alan, help us out.

Dr. Garber: Would it be out of order to make a motion to amend the voting question at this point?

Dr. Sox: By all means, and by that I mean go ahead.

Dr. Garber: This is prompted by Steve's comment. What I would like to propose as an amendment, instead of where it says meeting the randomized, et cetera, trial criteria, in Medicare beneficiaries comparable to the sample enrolled in the randomized, et cetera. In other words, rather than saying you just get over that bar to meet the

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criteria, say that you're comparable to patients who were actually studied. And in fact, I think, I feel very guilty that we didn't catch this before, because in general that's what we're looking for, not meeting inclusion criteria but being drawn from a comparable population.

Dr. Sox: Okay. So if I understand what Alan is saying, basically let's use words that describe or characterize a patient population that is comparable to the study population rather than picking an arbitrary and perhaps cut point that might in fact eliminate a lot of the patients that were in the study. Norman.

Dr. Daniels: I have a little worry about that wording because it's going to be continually contested what counts as comparable.

Dr. Garber: It will be continually contested who meets the criteria too.

Dr. Miller: In a patient advocacy comment, if you wait until people met that criteria, you're going to cause a lot of people's undue death waiting until they are Class IV-B heart failure and meet the tightest criteria of the worst prognosis involved in the study. The criteria as outlined in that question, I think, try to guide getting to that cohort that we can benefit the most.

Dr. Daniels: Doesn't that just not address the question that we were raising before, which is which part of

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this population you studied are you really looking to see the maximum benefit in, the sickest part or a much broader group? In which case the incidence --

Dr. Rose: But I think we're parsing a group of patients that are all sick, and there is no healthy group that meet the REMATCH criteria. Now the difference between one group and the other is 60 percent one-year mortality versus 80 percent one-year mortality.

Dr. Garber: No. The problem is, you have told us that you cannot infer from the results of the REMATCH study who within that benefits. You told us and you gave a cogent argument why you can't do the subgroup analyses. So what are we left with? We are left with knowing that in the REMATCH population there was an overall benefit. The criteria by themselves do not insure that the same population will be picked when this is disseminated, and that's the reason for my change in the wording, because I'm afraid if you tell us that we can't say that a population that met criteria was like this population in the study, we would probably have to vote no on this question. So I'm trying to phrase this in a way that I feel comfortable saying yes to, that is in a population like those actually enrolled.

Dr. Phurrough: Let me try and resolve the question issue, because the question that we're asking here is not a coverage question. We're not saying in this question, should

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we use REMATCH criteria as the criteria for providing coverage to Medicare beneficiaries. What we're asking is what did the evidence show, and based on that, I think Alan's observation is probably an appropriate observation, that we want to know, is the quality of the evidence in REMATCH adequate to draw conclusions about the patients who were treated in REMATCH, not about patients that were thought to be ones that we were going to include in REMATCH. So, I think that is the question we want you to answer, is the quality of evidence adequate to draw conclusions about the patients who were treated in REMATCH? So I think that is an appropriate motion to modify the question.

Dr. Sox: So now I'm talking to the voting members mostly and trying to get a sense of how they feel about Alan's suggestion, whether people are going to have trouble with that. Mark?

Dr. Slaughter: I may be a little confused, but I want to make sure if you drop certain criteria and maybe not ultimately, but my impression was a lot of the criteria were actually developed to make sure that an inappropriate patient did not receive a very expensive technology that carried significant morbidity and mortality. And the example being, you may have someone who has Class IV heart failure and their blood pressure is 70/80 and they can't get a beta blocker, but they have a VO-2 of 16. Well, that patient very likely

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may live two or three years in intermittent Class III heart failure. So some of those criteria are established not necessarily to give you the really sick patient population that's going to die, but equally important is to protect or to keep a less experienced clinician from implanting someone that could have done as well or maybe even better without the device.

Correct me if I'm wrong, and that's the reason I hesitate. And it may be that the question is okay, as long as we are not permanently removing those criteria from showing up in some kind of document or guideline.

Dr. Sox: The criteria may show up in the confidence intervals around the actual, you know, cut point that they establish for the study. Wade.

Dr. Aubry: I think my comment is more of a point of order. I think we're confusing coverage with evidence and what the evidence actually showed in the patient population. And my point of order, my understanding is that this is a CMS staffed recommendation and that it may not require a vote to

amend it if the CMS staff decides that the amended question is really what they want to ask.

Dr. Sox: I thought I heard from Steve saying that Alan's suggestion in fact was a good suggestion to them, but maybe I didn't hear that.

Dr. Phurrough: Interesting question, Wade, in that

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we have gone through this in many of our panel meetings and some changes of questions, and the panel has been given the freedom, though reluctantly, to modify the questions that we submit, because obviously we spend some time on these questions but as this discussion goes along, it's not uncommon for there to be some questions raised that would indicate the question could be worded a bit better.

So we don't object to minor changes, and I think this isn't a major change. We're not asking you to tell us what the coverage criteria should be or what the indications should be, we're asking you to tell us what does the evidence show. And if changing that to say, is the evidence adequate to draw conclusions about patients who were actually treated in the REMATCH versus the criteria, who meet the criteria of REMATCH, I think is a change that we would not object to.

Dr. Sox: So let's type it in. Alan, do you want to restate it so we get it correctly in the computer?

(Discussion off the record.)

Dr. Sox: Any objections.

Dr. Phurrough: I'm checking with my staff.

Dr. Sox: So, we will let that change stand. I think it will make it easier for the people who have to vote on the truth of the statement.

Well, Alan, I think effectively, but he hasn't actually made a motion. He has basically implied that he

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thinks that at statement true. And I guess --

Dr. Garber: So move.

Dr. Sox: So now he has moved that we vote that that statement is true. Would anybody like to second?

Dr. Gordy: Second.

