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Baltimore Convention Center
Room 327-9 One West Pratt Street
Baltimore, MD 21201

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Executive Secretary: Lauren K. Geyer, MHS

Roster of Panelists

Chairperson
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Veterans Administration

Executive Secretary
LAUREN GEYER, MHS
Coverage and Analysis Group
Health Care Financing Administration

Standing Panel Members
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College of Law
University of Utah

DR. KATHY HELZLSOUER, MHS
The Johns Hopkins University

ROBERT JOHNSON, MS
Midwestern University

RONALD JORDAN, RPH
Hospice Pharmacia

Temporary Panel Members

DR. JEFFREY LERNER
ECRI

DR. PAUL MINTZ
Arkansas BlueCross BlueShield

Consumer Representative
DR. LINDA BERGTHOLD
Researcher and Consultant

Industry Representative
CATHLEEN DOOLEY, MPA
Ortho Biotech, Inc.

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Head, Bone Marrow Transplantation Department
National Institutes of Health

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Greg Dean, Transplant Coordinator
Northwestern Memorial Hospital Dr. Robert Kyle
American Society of Hematology

P R O C E E D I N G S

1:00 p.m.

DR. BAGLEY: I just want to welcome everyone, and this is an historic occasion. It's the first meeting of the Medicare Coverage Advisory Committee, and this is the panel on Drugs and Therapeutics. It's something that we've been working for the past year and a half to bring into being. The committee's been chartered. We've worked -- we've worked very hard in -- in recruiting an outstanding group of committee members, and this is the first issue, the first committee meeting, and we think it's -- it's something very, very noteworthy, and just with that quick introduction, I'm going to turn it over to the Executive Secretary for this committee, Lauren Geyer, who is going to start on the agenda items, and the first one being the Conflict of Interest Statement.

Welcome and Conflict of Interest Statement

MS. GEYER: Good afternoon. I'd like to do a brief introduction to state who will be with us this afternoon and also to welcome all of you to our first panel meeting.

I am Lauren Geyer, the Executive Secretary of the Drugs, Biologics and Therapeutics Panel, and today on our panel we have Dr. James Adamson, who is a guest, and, in addition, we have Dr. Paul Mintz and Dr. Jeffrey Lerner, who are temporary members of our panel.

Dr. Holohan, who is our Chairperson, in one minute will go around and introduce the other panel

members. Prior to doing that, I'd like to take just a minute to read a conflict of interest statement as well as the appointment of temporary voting members memo. So, please bear with me.

First, the appointment to temporary voting status memo. Pursuant to the authority granted under the Medicare Coverage Advisory Committee Charter, dated November 24th, 1998, I, Mike Cash, appoint the following person or persons as a voting member of the Drugs, Biologics and Therapeutics Panel for the duration of this panel meeting on September 15th and 16th.

The aforementioned individuals are Dr. Jeffrey Lerner and Dr. Paul Mintz. For the record, these individuals are special government employees and are voting members of another panel under the Medicare Coverage Advisory Committee. Both members have undergone the customary conflict of interest review and have received the material to be considered at this meeting, signed Mike Cash, Deputy Administrator of the Health Care Financing Administration.

Next is the conflict of interest statement. The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interest. The agency has determined that all members and consultants 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.

Thank you. At this time, I'd like to turn the microphone over to Dr. Holohan, who will ask the other members to identify themselves.

DR. HOLOHAN: My name is Tom Holohan. I'm Chief of Clinical Programs and Patient Care Services at the Veterans Health Administration, Department of Veterans Affairs, in Washington, D.C.

I will take the easy way and ask the panelists each to introduce themselves. We can start with Dr. Adamson, who is a guest.

DR. ADAMSON: I'm Dr. Jim Adamson. I'm a Medicare medical director in Arkansas, and also the corporate medical director for Arkansas BlueCross BlueShield.

MS. BERGTHOLD: I'm Linda Bergthold, and I'm a consumer representative to the Executive Committee today sitting in for the consumer representative on this panel.

DR. MINTZ: I'm Paul Mintz. I'm Director of Clinical Laboratories and the Blood Bank at the University of Virginia Health System, where I'm a Professor of Pathology and Internal Medicine.

MS. HELZLSOUER: I'm Kathy Helzlsouer, and I'm a medical oncologist and a cancer epidemiologist at the Johns Hopkins School of Public Health.

DR. FRANCIS: I'm Leslie Francis. I'm Professor of Law and Professor of Philosophy and a member of the Division of Medical Ethics at the University of Utah.

DR. JOHNSON: I'm Robert Johnson, the Assistant Dean of the Midwestern University College of Pharmacy in Glendale, Arizona.

MR. JORDAN: I'm Ron Jordan, Senior Vice President at Hospice Pharmacia, Philadelphia, Pennsylvania.

MS. DOOLEY: I'm Cathy Dooley. I'm the industry representative for this panel.

DR. LERNER: I'm Jeffrey Lerner. I'm Vice President for Strategic Planning with ECRI, a non-profit health services research organization, and I direct the ECRI Evidence-Based Practice Center that's designated by the Agency for Health Care Policy and Research.

DR. BAGLEY: And I'm Grant Bagley. I'm the Director of the Coverage and Analysis Group in HCFA, that group charged with making coverage decisions and evaluating medical evidence, and also that group has this committee as its purview, and, so, as the federal official on the committee, I'm also a member of the committee.

MS. GEYER: At this time, I believe we will turn the microphone over to Ms. Andrea Argabrite and Dr. Bagley who will give a welcome and an introduction and a historical perspective on HCFA's policy.

Would you like to come forward? And for all of you who will speak this afternoon, there is a taller microphone on the table. So, you can help yourself to that, so we can all hear you well.

Overview

MS. ARGABRITE: Good morning. While Dr. Bagley is getting ready, he's going to be doing the initial presentation for --

DR. BAGLEY: Well, what we wanted to talk about real quickly is give you an introduction about how we got here and really what this process is about, and this really is a new process. This is a new

partnership. It's a new way in which we can do business and start looking at our coverage issues.

We've tried to put together a process which is open. I think the first place to look for it is on the Internet, and I don't know how many people have looked there, but we've got a web site up. You go to HCFA. You go to Quality, you go to Coverage, and you start to see what we're all about. You'll see the issues we're working on, and you're going to see how we're going to take care of these

.