Dr. Sox: Now here is what I would like to propose, is that we now discuss the motion, and I think especially we want to hear from people who are concerned about how to vote, so that we can try as much as possible to get more information to make it easier to know how to vote. And once we're kind of past that, then we will actually ask each voting member to state their opinion about that statement, taking into account some of the considerations for quality of

the evidence that CMS asked us to think about.
Then if we vote yes for that, if we vote that the evidence is adequate, then we're going to talk about how big the effect is, the size of the net benefit. So now is the time for voting members of the panel to raise issues that are troubling them about helping them to try to make a vote yes or no. Well, since I didn't hear any statements, I'm assuming that people are ready to vote. Is that correct?
Now the rules of the game state that before we vote, each of us individually who are voting will express their opinion about that statement, and this will help CMS when they actually go to the process of making a coverage
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decision. So, Linda? Oh, excuse me. At this point we need to hear from Kimberly so that we do things exactly right.
Ms. Long: For the record, the voting members present for today's meeting are Wade Aubry, Norman Daniels, Alan Garber, Cliff Goodman, Tracy Gordy, Mark Slaughter, and Louise Woerner. Dr. Sox will vote in the event of a tie, and no voting member has been recused because of conflicts of interest. Dr. Sox will call for a motion and ask the voting members to vote.
Dr. Sox: But I now need to ask, we have the motion, but we need to have a statement. And Linda, and Eileen, the statements would include the consumer representative and the industry representative, even though you can't vote. That's the latest interpretation.
(Discussion off the record.)
Dr. Sox: So we will actually start on my left, and Tracy, you're going to get the chance to lead off.
Dr. Gordy: Well, thank you for that opportunity. I think that the material that we have been presented does meet this criteria, certainly, if you compare the two groups, there's not a whole lot of question but that the LVAD group did better and that the quality of life which is in part a factor in here is well recognized, so I would support this motion.
Dr. Sox: Thank you. Alan.
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Dr. Garber: Yes. I think despite a lot of questions in interpretations and particularly about generalizability, that this is a very well designed trial that gave a conclusive answer to the question, so I believe the evidence is adequate.
Dr. Sox: Cliff.
Dr. Goodman: I would not have been able to say yes

to the previous question. However, the way it's reworded now, I would say the evidence is quite sufficient to answer yes to this question.

Dr. Sox: Louise.

Ms. Woerner: I think it's a very excellent study that was done for reasons not to establish some of the things that we're trying to draw conclusions about here, and so I don't think that the quality of the evidence is sufficient to draw the conclusions that we're asking in this question.

Dr. Sox: Norman.

Dr. Daniels: I think I share some of Louise's reservations. I think the study as designed, and looking at this question as asked, I would have to say yes to this particular wording of the question, but how useful it is for me in understanding what one has to know in order to make advice about other aspects of the implications of this study, I would like to have known more than what's shown in this study.

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Dr. Sox: Wade.

Dr. Aubry: My answer to this question is yes. I believe the study was well designed and well conducted, the type of study that we as a committee are looking for to make decisions about effectiveness. And there are some problems such as the under-representation of women, some deficiencies in the quality of life data in terms of sample size, but I don't think that they outweigh the overall conclusion of the study and therefore, I feel a yes vote is warranted.

Dr. Sox: Mark.

Dr. Slaughter: I would also have to vote yes. I think it's a well designed, well executed trial of a very sick patient population, and there is no doubt that the only sort of significant long-term survivors are in the assist device group. Quality of life is certainly variable amongst those survivors, but appears to be significantly improved in the device patients. I think it's just the beginning of a long task ahead, but I would say that the evidence is adequate.

Dr. Sox: Eileen, what would you say if you were going to vote?

Dr. Helzner: If I could vote, I also would vote yes. I do believe this is a well designed clinical trial. It's difficult to execute these trials, for those of us who are involved in doing them. And as Mark just said, this is

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the beginning to really understand how clinical medicine

really improves and grows, is through a continual collection of data, better, and in this case improvement in devices, improvement in technique, and really being able to maximize what you can do for the patient, and that's learned by gathering more data, and this will allow that to happen.

Dr. Sox: Linda.

Dr. Bergthold: I would concur that the quality of evidence is adequate to draw the conclusions, but I would also second the concerns about the quality of life issues and the under-representation of women and minorities. And bring up an issue that we didn't discuss but sort of looms large in my mind as a potential Medicare beneficiary myself some day, and that is the relative cost of the medical management treatment versus this treatment for a population of patients so small overall.

Dr. Sox: I'm not going to vote either unless there is a tie, but if I do get the vote, I would vote yes. This is a study that has shown that you can add about 250 out of hospital days of life at the end of an illness without really -- so you have delayed life with a quality of life that appears no worse and maybe better than the only alternative that's available. I feel as if we've had a remarkable experience to, opportunity to ask a lot of questions of the requestors, they have replied in a collegial

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and forthcoming way, and so any concerns that I had about the ability to draw a conclusion have now been satisfactorily answered.

Ms. Long: We are now going to vote on the motion shown on the slide. This will be a yes-no vote. For the record, all those that vote yes, please raise your hand.

I show six in favor.

And all those that vote no? One.

For the record, the vote is six to one in favor.

Dr. Sox: Thank you. So we have now decided that the evidence is adequate to draw conclusions about the net health outcomes. We now have to decide just how big that outcome is, so can we advance the slide to the -- okay. There is the question, does it demonstrate a positive net health outcome and if so, what is the size of the improvement? And the next slide basically allows us to choose any response from not as good, to better, to breakthrough technology.

So, who would like to make a motion about which of these we should pick as our measure of effect size?

Dr. Phurrough: And you do have definitions of

these in your packet if you need to refresh your mind as to what they are.

Mr. Bridger: Tab 6 of your second panel package.

Dr. Sox: Alan.

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Dr. Garber: I'd like to make a motion just so we can start the discussion. This is kind of a strawman motion, but I'm not sure where I stand on this, but I would like to move that it is effective and falls in the category of substantially more effective.

Dr. Sox: Do I hear a second?

Dr. Gordy: Second.

Dr. Sox: So, any discussion of that? Yes, Norman, and then Tracy.

Dr. Daniels: Well, you know, these relative terms, substantially and so on, it's not clear what the reference class is, but it seems to me that it's just more effective. It adds some time and with a better quality of life, but it's a modest amount of time. And this effectiveness judgment doesn't include information about cost and opportunity cost of using this on this population, but it's very hard for me to completely block out of mind the concerns I have that if this is rated as substantially effective, it's going to imply a judgment that really this is something that people should be very encouraged to pursue on a large scale, and I think that there are really still questions about what it means to lure a very ill population into a prospect of a very modest increment in life expectancy with some quality of life improvement at this stage of their illness, when the ultimate outcome is just death, just a short while later.

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Dr. Sox: It might be helpful to think about a scale, and I don't know, what's the average number of days of life overall of patients screened for, let's say breast cancer screening in middle aged women? Does anybody have any idea? It's measured in days, what is it, 30 days or 20 days? And on the other hand, maybe we can have the help of our requestors. What's the average gain in life expectancy for somebody who has left main disease and is successfully bypassed, about six years, something like that?

Dr. Miller: It's less than that, more like three.

Dr. Sox: Okay, so three years, and that's one of the more dramatic interventions.

Dr. Rose: Coronary bypass surgery alone is probably more in the whole population, is probably more like a year, 1.2, two and compared to other things which are --

you know, gamma knife for brain tumors, other things comparable to that, 250 days mean, as someone pointed out at the FDA panel, a lot of things happen over the course of that median nine months, and that is a median, it's not a mean. We have patients now three and a half years out. Kids get married, governments change, the world changes, and a lot can happen over that period of time. There are not many interventions that generate a median increase in survival of this magnitude, especially this early in the application of the technology.

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Dr. Sox: So, it's on a scale that's sort of bounded at the upper end by coronary bypass surgery for left main disease, and at the lower end of many effective screening procedures, just kind of somewhere in the middle, I guess. Alan, and then Wade.

Dr. Garber: Mark, did you want to add something?

Dr. Slaughter: I was just going to add, unfortunately, I'm on our IRV committee back home, and it always amazes me that new cancer chemotherapy protocols, which are about one a week, and the difference in survival is usually a week to three or four weeks, and in between their quality of life is, you know, is significantly less than what we see here. And I have to say, when you talk about small versus substantial, or substantial versus more, it does get somewhat subjective, but I think when you put it in perspective with what other people consider to be substantial improvement in long-term survival, that meets the criteria for substantial improvement.

Dr. Sox: Alan, and then I think Wade was next, and then Cliff.

Dr. Garber: Well, my uncertainty about which category to assign this to doesn't have to do with the survival benefit, which I think by any yardstick is a substantial improvement. The issue has to do with quality of life and although the trial did a really excellent job of

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getting some quality of life measures, my read of it, and it's also implicit in some of the comments of the panelists, is that the quality of life in the LVAD group was much better than in the optimal medical management group but it was far short of a healthy person. And I think Dr. Miller maybe had said, think of it as comparable to someone on hemodialysis. And so the length of life is definitely prolonged and quality of life is improved, but not to a very high level.

That by itself kind of keeps it out of the

breakthrough category from my point of view. And is it substantially more effective or is it more effective? Well, our language for more effective, I think says something like marginal improvement, and it's clearly well beyond that in survival terms. I still am having a hard time, though, to figure out how to interpret the quality of life findings, and so that's why I'm not sure whether it should be considered substantially more effective or more effective. I'm leaning towards substantially more effective. I would feel much more confident if I had more complete information about the quality of life and the people who had the procedure, and I think that's probably going to be a job, an ongoing research issue for people who do get the procedure, to know how well they're faring not just in terms of survival, which is pretty easy to track, but in terms of functional status. We've heard a lot of anecdotes but it would be nice to have some

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systematic information on that point.

Dr. Sox: Wade.

Dr. Aubry: Like other members of the panel, I find myself somewhere between substantially more effective and more effective. I was going to use the cancer therapy analogy as well, and I would agree that many cancer therapies are marginally more effective compared to the improvement in survival and possibly quality of life, although I have, as I've said a couple times today, I have some concern about the quality of life data.

But I'm also looking at how we define more effective, and it does indicate a marginal significant, albeit small margin, as compared to established services, so I think that substantially more effective is more representative of the data, although as I mentioned, I would like to see as well, better quality of life data.

Dr. Sox: Cliff.

Dr. Goodman: My concern about going to substantially more effective is kind of a simplistic one, and that is, the observed mortality and quality of life benefit for LVADs is due not only to how well the LVADs do but how poorly the control arm does. That spread works both ways and based on the literature provided to us, the term optimal medical management is a misnomer, it doesn't sound optimal at all, and it sounds as though the state of the art for medical

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management of these patients is pretty murky, and as the literature told us, it's based on kind of informal consensus than randomized control trials. And so my expectation would

be, or I might anticipate that if we do a better job of gathering RCT based data for medical management, that that spread might narrow over time.

So while I think I will go with substantially more effective, I am very concerned and kind of disappointed that that spread is due at least in part to variation in practice and uncertainty, and the lack of evidence on the control arm.

Dr. Sox: Tracy.

Dr. Gordy: Well, I too would agree with the substantially more effective based on the definitions that we have here. The only comparable group that I was able to look at was the group that did not get the LVAD and to me, that's more than marginal, the effect that these people got with their LVAD emplacement. The substantially more would put it above the 50 percent mark in my estimation, as compared to more effective being somewhere less than the 50 percent, to go back to your could we put it on a number scale question.

Dr. Sox: Other sort of discussion points, and then I actually am going to ask everybody to say how they'd vote, and then we vote. Yes please, Louise?

Ms. Woerner: I would say that I'm very concerned, as some of the others are, about the quality of life issues,

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and also back to some of the total patient population enrollment issues. But I really believe that the technology is more effective rather than substantially effective.

Dr. Sox: Other comments before we become systematic about this? Linda, can we start with you this time?

Dr. Bergthold: Yes, you can, thank you. I believe that on the basis of mortality alone, it is substantially more effective and because of my questions about quality of life and other issues, I guess I would, if I could vote, say more effective.

Dr. Sox: Eileen.

Dr. Helzner: I would put this in the substantially more effective, given the consideration of how we view other interventions and also looking here compared with best medical management, which I believe these people got. But I understand where that, given the wording of more effective, I would vote for substantially more effective.

Dr. Sox: Mark.