Now, you know, really what we're all about is this piece of the Social Security statute because Medicare is supposed to pay for medical care, but it's only supposed to pay for medical care which is reasonable and necessary for diagnosis and treatment of a disease or injury. That's a very important concept. It's not research. It's not investigational. It's not a lot of things. It has to be determined reasonable and necessary, and that's really the fundamental question that we're going to be addressing in panels such as this.

We're going to be looking at new treatments, new devices, new methodologies for testing, and our decision is to find out whether or not they're reasonable and necessary.

Now, reasonable and necessary is all Congress said. So, what we really have to do is we have to make that decision because it's been given to the Secretary to do. It's been delegated, and that's the decision we have to make about new treatments.

We've had a lot of criticism over the last several years that the process we used to make that determination about what's reasonable and necessary was hard to understand. It was in a black box. People couldn't participate in it, and that it really needed to come in the open, and, so, we set about two years ago to change the process, and the first step we did was to say let's make it a process people understand.

We put a Federal Register notice out. That Federal Register notice was published in April of this year. The Federal Register notice is available on the Internet for those of you that don't subscribe to the Federal Register. It's available, and it's there, and it explains how we go about the process of looking at new issues, addressing new issues, and bringing them into the light of day, such as we're doing here.

Now, as part of that process, we went the next step. We not only delineated how that process would take place, how people could request that an issue come before us for coverage, how people could present evidence to us, but we put a second piece in place. That's an advisory committee, and that's what you're here to see, and this is the first time it's met.

This advisory committee has a lot of rules. It has a lot of formality because it's a federal advisory committee, but the important thing is that it's an open public meeting which allows for public participation and public discussion of all the issues that are here.

So, we've put two steps in place. We've got an advisory committee. You're here to see it for the first time. We have a process that we've delineated, put in the Federal Register. It's on the Internet, and it's all out there, and we still have some work to do, but we're still -- nevertheless, we're going about our business and looking at new issues that we have been requested to consider, and what reasonable and necessary means, we think, still further needs to be delineated by a regulation which is going to state the criteria.

We're working on that, and that's going to be very much something that occupies part of our time over the next year and will also occupy the attention of the advisory committee on occasion.

Now, what we did was we chartered this committee in '98. That seems like a long time ago, but I can tell you in terms of the government, it's been a lot of work to put it together. We've got the notice up. We're working on the criteria regulation, and we're ready to start this process. We're starting it now with this issue, which is multiple myeloma.

I think it's important that you're all here. You're here to see the process, and I think that the process as well as the topic at hand are both important, and we look forward to the public participation and the public debate we'll have in handling this issue.

MS. ARGABRITE: Okay. Good morning. We'll move forward just for purposes of time. This really talks about the documentation that we're going to cover about the compilation of medical and scientific evidence, and the coverage requests, again acceptance of complete staff evaluation, technology assessments, if need be, and then the advisory committee. These are decisions to get to whether or not to go to the issue.

Internal staff review. Once a coverage request comes in, we have to answer three questions. Is there statutory benefit for which this would fit? Are there no statutory exclusions to coverage, and is there sufficient evidence to enable HCFA to conduct a review?

These are general guidelines for looking at the strength of the evidence. Those really are part of what we're going to be looking at and clarifying further in guidance documents. Peer-reviewed published studies, adequate controls, absence of bias, and directly addresses issues of coverage.

For time, we won't go into it, but this was really more of a discussion of the MCAT committees that have been created. Multiple panels and executive committee, and this is our first meeting. This is basically to show you just a little slide of the structure of the major coverage advisory committees and the panels below the executive.

Again, being an open process, these are our coverage criteria. Safe and effective, clinical benefit, appropriate, and the risk versus benefit. All of those need to be weighed, and this is my section here.

Introduction to why we're here today. The issue is looking at autologous stem cell transplantation for

multiple myeloma, and that's really what we're going to be addressing.

The definition for today is the process in which stem cells are harvested from a patient's bone marrow or peripheral blood, stored and then given back to the patient following severely-myelotoxic doses of chemotherapy. You'll see the acronym HDC or hydrous chemotherapy or radiotherapy used to treat various malignancies.

Now, where our coverage manual specifies currently about multiple myeloma and stem cells is in our Coverage Issues Manual, Section 35-30.1, which currently says "stem cell transplantation is non-covered for the treatment of multiple myeloma".

The reason given for this is in our research, the data currently and prior data have been found insufficient to establish efficacy. It did not meet the definition of reasonable and necessary under the Social Security Act of 1862(a)(1)(a), and that's what Dr. Bagley had discussed before, is looking at that definition.

Today's objectives for the panel meeting and what HCFA and also the panel have to do today. HCFA must evaluate whether new scientific data on autologous stem cell transplants supports the national coverage decision in multiple myeloma populations.

Looking at the history of autologous bone marrow transplants and autologous stem cell transplants, those being the acronyms you'll probably be seeing today, this actually started in 1988, was the first -- there was an assessment done for the Office of Health Technologies Assessments, performed in '88, and their opinion was that the use of autologous bone marrow transplants for treatment of solid tumors, other than neuroblastoma, be excluded from coverage. That was their initial -- the initial technology assessments that were done on bone marrow transplants.

In 1990, HCFA began looking at the coverage of autologous bone marrows as part of the treatment of breast cancer. In '93, regional offices, which are -- HCFA has a central office and then four regional offices which stay in communication with us. The regional offices requested the autologous bone marrow transplants for multiple myeloma be evaluated at a national level. Again, that happened sometimes when there's controversies between the states on their own ability to cover.

We had given it to the states to make that decision prior, and they had asked us for help in '93. Because insufficient literature was available for us at the national level to draw a conclusion, it was left to the state level at that time.

In '94, HCFA revisited the issue, and the medical hearing body of HCFA of outside experts reviewed the literature and the technology assessments that were available at the time, and they upheld their previous decision that it was going to be left at what was considered carrier discretion which means the state carrier medical directors would be continuing on a case-by-case within their own states to make that decision on the coverage for autologous bone marrows.

This is again the data was insufficient on, you know, from the only assessment available, the health care technology assessment, for us to really feel that we could make a national decision.

In '94, BlueCross BlueShield technology assessment came out. Their assessment identified problems in the literature, recommended randomized trial, larger sample size and follow-up of outcomes and survival data.

The BlueCross BlueShield at that time really had just given the recommendations that they really needed to see more information, too, to make an informed decision.

In '95, conclusions from the Center for Health Care Technology. We had requested that HCFA formally request that the Center for Health Care Technology to do that review because of the lack of available evidence that we could find to make this decision.

Their conclusions in '95 stated the lack of well-constructed clinical trials, sample sizes in the population in question were too small to draw conclusions as to the clinical efficacy in our population, and that was the foundation for the decision in '96. BlueCross BlueShield issuers, other technology assessments, and on looking at all the literature, it was BlueCross had also recommended providing high-dose -- for final recommendations within their agency for BlueCross BlueShield was recommending high-dose chemotherapy with autologous stem cell transplants for newly-diagnosed or responsive multiple myeloma patients but did not recommend high-dose chemotherapy in autologous stem cells for patients with refractory multiple myeloma.

They advised offering it within the confines of a national study. So, again they did recommend coverage but within those specific criteria.

In '96 was when HCFA, based on the evidence that they had to review, issued their national non-coverage policy for autologous stem cell and bone marrow transplants for multiple myeloma. The rationale was again limited inclusion of patients, and this was predominantly the patient population, 65 and over being ours, was not included in many of the studies that were available for review.

There were methodologic concerns where at that time, the only real randomized study was at trial, and there was a question as to choice of drug therapy. If a conventional treatment group in the trial, selection bias cast a doubt as to why the high-dose chemotherapy group appeared to have higher survival rates. They had felt at the time there really wasn't enough evidence to really be able to make that conclusion.

In '97, HCFA revisited the autologous stem cell, and again there was still at that time, there was research being conducted in the field, but it wasn't available in the peer-reviewed journals to change their non-coverage decisions. So, it was upheld in '97.

In '99, HCFA received a formal request for coverage at the national level, and we decided to take it to an

MCAT really to be able to look at it further and to have an open forum to discuss the issue.

Also, there really has been significant public support for the stem cell transplants of multiple myeloma for autologous. We actually have a file of letters that is available for the panel to review. We have received many letters from the public in support for autologous stem cell. So, there's that for the panel to review.

So, today, the questions really being presented for us are to determine coverage, to help us to determine coverage and assist in policy development. We're asking for recommendations by the panel, and these are on the specific questions that will be raised today and throughout the panel meeting.

Questions for the diagnostic -- I'm sorry -- the Drugs, Biologics and Therapeutics Panel, related to stem cell transplant for multiple myeloma are. The first, is there sufficient evidence to support autologous stem cell transplantation for the treatment of multiple myeloma in the Medicare population, these being individuals over 65, disabled or have end-stage renal disease?

Second question we're presenting to the panel, what factors should be considered when developing a Medicare coverage policy for autologous stem cell transplants for multiple myeloma; i.e. age, prior treatments, co-morbidities, response to treatment? So, we're looking at what should be considered.

What is the most appropriate measure of successful outcome with autologous stem cell transplantation? What else supports the efficacy of more than one autologous stem cell transplant per patient?

The next question we're presenting the panel, what qualifications should apply for providers and centers performing the autologous stem cell transplantation procedure? Should there be a specific protocol for performing the procedure? And based upon current evidence, how does the source of stem cells,bone marrow versus peripheral, is there a difference, and should there be -- should there be one specified for therapy? And are there any other questions or concerns that the panel would like to address?

So, our final question to the panel is, if there are any further questions that need to be addressed, especially, you know, evidence that would need to be done, that's just to give that to the panel, if they would feel the need for that.

Thank you very much for your time.

Scientific Levels of Evidence

DR. HOLOHAN: I promise I can keep us on schedule. I want to make a comment about evidence. Before I do that, I should state to inform the members of the public that, in addition to my job in VA, I am board-certified in medical oncology.

This is the first official federal advisory committee panel meeting for the purpose of recommending Medicare coverage. This is a significant event, and I know I speak for us all when I say that this panel takes its work quite seriously.

We will hear testimony, review other information and evaluate the available medical evidence. Our charge from the Health Care Financing Administration is to weigh available evidence, to provide independent expert scientific advice, and to help the agency make sound decisions based upon the reasoned application of good science.

Therefore, we must and will consider objective medical evidence as the paramount factor in our considerations. To do otherwise would be to act in an arbitrary and therefore an ultimately indefensible fashion.

We're here only to consider the safety and effectiveness of high-dose chemotherapy and stem cell support for multiple myeloma. We are to judge whether or not the evidence supports its use in the Medicare population, and, if so, whether any conditions or limitations on such use are indicated.

We have no authority to address issues of financing or levels of reimbursement.

Arguments have been advanced that new technologies are subject to higher standards than were more mature interventions, many of which were or indeed are covered by the Medicare Program. While there is some truth in that statement, such circumstances do not support a conclusion that those higher standards should be abandoned.

Careful evaluation of the quality of evidence, so-called evidence-based medicine, is the contemporaneous but not a novel scientific tool that enables us to judge the relative worth of treatments.

The fact that this may not always have been applied in evaluating medical therapy in the past does not detract from its current essentiality.

We know that certain types of evidence are more likely to permit a valid and a reliable conclusion as to the effectiveness of a treatment. While the physicians and clinical researchers in this gathering are well aware of this hierarchy, not all here may be as well informed.

There is no perfect type of study. Those that are most likely to provide valid and reliable results are the more expensive and the more difficult to conduct. The critical point is to understand the assumptions we must make and the confidence we may have in the data generated by different methodologies prior to reaching our conclusions.

The table that we are making available comprises a widely-accepted stratification of the quality of evidence that is associated with different research techniques. While the citation on the table that HCFA will make available to you is recent, the concepts are not, and they have been employed by physicians,

researchers, statisticians, and other analysts for many years.

Indeed, much of this information may be found in the First Edition of Principles and Practices of Oncology published in 1982, in the chapter authored by Simon and entitled "Design of Clinical Trials", and I think at that point, I will turn the panel over to Ms. Geyer who will introduce speakers.

MS. GEYER: Thank you. At this time, I'd like to introduce Dr. Michael Bishop who is with us today from the National Institutes of Health, and he'll be providing a 15-minute Overview of Stem Cell Transplantation.

If Dr. Bishop will come forward? I would very much like to thank him for coming, and we've had great support from the National Institutes of Health in preparing for today's meeting. So, thank you again.

Overview of Stem Cell Transplantation

DR. BISHOP: I have provided the panel with an overview of my talk. I have been limited to 15 minutes in trying to discuss transplantation in multiple myeloma, and the hand-out goes along almost verbatim with my talk.

I have made the talk as broad as possible, not knowing the expertise with regard to multiple myeloma among the panel members, and I apologize to anybody who is more familiar with this disease.