Dr. Slaughter: I believe that based on the current data that we have and comparing it to the optimal medical management group, that it would be considered substantially more effective based on definition.

Dr. Aubry: Substantially more effective.
Dr. Daniels: I'm going to stick with more
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effective because I don't like grade inflation.
(Laughter.)
Dr. Sox: I'm glad I'm not your student.
Ms. Woerner: More effective.
Dr. Goodman: For this window, and for these interventions as performed in this trial, and in this enrolled population, this is substantially more effective.
Dr. Garber: Substantially more effective.
Dr. Gordy: I'm going to stay with substantially more effective.
Dr. Sox: If I get a chance to vote, I would also vote for substantially more effective, basically based on comparing it with other interventions that everybody thinks are really pretty special.
So at this point I will turn it over to Kimberly to do the official vote counting. So given that the quality of the evidence is adequate as determined by the earlier vote, the LVADs demonstrate a positive net health outcome that this panel would characterize as substantially more effective than the comparison therapy, optimal medical management.
Ms. Long: Okay. And we are now going to vote on that motion. Those in favor, please raise your hands. I have five in favor.
And those against? One against.
Dr. Daniels: No, no, sorry.
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Ms. Long: Okay, it was six to one.
Dr. Daniels: I'm sorry, which --
Ms. Long: This is substantially.
Dr. Daniels: No, I stick with what I said, so mine is a no vote.
Ms. Long: So it's two against. Okay. So the vote is five to two in favor.
Dr. Sox: Now Steve, perhaps before we start the discussion questions, and we have about a half hour before we're going to start to lose folks, you could tell us the purpose of the discussion questions and what you hope to gain from our discussion.
Dr. Phurrough: The discussion questions are added just to get a feel for what you think we ought to do in the implementation of a positive coverage decision. You have recommended that the evidence is advocate. If we take that recommendation and do a positive coverage decision, here are

some implementation issues that we would like your advice on. Many of them have already been discussed throughout the morning, particularly the five public speakers did address a number of these questions, and so we're just wanting to get a flavor of what you would recommend that we do in implementing around these particular questions. And so we're not asking for a yes or no, we're just asking you to discuss what you think our position ought to be.

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Dr. Sox: So one sort of efficient way to do this would be to just ask each person to comment, and then if we start to see some disagreement, we can have more discussion that will help CMS make a decision, but if we're all saying the same thing, then you'll hear that as well and we can move on to something else. So, does that sound okay to everybody, to just let each person kind of say what they want to say on each of these issues? Would that be okay, Steve, or would you prefer a --

Dr. Phurrough: That would be fine, though as they make comments, if there are other discussions or questions that occur at that particular time, I would not want to hold those until after everyone has made comments.

Dr. Sox: Yeah, if we stumble on things that are new, we will be sure to discuss them. So, let me see, Tracy, could you start?

Dr. Gordy: Sure. Yes, I think that the risks of implantation are justified. I think the study demonstrated certainly the extension of life and the limited improvement in the quality of life as compared to the other group, so the risk, while there is some material that indicates that in the beginning your sepsis and your failures were fairly high, as you've gone on and learned from the process, they have improved, and I think that's sort of the nature of medicine, in any kind of new implementation of a procedure or therapy,

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that with time it does get better. So I think yes to the question.

Dr. Sox: Alan.

Dr. Garber: I think my yes answer was implicit in the vote on the preceding two questions.

Dr. Goodman: I think the answer to this question is not one that I can answer, it is a question that a well informed person considering to have LVAD implementation who is informed by the information that you probably provide in informed consent as augmented by the findings of your trial would be better fit to make, so I will defer the answer of

that question to the person who is facing the choice.
Dr. Sox: But implicit I think in what you said is, if a person had a preference for LVAD and didn't have any obvious contraindications, that it would be a good idea to do it.
Dr. Goodman: There was nothing I heard today that would stand in the way of allowing a person to agree to have this, yes.
Dr. Sox: And he should therefore get it.
Dr. Goodman: If he or she so chooses, that is all I'm doing.
Dr. Sox: Louise?
Ms. Woerner: Well, as we're hearing, this is a very philosophic underpinning to how you look at this

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question, and I guess I would agree with Cliff that I wouldn't make this decision for other people. But I would say that if I were looking at it myself, I would be very concerned because of things that are happening, are very bad things that are happening to many of the people, and there's a cascading effect which really affects quality of life as I think of it. As I say, I would agree with you, I'm not sure I would like to generalize for other people, but the cascading bad effects can be something that would certainly give me pause.
Dr. Phurrough: You know, it might be easier to sort of restate this, because the comments are fairly similar. Should Medicare beneficiaries have the option of making this choice? Right now they don't have the option of making this choice.
Ms. Woerner: That's a pretty different question.
Dr. Phurrough: Well, the comments that you all are making, you know, beneficiaries need to get good informed consent and then once they get good informed consent and decide they want to have it, then they ought to have it.
Ms. Woerner: But I think where you're going with the question that you just posed is really, is it good public policy to spend a lot of money on a few people who we don't have resources to do things otherwise, so that's a different question.

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Dr. Phurrough: That's not where I was intending t go, no. I was only intending to go, should --
Ms. Woerner: But should Medicare beneficiaries have this choice is that kind of question.
Dr. Phurrough: Has the REMATCH trial provided

sufficient evidence that a beneficiary who is appropriately informed and meets appropriately defined criteria and is being provided services by an appropriate provider and facility have the option of making that choice? Should we provide that service for the beneficiary, meeting all those --

Dr. Slaughter: By service, you mean the option of having a device?

Dr. Phurrough: Yes.

Dr. Daniels: I guess I found your clarification more confusing than the original question, simply because I find it impossible to make a judgment about whether that Medicare beneficiary should have the option until I ask what are the opportunity or costs of making those options available to that population versus doing other things with the kinds of resources. If we were in a completely resource infinite world then we have a different option, and if the assumption is that Medicare policy is based on the assumption that efficacy and nothing else matters, then that's the way to frame the question.

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Dr. Phurrough: And for the most part, that is the framework with which Congress has given us authority to act, is it efficacious or not, versus is it cost effective or not.