Multiple myeloma. There are approximately 12,000 cases diagnosed each year. Its incidence among United States citizens is approximately four per 100,000, and it makes up approximately 10 percent of all hematologic malignancies, including leukemias and lymphomas.

The median age for this disease is 62 years, which will put it within the Medicare population. In specific, less than 18 percent of patients are under the age of 50, and less than three percent are under the age of 40. It affects males more than females, and there's a significantly-higher incidence in people of African descent as compared to Caucasians.

When we talk about treatment for multiple myeloma, most medical oncologists divide up treatment into induction, consolidation and maintenance. The standard or conventional therapy for multiple myeloma is induction chemotherapy. The gold standard considered for this disease is a combination of melphalan and prednisone or a combination chemotherapy with an anthracycline-based regimen which is, in the United States, the most commonly-used regimen. It's a bad regimen which consists of vincristine adreomyacin and dexamethasone, a steroid.

Following induction, one can consider consolidation with either allogeneic or autologous stem cell transplantation, and I will go more into the differences between autologous and allogeneic stem cell transplantation in the latter portion of my discussion.

There's also been considerable interest in the use of maintenance therapy following the induction phase. This can be with continued chemotherapy, often steroids, or the use of a biologic response modifier, alpha Interferon.

These are the results of continuous trials performed by the Southwest Oncology Group. You'll note by the first two numbers with them following the swab designation is the year the trials were initiated. Disappointingly, over the past 22 years, we have not seen a significant advancement in the primary treatment of multiple myeloma, despite the introduction of new agents into our armitarium of chemotherapy. These are generally all randomized trials, and they are compared to the gold standard of melphalan and prednisone.

Of significant note is the average median survival, which is approximately three years for this disease, and the continuing decline over a 10-year period of time in the number of survivors and increasing number of deaths that are observed of the patients at risk.

Unfortunately, in the last 10 years, there have not been any significant advances over the results that are demonstrated on this slide.

In regards to stem cell transplantation, bone marrow transplantation has become a relatively archaic term, and stem cell transplantation is the more appropriate term for hematolytic stem cell transplant.

Stem cells may be obtained from a variety of sources. They may be obtained from the bone marrow. They may be obtained from the peripheral blood, and in relative to the use and allogeneic stem cell transplantation may also be obtained from umbilical cord blood.

The differences between allogeneic and autologous. Allogeneic is where the stem cells are obtained from a person other than the patient. They have a donor as opposed to autologous stem cell transplantation where the cells are taken from the patient themselves.

Differences relative to allogeneic and autologous is donor availability. Where there is the ability to obtain a donor, it's basically quite limited and is approximately 25 to 50 percent, dependent upon the use, whether the donor is a family member or is obtained from one of the bone marrow transplant registries, as opposed to autologous transplantation where the overwhelming majority of patients are able to donate stem cells for themselves.

The limiting factor for an individual to donate stem cells is the ability to collect the stem cells either from the bone marrow or from the peripheral blood due to the extent of prior chemotherapy or to the degree of stem cell contamination.

In an allogeneic transplant, you do not have to be concerned about tumor cells being within the stem cell product as opposed to autologous stem cell transplant, especially for a disease like multiple myeloma,

where the disease itself arises from the bone marrow.

There is also an entity known as graft versus host disease, and an entity known as graft versus leukemia, a graft versus lymphoma. This is seen in allogeneic transplantation, and because where the stem cell transplantation in the allogeneic setting, one has a new immune system, and therefore that new immune system, even though it's matched as perfectly as possible, is not perfect, and therefore the immune system reacts against the individual causing -- resulting in the entity known as graft versus host disease, which primarily affects the skin, the gastro-intestinal tract and the liver. In autologous transplantation, this is rarely, if never, seen.

The biggest difference between allogeneic and autologous transplantation at this point in time is in treatment-related mortality, mortality directly associated to the treatment itself. The allogeneic transplantation, the transplant-related mortality may vary between 10 to 40 percent, dependent upon the disease state, the preparative regimen, stem cell source, and the use of prevention of graft versus host disease, as opposed to autologous stem cell transplantation which does not have any graft versus host disease, the treatment-related mortality varies anywhere from most institutions between zero to 10 percent, again often dependent upon the status of the patient themselves.

These are the current indications for both autologous and allogeneic stem cell transplantation as reported by the International Bone Marrow Transplant Registry which is based in Milwaukee. Approximately 65 percent of all transplant programs within the United States report to the International Bone Marrow Transplant Registry.

The Number 1 indication for transplantation is breast cancer. If we look at multiple myeloma, and these are the most recent updates for transplantations performed in 1997, we can see that approximately 1,500 transplants were performed for multiple myeloma in 1997. Approximately 80 percent of those were autologous stem cell transplants, and approximately 15 to 20 percent were allogeneic stem cell transplants. Those numbers continue to increase.

Now, this is data on Phase 2 trials of autologous stem cell transplantation in multiple myeloma. I tried to select from peer-reviewed literature with large patient populations and tried to choose a variety of patients who had multiple myeloma to give some contrast relative to outcome.

The first is a report from the European Blood and Marrow Transplant Registry. This is a group of institutions within Europe who collect data and also perform studies together. They reported on 207 individuals who underwent an autologous stem cell transplant for multiple myeloma. The treatment-related mortality in this patient population was four percent.

Approximately half of these patients were newly-diagnosed multiple myeloma patients, and half of them were patients who had failed the induction chemotherapy either by not responding to initial therapy or relapsing after initial therapy.

The complete response rate in this entire mixed population of 207 patients was 46 percent. A complete response is defined by either an improvement in the serum immunoglobulins that are with multiple myeloma by down to levels that are normal or an improvement, complete improvement of the bone marrow relative to the number of malignant plasma cells in the bone marrow, and that this would go back to normal numbers of less than three percent.

The event-free survival for this median event-free survival is 2.4 years, and the overall survival is 2.7 years in this mixed population, and again going back to our standard therapy where complete response rates are seen in less than 10 percent with conventional chemotherapy, and that overall survival rate was approximately three years, and this with a mixed patient population of patients with refractory disease and newly-diagnosed.

In comparison, results initially reported by the Fred Hutchinson Cancer Research Center in Seattle looked almost primarily at 63 patients who either had primary refractory or non-sensitive disease; i.e., when they had their induction chemotherapy, that they did not obtain at least a partial remission defined as either a 50-percent reduction in serum immunoglobulins or a 50-percent reduction in plasma cells or they had failed salvage chemotherapy.

The treatment-related mortality in this situation, and again this is over a long period of time of approximately 10 years, was 25 percent and primarily involved the use of bone marrow. The complete response rate, however, was 30 percent in patients who had refractory disease. However, event-free survival time for achieving that response to the time of disease progression was only 0.8 years, but the overall survival was 2.8 years.

The Royal Marsden in England was one of the first to take newly-diagnosed patients, give them induction chemotherapy and consolidate them with high-dose therapy and autologous stem cell rescue. Of these 53 individuals, the treatment-related mortality was two percent. The complete response rate, although very liberal in their description of a complete response, was 75 percent, the event-free survival was two years with an overall survival of 6.7 years.

The French Registry took all their patients together, and in a 133 individuals with newly-diagnosed multiple myeloma, they found treatment-related mortality of four percent, complete response rate of 37 percent, and event-free survival of two years, and an overall survival of 3.8 years.

The University of Arkansas reported on an aggressive double-transplant for patients with newly-diagnosed multiple myeloma. The treatment-related mortality was two percent, achieving a complete response rate of 41 percent by very strict criteria, and event-free survival, median event-free survival of 3.6 years, and an overall survival of 5.7 years.

All of these are Phase 2 trials, and there was no control group, except for a historical control group, in the comparison.

Probably the only Phase 3 trial with -- that has been reported as of yet with long-term results was reported by the French InterGroup on Multiple Myeloma, and this is -- the name of the study is IFM-94, which was reported in the New England Journal of Medicine by Attal and et al.

In this group, 200 newly-diagnosed individuals with multiple myeloma received induction chemotherapy with what was known as the VMCP and BVAP regimen. This was a standard used by the French InterGroup. It's an alternating chemotherapy regimen. The two regimens were alternated every three weeks.

Patients were randomized up front to either receive a continuation of VMCP BVAP for 12 months or to receive VMCP BVAP for approximately four to six weeks and then go directly to high-dose therapy which consisted of high-dose melphalan and total body irradiation, followed by autologous stem cell transplantation.

In regard to response, when looking at the conventional arm of just VMCP and BVAP alone, five percent of patients achieved a complete response, and 52 percent achieved a partial response, consistent with most results with conventional therapy. The transplant arm had a complete response rate of 22 percent and a partial response rate of 59 percent.

These are the results of event-free survival, looking at, on the white solid line are the patients who received conventional dose chemotherapy as opposed to high-dose chemotherapy. There was a significant survival advantage for the patients who received consolidation with the high-dose therapy and autologous stem cell transplantation arm.

This event-free survival also resulted in a significant improvement in overall survival for these individuals in comparison to the conventional treatment arm.

I believe Dr. Barlogie will speak. I didn't know that he was speaking after me. I will mention the other form of therapy is not as known, the total therapy regimen. I'll only speak briefly into this in terms of what is the current state-of-the-art for treatment of multiple myeloma. This consists of induction with the bad regimen for three cycles.

This is followed by high-dose cytoxin with growth factor which is used to collect the stem cells for storage. The patients go on to receive EDAPT, which is a platinum-based regimen which attempts to overcome resistant cells, and then the patients undergo tandem transplantations with high-dose melphalan, the addition of TBI based upon the initial response to the first transplantation.

Just giving some -- I don't want to steal Dr. Barlogie's thunder on this, but there is -- this gives some of the results, and this is the bottom line, as that overall survival exceeds five years in this patient population.

This is the EBMTR data on autologous stem cell transplantation, and I would note that these are patients

who were treated within 18 months of diagnosis as opposed to greater than 18 months, and median survival is approximately three years for this patient group.

Briefly on allogeneic transplantation, to give some contrast, the largest was reported by the EBMTR and recently updated in the British Journal of Hematology. Treatment-related mortality as opposed to autologous stem cell transplantation is significantly high, varying between 42 and 54 percent.

It should be of note that the EBMTR is a mixed population of both refractory -- primarily refractory patients. The Fred Hutchinson Cancer Research Center, almost all patients were refractory, had treatment-related mortality, yet 33 percent of these were able to achieve a complete response, and 21 percent at a median follow-up of five years were able to achieve continued overall survival.

The University of Arkansas was unique in this report. These are patients who had failed a prior -- the majority had failed a prior autologous transplant. The treatment-related mortality went up to 54 percent. However, they were able to achieve a 26-percent complete response rate and an overall survival of 17.5 percent to a median fault of three years.

This is a report by Gahrton et al in JCO, showing this is the EBMTR results, and you can see that approximately -- there's a plateau phase as opposed to the curve that was seen with conventional therapy, and the results of the EBMTR data showing approximately the same results of approximately 30 percent.

I think that concludes my talk.

DR. HOLOHAN: Before you leave, one of the panel members had a question. We'll have to make this very brief. We're already behind.

The question that I have is could you describe in 25 words or less to the audience what is a Phase 2 trial, and what is a Phase 3 trial?

DR. BISHOP: Yeah. I apologize for not doing that.

A Phase 2 trial is where a therapy has been demonstrated -- a Phase 1 trial is looking for toxicity, whether or not this has any -- the safety of the procedure. Phase 1 trials are generally new drugs or new procedures or new devices, and the sole goal of that is to determine safety, although efficacy is always looked at.

If there is substantial evidence that the device, treatment or new drug is relatively safe, and it has potential for efficacy, it's taken on to a Phase 2 trial, where patient -- where it's used as an up-front or as the treatment, and in this, we're looking for efficacy. However, it's not being compared to anything. All the patients receive this device or treatment.

A Phase 3 trial, if there is significant evidence from the Phase 2 trial that it looks promising, is take it to

a Phase 3 trial, where it's compared to the gold standard.

In this situation, where the Phase 3 trial that I demonstrated from the French InterGroup, was the conventional therapy, their VMCP treatment, versus consolidation with the high-dose therapy arm.

MS. BERGTHOLD: That helps because the question that I had is, are you aware of any Phase 3 trials that are currently underway but you said not reported yet?

DR. BISHOP: Yes, there are. Actually, the -- within the United States, there's an intergroup trial which is a cooperative trial between the major cancer groups, the Southwest Oncology Group, the Eastern Cooperative Oncology Group, the CALGB, Cancer and Leukemia Group B, and the -- I believe that North Central Cancer Group which is based out of the Mayo Clinic, and because of the high priority of this trial, that's why it's an intergroup trial, and that patients are being randomized after conventional treatment with the bad regimen, and they're having either randomized to consolidation with transplant or to continuation with conventional therapy.