Dr. Daniels: Well, I guess my -- if I were answering the question myself, I have too many reservations about the quality of life judgment to know what I think about this trade-off of life extension versus not, despite the results that we have seen in this study.

Dr. Sox: Alan, did you want to add?

Dr. Garber: I just want to take a stab at clarifying what I think was Steve's intent, and I think that Louise and Norm are raising very valid issues, but I don't think that's what the question is about. We're often faced with a situation where we have an intervention that both causes harm and provides benefits, and you're faced with the issue of how do you weigh them. And one way to think about it is, would a reasonable person choose to have this given what we know about risks and benefits.

So if you assess for something like radial keratotomy, there was a 75 percent mortality rate, and probably most of us would say they shouldn't be given that option. This is a case where there is quite substantial morbidity and mortality from the procedure but very substantial benefit. So I understand Steve's question to be given the whole set of outcomes that you can expect from

this, would a reasonable Medicare beneficiary choose to have this. Is that a fair statement, Steve?

Dr. Phurrough: Should they have the option.

Dr. Garber: Yeah, should they have the option. In other words, is it a reasonable choice for them, and it has nothing to do with costs.

Dr. Sox: Wade.

Dr. Aubry: I will say yes and add some I guess additional comment about the evolution of the technology. I think based on the current status of the device the answer is yes, but we've heard from Dr. Long that there are incremental improvements which are ongoing, and so that we might expect in the future that these results would be even better in terms of the safety profile. So I think it just sort of underscores the need to track that, particularly as technological improvements are made, it makes the case for a registry, the mandatory data reporting and follow-up trials on newer modifications, improvements in the technology.

Dr. Sox: Mark.

Dr. Slaughter: I agree with the last two comments, and the answer is yes. It is a potentially life prolonging procedure. It certainly has some morbidity and mortality associated with it, but the benefit certainly is significant compared to the risks, and they should have the option of at least having the opportunity to say yes, should they choose

this.

Dr. Sox: Eileen.

Dr. Helzner: I agree also, that this is an option that Medicare patients should have, and with all medical decisions, the risk-benefit ratio has to be weighed by the clinician, by the person, and make sure it's the appropriate patient who it's indicated for, but definitely they should have the option.

Dr. Sox: I agree that Medicare beneficiaries who have the facts about this form of therapy and want it ought to have the opportunity to get it. I am concerned about this issue of informed consent and the potential for the informed consent to vary considerably between different sites offering the intervention, and wonder whether one way in which to try to control the dissemination of this would be to standardize the information that's provided as part of the informing process, by a videotape that covers harms and benefits, and one that everybody agrees does it in a fair and objective and balanced way, that that might be a contribution to trying to

make informed consent truly informed.
Dr. Goodman: That was why I raised my initial point, I believe this morning, which was we would like to see some guidance and assurance that the care that was apparently taken by at least some if not all of your centers, in the kind of multistep aspect of informed consent, would be

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augmented by the findings of your trial and other research, and implemented in a comprehensive and standard way if this does become available to the Medicare population. And I'm concerned that it may be too easy to allow that careful informative clear objective process to be eroded.
Dr. Daniels: I wonder if I just could add a remark.
Dr. Sox: By all means.
Dr. Daniels: I said that were I in a situation of making this choice, I would be hard pressed to know whether the risks were outweighed by the benefits. And part of what was on my mind goes to some of the missing information around quality of life, because there was clear evidence in the earlier discussion and in the exchanges we had that some of the, that there wasn't a careful look at neurological deficits and other factors which may be significant following a procedure like this. And I would, I can imagine, I guess for myself and perhaps for some others, anticipating the strong possibility of cognitive deficits of a certain sort and what impact that might have on the kind of life you want to lead in your last nine months or a year, or whatever of mean life in this remaining period would make a big difference. So I think there is a lot of missing information and it doesn't show up in the quality of life measures that were being taken, that would necessarily for a lot of people

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offset the functional differences that those quality of life measures do show, other functional measures. That's what's missing for me and that's why I wouldn't know how to make this risk-benefit judgment just on what's there.
Dr. Sox: Okay, it has been a really good discussion, it has taken 15 minutes, and we have four more to go, and I've never finished a meeting late yet so I'm not going to start now. Wade, do you want to say something?
Dr. Aubry: Yeah, I just wanted to make a suggestion. Perhaps it would be worthwhile just to have each panel member comment on the questions as a group, anything about that. I'm just wondering if there would be enough time to go through each question one by one.

Dr. Sox: Well, I am concerned about running out of time. Well, one option would be for us to take a couple minutes to read them, just two minutes, and then comment on all of them together, and see if that doesn't move it forward more quickly. So we'll take two minutes to read, and then we will go around the room.

(Pause.)

Dr. Sox: I'm actually going to suggest that we do two, three and four together, since they're closely related, and we've already heard a lot about that, especially from the distinguished panel of invited commentators. So let's go around the room and handle two, three and four, and Tracy,

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you want to get thins started?

Dr. Gordy: Sure. I think that yes, to question two, that the transplant centers that are approved by Medicare should be the place where this start, and so that basically answers the second question too, initially, that that would be the place to start. Those are the places that have had some experience with this type of patient and would be more easily adaptable to the criteria.

The one concern I have about that is where do you stop with initial, but that's not part of what's addressed in one of our questions per se. At some point, in order to not disenfranchise the Medicare population, for example, it's going to have to be extended to a larger area and there probably is criteria, well, as a matter of fact there is criteria for applying for and receiving credit as a transplant center, so I suppose that takes care of that question, it's just the question of when does initial stop.

I think that from our reading material, the ISHLT criteria and reporting mechanism would certainly be, at least from my viewpoint, the most cogent area to focus the data that's coming back and have it collated.

Dr. Sox: Alan.

Dr. Garber: Well, for number two and three I think the goal really has to be to match REMATCH as closely as possible, that is, the treatment and the patient selection

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both, and I think that CMS can decide how best to insure that, and my guess is that it could be done at any Medicare certified transplant center, but that is not my area of expertise so I would defer to their judgment.