This also had an allogeneic transplant arm attached to it, but that arm was closed down due to significant mortality associated with the early patients on the allogeneic transplant arm.

DR. HOLOHAN: Thank you. I was asked to make sure that people understood, despite the fact that Dr. Bishop referred for comparative purposes to allogeneic transplants, that that's not the subject of discussion today.

We now move to the Open Public Session, and we're going to ask people to come up basically two at a time, so that we don't run behind any more than we are right now.

The first speaker I have scheduled is Kathy Giusti.

Open Public Session

MS. GIUSTI: Can I have my slides, please?

DR. HOLOHAN: I've been asked to remind people that there is a timing system. Green, yellow, and red lights, which are self-evident.

MS. GIUSTI: Good afternoon, and thank you for the opportunity to address the committee on the important issue of autologous transplant for Medicare patients.

My name is Kathy Giusti, and I am a myeloma patient, but I'm also President of the Multiple Myeloma Research Foundation. Today, I'm also honored to be representing the International Myeloma Foundation and the Macardi Cancer Foundation. All three of these patient foundations are geared toward raising

awareness of myeloma, raising research for myeloma, but, most importantly, we also focus on educating patients and family members on the best treatment options.

I was asked to help you to understand a little bit about the disease, which I think has already been covered, some of the grim statistics with the disease, but, most importantly, why it is so critical that we make appropriate treatment options available to all patients with this disease.

I don't really need to go into this, except to say that multiple myeloma is an incurable cancer of the plasma cell, and I have to say that as someone who deals with patients every single day, it's this incurable nature of the disease that causes incredible emotional problems for them, but it's also the symptoms that cause incredible physical problems for them.

Two-thirds of them have severe bone pain, many of them have fatigue and anemia. They're susceptible to infections, some do go into dialysis.

Most people have never heard of myeloma, but I think it's really important to state today that multiple myeloma is the second most common blood cancer, second only to non-Hodgkins' lymphoma, and 13,000 people will be diagnosed, and 11,000 more will die.

I think it's also important to note that myeloma is one of the fastest-growing cancers in the United States today, and while some of that may be earlier diagnosis, we're not really sure exactly what's causing this disease.

Myeloma is definitely a disease of the elderly, of the people over 65, but I think we all wonder what that really means these days. People over 65 aren't really elderly or frail any more. Most of the 65 year olds that we talk to in the foundation tend to be leading very full, vibrant, productive lives. But it does skew that way, and you can see that for people under 65, the incidence is 1.8 per 100,000, over 65, it reaches 28.7 per 100,000, and as Dr. Bishop already pointed out, it's twice as prevalent in terms of African Americans to whites.

Now, I would hate to say that it's age or race that has caused the dismal statistics of this disease, but I think the next two charts speak for themselves.

The five-year survival for multiple myeloma is 28 percent, meaning that 28 percent of people diagnosed will be alive five years down the road, and I think you can compare that to other cancers, such as prostate cancer, breast cancer, which get a little more support, a little more attention than myeloma does, and this creates a very difficult situation for patients.

They know these numbers, and they're beginning to get incredibly frustrated feeling that nobody's watching out for them.

I think the next chart also shows this in the fact that when you look at how blood cancers may be a more

fair comparison have changed over time, you can see that we've done a tremendous job in terms of childhood leukemias. We now have 80-percent five-year survival rates, and when you look at Hodgkins' Disease, it's up to 81 percent.

But imagine when you're dealing with myeloma patients, and you tell them in the past couple of decades, their five-year survival has gone from 24 percent to 28 percent. I have to say this is a really difficult thing to help them through, and I think it creates an issue where they're struggling to find the positives of this disease.

But, finally, finally, we've found some good news, and that was the fact that as clinicians started to move from regular chemotherapy, such as melphalan and prednisone, to high-dose therapy, we started seeing a drastic improvement in complete response rates, from five percent to 40 percent, and we started seeing survivals creep up, from two or three years to five or six years, but now imagine you're still us, you're still answering the phones, and a lot of these people, at least half of them, are over 65, and you're saying the good news is there's good things happening, but the bad news is it's not available to you.

The frequent question we get is why isn't this covered by Medicare, and I have to say that I really feel like at our foundation, we don't have a good answer to that question, and part of the issue is that when you look at what are the prognostic indicators of who does well with high-dose therapy and stem cell transplant, we're finding that it falls into the area of cytogenetics, Beta 2 microglobulin, or duration of therapy.

For example, you want to be on fewer chemotherapeutic options before you have your stem cell rather than more.

The bottom line is age has not been shown to be a prognostic indicator in terms of how well people are doing with high-dose therapy and stem cell transplant.

So, I just want to take a couple of minutes here to put things in perspective because I want you to get a feeling of how three different foundations are dealing with patient issues, but imagine just for a minute that I'm 65 years old, and I've been diagnosed with a relatively aggressive myeloma. I've been living a relatively productive life, and I feel well, despite my disease.

My family has researched this disease with me, and we've found out that high-dose therapy and stem cell may indeed prolong my life, but it isn't covered by Medicare, and I don't have the money to pay for it. So, I have only one choice. I get chemotherapy, and I wait, and I pray that Medicare might change its decision, and I get more chemotherapy, and I get more chemotherapy, and as I've just said, the more chemotherapeutic regimens you have, you may not do as well when you finally do get a stem cell transplant.

Now imagine that I'm 60 to 64 years of age. I may be in an earlier stage of myeloma. Again I learn that stem cell transplant down the road might be a safe, effective treatment for me. I could potentially wait to

receive this treatment because I'm not in an aggressive state right now, but I may rush into it. Why? Because it's covered for me now, but when I turn 65, it won't be. So, I may make a hasty decision, and, finally, imagine that I'm a patient about 62 or 63. I did all the right things. I got my chemotherapy. I harvested my stem cells. I've enjoyed my remission. I've been working, having a productive life. But like all myeloma patients, I've relapsed, and now I'm over 65. I can't get my stem cells back, and I think that's an issue.

All three of these situations are truly real-life situations that we hear at our foundation office all the time. People making difficult, maybe poor, maybe sub-optimal decisions because they're trying to work around a Medicare system, and the frustration is exacerbated by the fact that, as these patients do more research, they find out that stem cell transplant is indeed covered by Medicaid, the Veterans Administration or for those under 65, and I have to say that in today's day of the Internet, believe me, patients find out very quickly whether they feel they're being treated fairly or whether they don't, and they talk about it endlessly on these chat rooms.