The one thing I would point out, though, is given the importance of the gatekeeper function, even in REMATCH institutions, I think it would be important to have some kind

of standardized well agreed upon criteria for selecting the patients, and I think that CMS will have to get involved or there may need to be some kind of national training to insure that there is some standardization to closely match what was done in the trial. I doubt that this can be done mechanically, it seems that these patients were very sick, and I think that this needs to be a fairly well defined set of criteria, and clearly with any intervention of this complexity, having all the pieces in place including the social support, follow-up care and so on, it is crucial, so the centers clearly need to have that, and I think transplant centers do.

Dr. Sox: Cliff.

Dr. Goodman: Question four, I'll just address this one for now regarding should mandatory data reporting be required as a condition for Medicare reimbursement, a very strong yes for that, including registry and to the extent possible provisions for explants and examination of those to

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best track any unexpected developments in the device, and how it fared in the body, that would be a very valuable aspect of data reporting.

Dr. Sox: Louise?

Ms. Woerner: I think everyone would agree that places that do more have the opportunity to do a better job in these highly technical procedures. I do think it's a challenge to try to balance that out with the access issues that some of the others had raised, so some kind of a stepped process of the type that's been discussed, I think would be important. Medicare coverage will certainly change the utilization rates of this kind of technology and so as that happens, the access issues, because these are very sick people, would be even more important, I think.

Also, I would agree that more study is needed, more data is needed, and the reporting would be very important.

I guess I would also just add finally that I think it's very encouraging and I appreciate the continued work that you all have done, particularly in the area of improved medical management of these patients, I think your improvements there as well as in the technology itself are very promising for us, and as you continue to focus on how to do it better, I really think that we will see some improvements as you indicated, that the folks following on should be more successful than the original people. So I

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applaud your efforts in medical management.

Dr. Daniels: I guess we're all concerned, and the comments I have heard all suggest my concerns which are about protecting quality of outcomes and guarding against a kind of non-data driven creep in the scope of the use of the technology. So I guess I'm in favor of a phased process but I want to put strong emphasis on the mandatory reporting in an appropriately designed database that has good access and can really inform the results of ongoing clinical research involving these categories of patients.

Dr. Aubry: Regarding question two, I would agree that the presentation of the American Society of Transplant Surgeons that a patient being considered for LVAD for destination therapy undergo a heart transplant evaluation by a Medicare certified heart transplant center first.

And in terms of question three, I think there should be a phased approach, and I think that most of the speakers today have agreed with that in one way or another, it's just a question of how to design that type of phased approach to insure reasonable high quality dissemination of the therapy. And I made in one of my slides a recommendation that could be considered along with the others in terms of the phased dissemination.

And then question four, I have already answered, I agree with the mandatory reporting and the registry part of

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this, which I don't think there is any disagreement about.

Dr. Sox: Before we go on, I just want to warn the nonvoting guests that we would like to hear your opinion as well, so be preparing one. Mark.

Dr. Slaughter: I agree, I think, that reporting should be mandatory. I have some concerns and reservations about the initial limitations to even transplant centers only, or even the current REMATCH trial centers. The example being, is that many of these patients are bedridden, in the ICU on inotropes and are not easily transportable, and so the suggestion was that they would have to be transported to a Medicare approved facility to be evaluated for transplant, which the answer is going to be no, because a majority are turned down by age alone, and then you have the issue of, are you going to send them back, do they want to go back. So what happens is they don't get referred to that hospital initially, and I think that is part of the reason why the initial enrollment in the trial took so long, was a lot of these patients aren't easily transportable, they can't travel, and it's an elderly population.

So I would agree with the recommendations made by

the ISHLT and the ACC that what you do want to do is try to develop centers of excellence that have an institutional commitment as well as the expertise of the staff, not only physicians, but nurses, you know, rehab services, and the whole gamut. But I think ultimately it would best serve the Medicare population.

Dr. Sox: Eileen.

Dr. Helzner: First of all, regarding the physicians and facilities to do this, I do agree with Dr. Slaughter in the sense that there should be very clear criteria of physicians, the facility, et cetera, and the expertise and centers of excellence that can do this. Whether that then can be expanded from only transplant centers to some others which can meet this stringent criteria, I think needs to be considered, especially for reasons of access.

With regard to data, I believe strongly that our commitment has to be a commitment that the folks doing this has to be a robust registry, really continual ongoing collecting of data, and continually updating and understanding better which patients will really benefit from this, so we can better characterize and answer some of the questions that were asked by our panelists, and so we can provide people with better information to make choices, and to provide our physician providers with an ability to give better care, so I believe that the data is clearly important.

Dr. Sox: Before we go on to the guest panel, I will put in my two cents worth. I certainly agree with the thrust of questions two, three and four. I did want to raise a couple of questions. When I saw the requirement for maintaining a certain volume of patients, a little red flag went up which made me concerned about perverse incentives, that is, offering it to patients that don't need it quite as much as others in order to keep your volumes us. And it seems to me that we need to prove that there is a relationship between volume and outcome before we stipulate that volumes have to be at a certain level.

The other point has to do with the REMATCH criteria. The REMATCH criteria have led to a certain gap between benefit and harm, which we take as being a reasonable gap, and so that's why we voted that it was, it had a substantial advantage. Imagine what happens when the harm starts to go down as the technology gets more improved. Does that mean if we don't change the criteria, then we're going

to be denying patients who don't meet those criteria but might meet more relaxed criteria, the opportunity to experience the same benefit as patients who experience the technologies during the early time when the harms are still high. So I think we have to be careful not to enshrine those criteria but in fact think about how to change the criteria so that the net benefit that's offered stays the same or at least that we don't deny to patients who would gain considerable benefit as the harms go down, the opportunity to have the intervention. We have to be even handed.

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So with that couple of squirrelly ideas, Julie?

Dr. Swain: Yes. I agree complete with that, and I agree with the panel's vote by the way, since we are talking about all the discussion questions, that this definitely improves survival and should be available to beneficiaries. The whole question, though, rings to the quality of life questions, and we've seen debate on the QOL questionnaires and the questions made up that these patients sometimes give answers that are unexpected. You know, they are on a ventilator and they're giving QOL answers.

So, I agree with the 1999 publication of the REMATCH study group that said, quote, because of this unblinded study, that objective measures of physical functioning were necessary. Therefore, they were prespecified to be six-minute walk and NVO-2. And the problem when you're comparing QOL and functional quality of life is what those data show. And in fact, the last public time we've seen this data is at the FDA meetings, and there was really no correlation between QOL and the results, and in fact there was no significant difference at any time period between the two groups on NVO-2 or six-minute walk and in fact when you just looked at how high the bar was, that six-minute walk was better in the medicine group at 18 and 24 months, and NVO-2 was better at two years, and nothing was significant because there is not enough data.

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So, I think we have to compare the QOL questionnaires with the lack of correlation with objective functional tests, the fact that 22 percent of the device patients chose to die rather than continue on the device, and the data presented again at the FDA was that the device patients spent on an average of 50 percent of the rest of their lives in the hospital.

Dr. Rose: That is incorrect. That is just incorrect.

Dr. Swain: Well, that was the data that was --
Dr. Rose: It was incorrect on the FDA slides as well. It is not correct. They spent 90 days at a mean of 450. You saying they spent half their life in a hospital is just incorrect.
Dr. Swain: That's why that data was actually given to the company to comment on and that was commented on as correct.
And finally, that 49 percent of the patients had neuro events and there were no cognitive tests done. So I think it is appropriately tempered, but I also think it's the best study that's ever been done in a surgery group, and there was a definite survival difference, and therefore, I agree that it should be compensated for.
Dr. Sox: George, let's focus the response on the answers to questions two, three and four.

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Dr. Agich: That's going to be a little hard. I mean, I guess I agree with all the comments or most of the comments that were made before. I mean, I think there is a clear demonstration of extension of life and improvement in the quality of life in the REMATCH study, and I do think that justifies the risks of LVAD implantation. But that's with the qualification, in appropriate patients.
And I think the worries about quality of life that have been raised here are ones that I have as well, because I think it's a matter of trying to define what are the appropriate patients, and I don't think the REMATCH data really allows us to do that, and wasn't designed to answer that question. But I think that's an ongoing problem that may be partly addressed by having robust registry or data that would allow for feedback of that data as clinical decisions are going to be made, because patients need to understand that they have an option to, you know, accept some medical intervention, a device, or they have an option of moving to palliative treatment, and it's not clear to me that the patients that we're talking about really had those options, at least with respect to palliative care. They were kind of self selected patients because of the research design issue.
But when we roll this out and make this more widely available, we're talking about some patients who would

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naturally, when they realize that they really do have a genuinely terminal illness, they may elect some nonaggressive intervention at life extension. I don't know how many those

patients are, but I think I'm concerned, as other voting panelists were, that appropriate informed consent is obtained, and that means that patients really do genuinely understand the range of treatment options, where I regard palliative intervention as really a treatment option here for an end stage disease, because you know, as good as these results are, and I do want to say that I think these results are remarkably good with the device, they are really still in the course of a terminal illness. I think I'll end my comments there.

Dr. Pina: I don't think it's that difficult to assess the patients who are at high risk for death. We have had it in the heart failure literature for a long time, this isn't anything new, and we know that study after study, patients with ejection fractions below 20 percent, and initially VO-2s below 14, which I think Les can attest to, need to be modified, to below 50 percent predicted will fit the category of the highest risk mortality, barring anything else. And then if you want to tack on renal dysfunction, that adds another bar to the sicker patients. So I think that in transplant centers, these patients are recognized.

I agree more with the STS decision of having

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transplant centers, Medicare approved transplant centers being the first tier. Why, because it takes more than one or two individuals to render a patient transplant candidate or not transplant candidate. This is a committee decision, committees are put on very very carefully by transplant centers that include lots of different disciplines. It includes ethicists, it includes social service people, psychologists, nursing. It includes some of our home care workers, some of our home care nurses, and you're just not going to find that level of commitment in non-transplant centers.

It is also at that place where the best heart failure cardiologists are kept, and the heart failure cardiologists are the ones who as Dr. Miller has well said, will take a look at the patient and say this patient can be maximized here and here and here, and they don't need inotropes, which we avoid at all costs, as has been said, and no, they do not need a device because what they needed was better medical therapy. So you're likely to capture the best care for the Medicare population patients and the best true assessment of transplant candidacy at a transplant center, regardless of how much experience somebody has in putting in devices in a non-transplant center.

The second tier, I would make those Medicare transplant centers who have LVAD experience. Not all transplant centers approved by Medicare have extensive LVAD experience, and it takes a huge commitment from the institution to care for the LVAD patients. It requires much more than a surgeon and a cardiologist. It requires nurses who are very adept at caring for these patients in a home care environment. Dr. Long has talked about training people out in the field. I mean, we have gone out and trained EMSs on how to take care some of our patients who go home. So it's much more than just the surgery, there is this whole encompassing clinical care that can best be delivered by a transplant center who also has a certain number of LVADs under their belt by the same surgeons.

Some of the initial REMATCH sites may not be the same surgeon anymore, and may not have the same cardiologist, people move around in this field considerably, but Medicare transplant centers have met a bar of transplants to be included. So I agree more with the STS decision than I do with the ISHLT, which encompasses other centers.

Dr. Gottlieb: First, a comment about VO-2 max, which I think CMS and the committee should know, if you really look at that number of 14, greater than 14 people have a good prognosis. However, the VO-2 max is affected by many things, not the least of which is deconditioning and the value of less than 14 or even less than 12 does not necessarily mean that that patient is severely limited. So in terms of making criteria, I think one has to remember the low number may not reflect a sick patient.

Next point, certainly informed consent, I would agree with most permanent members of the panel. Informed consent is essential. I think the recommendation from this committee is based upon REMATCH as far as I can tell, those are the data that I think that right now patients need to receive. They can't receive data that, well, we know that we're a lot better now. I mean, any data the patient receives should be based upon proven facts.

Related to that, I strongly support a registry, remembering however that the registry is just giving one part of the equation, and that's the implant part, and presumably it will show improvement over time, but we have to remember to compare that to what's happening with the other patients as well, which actually will be very difficult to do because we will not have a registry of that unless somehow we are a

little innovative and come up with a way to follow what's going on.