Patient frustration will reach a point where they start to take legal action, and I know for our foundation, we got phone calls from both Dr. Cerny and from Klaus Karsten, both of who did take legal action and have won their suits, setting somewhat of a precedent in terms of autologous transplant for myeloma.

So, I want you to know that all three foundations that I represent today have taken this very seriously, and while we are going to leave all the clinical data to the excellent group of clinicians that are going to present to you, it's important that you know we all have consensus, and that is the fact that we agree high-dose therapy is effective for myeloma. High-dose therapy can prolong life. Age does not surface as a prognostic indicator, and patients 60 to 64 years of age should be able to have a stem cell harvest without rushing into it and should be able to get their stem cells back if they relapse.

Finally, patients 65 years of age or older should not be excluded from this promising treatment if it's deemed appropriate by their doctor.

So, in summary, I just want to say that myeloma is a cancer of people over 65. It is also one of the most devastating cancers out there, and I truly believe that most people feel it is neglected. I find it very hard, even as a patient or as an executive of this foundation, to give these patients hope.

Today, you do have the opportunity to show them that they will be treated fairly, that this will be taken into fair consideration, and I personally look forward to the day when I can tell them that new, promising treatment options are finally available to everyone.

Thank you.

DR. HOLOHAN: Ms. Giusti, I should remind you of the request that Ms. Geyer made about conflict of interest statements. Do you want to repeat that?

MS. GEYER: Yes, thank you. Ms. Giusti, we did forget to ask, are you here on your own --

MS. GIUSTI: Yes.

MS. GEYER: -- personal behalf?

MS. GIUSTI: Yes.

MS. GEYER: Okay. Thank you, and for the rest of you who do speak this afternoon, if you could please state before speaking whether you are here on your own behalf or whether someone funded your trip.

Thank you.

Our next speaker is Ms. Kathy Hill.

MS. HILL: I also am here on my own behalf. Good afternoon. My name is Kathy Hill, and I'm a registered nurse and a volunteer patient advocate for patients with multiple myeloma.

I became involved in this issue a little over a year ago when a friend told me that his father was diagnosed with multiple myeloma, and he asked me to pray for him.

I then spoke with his father who briefly explained what myeloma was and said that his primary health insurance, Medicare, which he paid into all his working life, would not pay for a stem cell transplant that his doctor said was medically necessary for him.

The Medicare representative had told him this was not a covered condition, despite the fact that his doctor said that it would prolong his life. In disbelief, I began researching facts surrounding this issue and found many inconsistencies that I'd like to share with you today.

In the state of Illinois, Medicaid and the VA routinely pay for autologous stem cell transplants in those over the age of 65 with multiple myeloma when their physicians find it to be a medical necessity. Medicaid is a state-run program, and two-thirds of the cost of autologous stem cell transplant for a Medicaid recipient is from state funds. However, the remaining one-third is paid for by federal funds.

I was told by Medicaid that each time a patient care plan is made out by them, it's submitted to HCFA for approval. In the case of autologous stem cell transplant in patients with multiple myeloma, under 65, this is considered a covered expense and over 65, as long as the patient meets the protocol.

As stated before, Medicare, Medicaid and the VA all receive federal funds. HCFA reviews care plans and either approves or denies payment based on efficacy and necessity.

The question raised is how can autologous stem cell transplant in multiple myeloma be covered and deemed necessary for those on Medicaid and the VA but not in those on Medicare? This is inconsistent and perceived by patients to be discriminatory.

Medicare has said efficacy of stem cell transplant has not been proven in those over the age of 65, but the technical advisory committee concluded in 1996 that autologous stem cell transplant was effective in improving outcomes in those under 65.

The slide I'd like to show you, I believe you have it on your folders. According to 1997 statistics by Medicare, there are over 6,000 patients under 65 with multiple myeloma. 894 are on Medicare, under 65. A number of those may require a stem cell transplant. However, due to the current policy, even though they meet the present criteria for coverage as stated by the TAC committee, they've been excluded from this life-prolonging procedure. Based on this data alone, the blanket policy of non-coverage needs to be corrected.

If Medicare were to cover autologous stem cell transplant for multiple myeloma, the cost would be shared by the secondary insurance company. At the present time, many large insurance companies do pay for this treatment.

When a patient turns 65, their primary insurance then becomes Medicare. If initially their insurance was Aetna, at 64, they'd pay for it. Aetna is now their secondary insurance company. Since Medicare considers this a non-covered expense, Aetna also refuses to pay, whereas they did just a year prior to that when the patient was 64.

The majority of large insurance companies have said they take their cue from policies enforced by Medicare. In turn, if Medicare pays, they will pay.

How do you think the patients and their families react to this disparity? There have been instances when I've attended support group meetings where there will be a Medicaid recipient of an autologous stem cell transplant sitting next to a patient who's on Medicare who's been denied the same treatment, even though they're the same age. They could both be 66 years old.

You would think that there'd be animosity, and maybe internally there is, but what you see is an individual supporting the other and encouraging them to keep fighting. This is compassion and graciousness that could profoundly change how you view life.

It is also unconscionable and unethical when you realize the Medicare recipient has been denied coverage because he may have a small savings or a home that's paid for that's made him ineligible for Medicaid.

I believe this is sending the wrong message. We should applaud those who have been able to secure their retirement, not penalize them by withholding life-prolonging treatment.

We should search for ways to alleviate trauma caused by a disease, not add to it by having inconsistent policies between federally-funded agencies.

To conclude, on May 24th, 1996, listed in the Medicare Coverage Manual, ICD-9, Code 203 and 238.6, an amendment against payment for autologous stem cell transplant for myeloma was placed in the Medicare Procedure Manual as a non-covered expense because at the time, it was not considered reasonable and necessary within the meaning of the Social Security Act, 1862, as stated previously.

I feel this amendment needs to be removed from the manual, and I'm confident that after all the testimony and overwhelming scientific evidence supporting the efficacy of stem cell transplant in those over 65 as presented to this committee, a favorable response will be provided for Medicare coverage to those suffering with multiple myeloma.

Thank you.

DR. HOLOHAN: Thank you. Since the first two speakers have made the same comment about the Veterans Administration, as Chief of Patient Care Services, I think I have to clarify that.

I noticed there's another patient speaking later who received a transplant at the Nashville VA.