I would strongly agree that all patients have to be evaluated by a transplant center. I think that goes without saying. Right now as the data for patients who are transplanted is consistently better than the data for a device, they are not competing therapies, right now I think that the approval really would be for people not transplant

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eligible, so we would have to make sure that that is determined by people who do transplantation.

And then of course, there will have to be criteria for the surgeons as well. I'm not convinced that because a site has been in REMATCH, that that means that they will necessarily have the capabilities or be the best in terms of placing devices, for some of the reasons that Ileana mentioned, and I think we have to come up with some surgical criteria as well.

Dr. Lynn: I'll work from the high numbers down. First, a comment on Dr. Sox's comment about the expansion of the criteria. In this particular case there are two criteria that are especially problematic. One is that we have really skimmed over the fact of serious cognitive disability and mental disability in this population. Over half of the people who die with a diagnosis of heart failure in Medicare die in nursing homes or in long-term care. Most of those people are seriously disabled. Under the Americans with Disabilities Act the device must be made available to them in an equal way as it is to every other person. We have to really think about this sort of investment in that population.

And secondly, the criteria right now requires 60 to 90 days of serious sitting by and watching a person with terrible fatigue, unable to get out of bed, which probably

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actually worsens outcomes, so if the study criterion, and that criterion for eligibility is probably a contributor to a harm. There is going to be tremendous pressure to reduce the length of waiting, which both gets more people who are eligible and probably actually better outcomes, but many more people will be eligible if we move that to 20 days or 15 days.

The fourth question as to mandatory data requirement, yes, of course we should have mandatory data requirements, but I think that the parties speaking to this are seeing very different things, they are not saying all the

same things as to whether this is going to be heavily a quality improvement endeavor, heavily a way of organizing data so as to inform future decisions, heavily a way to monitor and police the bad centers so you can get centers out of the mix. There is a very different agenda and very different rules on how registries operate, and I think that we are not yet coherent about exactly what the vision should be.

The third question person was whether there should be facility and personnel requirements for evaluation, and yes, of course we should make sure thoroughly competent people are doing this evaluation.

Which relates to the second question, whether it should all go to transplant centers, I think that's a

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convenience at the present time, but there's no intellectually coherent reason why it has to be a transplant center. It could well be another well set up cardiology evaluation endeavor that is tightly tied to a transplant center so that those are eligible go to a transplant list.

But it seems that the main thing that we've overlooked here is that of the thousand people who came at this project, the biggest diversion, it seems, or at least a major diversion, were people who were not getting good care and who should have been getting a different sort of care and when they got that, they were not eligible for this because they were doing too well.

And it seems that that cycles, then, to the first question, which never made it down to the tail of the table here, and I will take a chance and just say a word on that. We should not only require very good consent, we need to be honest with these patients, that they are going to die, as we all are, but they are going to die of their disease within two years overwhelmingly, even with LVADs. That we have to make clear up front, that all of this is about palliative care, all of it is about living well in the shadow of their disease, and the consent process has to make that really intrinsically part of deciding how you're going to live out the end of your life. So it has to do with spiritual issues and issues of family closure and relationships, and what it

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is to live a life. It's not mainly about golf, it's mainly about saying good bye to your children.

And you know, there is something about coming to the end of life that is distinctly different that we do need to come to grips with. This is Medicare. 83 percent of us

die in Medicare. This is not a 30-year old with cardiomyopathy.

And then as to the merits of this device for the overall program, as a person who works mainly in long-term care, hospice care, care for people out of institutions who will never be referred to a program like this, I have to say, this is profoundly distorted. The allegation that we should be spending $1 to $2 billion on this device, this population, at a time when we can't get home health aides and we can't gets Meals on Wheels on weekends, we can't get basic things.

Remember, if you went to serve the heart failure population, surely the bigger investment should be seeing that everybody got the right treatment first, and then maybe yes, we should keep doing this device, but in an experimental sort of way, in a small way, figuring out where it really works, trying to get the cost down, trying to get it to be a better device. But as a general purpose thing for the population, we have to come to terms with the fact that life is finite. We should not be the kind of society that is willing to distort our application of our resources in a way

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that diverts it so substantially to a very small yield for a very small number of people when we have such need in such large numbers of people that we're walking away from.

Dr. Sox: Well, Steve just told me that he feels he has heard enough discussion of the discussion on number five, so we're not going to talk about that. Instead, I'm going to turn things over to Kimberly to dismiss us.

Ms. Long: Okay, to conclude this meeting, would someone move that this meeting be adjourned?

Dr. Daniels: Just before adjournment, I wanted to thank Joanne Lynn for her comments and to second the thrust of her remarks regarding the underlying decision that is at stake here, and the opportunity costs of the use of this experiment, this technique on a group of people who unless this is managed as a real learning experience that can expand that benefit for an appropriate subgroup of people over time.

Dr. Sox: Thank you. Any other last comments? Yes, Cliff?

Dr. Goodman: I can't let this go by. It's important to point out thanks to this trial and other research that the magnitude of people, this is responsive to your question part, the number of people who may be indicative of this technology has changed, we're learning a lot about that. The ION study in 1991 said this kind of thing could be useful for 60,000 people. The CMS summary of

evidence that looked at the 2000 census comments from Mechanical Cardiac 2000 talked about if this thing could be shown to work for, as destination therapy, it might apply to between 50,000 an 100,000 patients. However, as I think we heard Dr. Rose and perhaps Dr. Long say today, that the patient population that would be comparable to the REMATCH in the country is an order of magnitude less, perhaps between 5 and 10,000 people. I think there's a lot in there about the indications here and the size of this problem.

Ms. Long: Do we have a motion to adjourn?

Ms. Woerner: Yes.

Ms. Long: And do we have a second to that motion?

Dr. Gordy: Second.

Ms. Long: Thank you to everyone.

Dr. Phurrough: Just one final comment. I wanted to thank the panel. This has been a very good meeting and we appreciate your work, and thanks to the guests who took time out to join us, thank you.

(Whereupon, the meeting ended at 3:35 p.m.)