By statute, the Veterans Administration has four requirements. One is to provide clinical care. The second is to provide education and research for medical professionals. The third is to conduct research, and the fourth is to act as a back-up system for the Department of Defense.

In the VA, this treatment is provided under the aegis of research, not under the aegis of clinical care. So, in that sense, it is not a covered benefit, and patients receive it when they're participating as part of a cooperative group trial.

If you want to respond, that's fine.

MS. HILL: I have three statements from three physicians from each of the VA hospitals, and Dr. Cesar Freitas --

DR. HOLOHAN: I'm well -- I'm not trying to interrupt you. I know what their beliefs are.

MS. HILL: Okay.

DR. HOLOHAN: And the fact that a VA physician has a belief about VA policy does not ipso facto make it true. Dr. Freitas, Dr. Goodman and Dr. Chauncey are wrong.

MS. HILL: Okay.

MS. GEYER: I believe at this time, Cathy Callahan is our next speaker.

MS. CALLAHAN: Good afternoon, ladies and gentlemen of the Medicare Coverage Advisory Committee.

My name is also Cathy. I'm Cathy Callahan. I am a radiologic technologist, a nurse, and a consultant in the field of magnetic resonance imaging and research.

But I am here today on behalf of myself, my family and all the other families who have fought the disease of multiple myeloma while relying on Medicare for their health care coverage, and especially for my father, Jack Carroll, who was diagnosed with multiple myeloma in May of 1997 at the age of 65.

Although I've been a member of the health care profession for over 10 years and very familiar with the various diseases, treatments and classes involved, it still wasn't enough to prepare us, our family, for the work and frustration and the disappointment that we faced with this reimbursement rejection.

Our family, like many others, faced not only the initial dilemma of a disease as devastating as multiple myeloma but the desperation of the need for immediate treatment by a specialist in the field.

Fortunately, we found a multiple myeloma specialist immediately at a renowned institution in our city that accepted Medicare as a provider. However, the counsel we received from local Medicare representatives in regards to their support of physician-recommended standards of treatment at this renowned institution was not clearly conveyed to us with concrete responses to our inquiries about coverage for specific treatments.

For example, one representative told us that these treatments would be covered if they were deemed medically necessary by the physician, the specialist. Others told us it wasn't covered, but it could be if an appeal was submitted. These physician-recommended treatments were high-dose chemotherapy followed up by an autologous bone marrow transplant.

The problem with this feedback from Medicare representatives, as my family and I later discovered when we began scheduling this treatment with our institution, was that the feedback from these representatives turned out to be very inconsistent, so inconsistent in fact that we found ourselves forced to undertake an investigation.

What exactly does Medicare cover? After months and months of back and forth, phone calls, e-mailing, and letter-writing, to Medicare representatives, other institutions, physicians, congressmen, the AARP, other Medicare patients and patient advocates, we found out the answer. Although covered by Medicaid, autologous bone marrow transplant was in fact not on the Medicare reimbursement list, and therefore it would not be covered by Medicare, regardless of whether or not the patients fit a strict protocol criteria or not.

Because this reimbursement was not on the Medicare list, our institution denied treatment up front to patients regardless of their doctor's recommendations for reasonable and necessary treatment for their patients, unless the patients agreed to pay the six-figure plus sum up front in advance.

When we realized we hit a brick wall with Medicare, we had to take matters into our own hands. Because our biggest problem with this disparity, besides the obvious lack of financial support at this point, was the amount of precious time that was ticking away on my father and thousands of other patients, we knew the answer.

According to our oncology doctors who specialize in this field of bone marrow cancer to get active multiple myeloma to a state of remission, we needed to have an autologous bone marrow transplant. It was that simple.

So, why is this so hard to come by? Meanwhile, the clock continues to tick. My father's body continued to deteriorate right in front of us with a disease that was too powerful for the alternative treatment of chemotherapy alone, not to mention the prolonged alternative treatment continues to weaken the body even further.

Now, we have seen hundreds of thousands of dollars in bills that it took for his prolonged high-dose chemotherapy, even though an autologous bone marrow would have been more cost-effective, we still knew fund-raising was the only logical means to raise funds for this out-of-pocket medical expense which was the only treatment his doctors felt had a chance of inducing remission.

What kind of message does that send to these individuals with multiple myeloma who have worked their entire lives and have bought into Medicare over the years, to have to their family and friends working desperately to raise funds for them because Medicare won't support them? Why should families be forced into spending countless hours of time and effort for fund-raising for a procedure that is considered standard treatment by specialists in the field and that are already covered by Medicaid?

This time and effort my family had to spend fund-raising far outweighed the time, the amount of quality time we deserved and would have liked to have been spending with our father throughout his disease process.

This is a system that they've paid into and supported their entire lives. The amount of disappointment and betrayal that is felt by these taxpaying citizens because this decision by Medicare to reject such a blatant standard treatment for them is not only unfair and unjust, but it is plain unethical.

Unfortunately, like many multiple myeloma patients waiting to be given the support from Medicare, my father, Jack Carroll, lost his battle with multiple myeloma on January 4th, 1999, 14 months after he could have received an autologous bone marrow transplant, if it was paid for by Medicare in September of '97.

Excuse me. Although my father can never reap the benefits of a favorable decision, time is of the essence for hundreds of other patients. They deserve the support. Please allow these patients and their families the support they so richly deserve.

Thank you for your attention.

(Applause)

MS. GEYER: raymond Stevenson is the next speaker, and, Mr. Stevenson, please state if you're here on behalf of anyone or just yourself.

MR. STEVENSON: Yes, I will.

MS. GEYER: Thank you.

MR. STEVENSON: My name is Ray Stevenson. I'm here as an individual, and I paid for my own way out here and my own expenses.

I'm age 71. I live in Prospect Heights, Illinois, a suburb of Chicago. I have multiple myeloma, cancer of the bone marrow. Six months ago, on March 8, I received a stem cell transplant on my own stem cells following high-dose chemotherapy.

My family, my friends, my doctors and I are happy to report that because of the stem cell transplant, my cancer's currently in remission, and I'm feeling better now than I have for two years.

My cancer was diagnosed two years ago, in September 1997. A bone marrow biopsy showed that my plasma cells were over 80-percent cancerous. I was immediately placed on heavy chemotherapy. After four cycles, the chemo had significantly lowered my cancer count. Adversely, it had almost destroyed the muscles in my legs and had caused other problems.

With my cancer count down, I was ready for the next recommended step. This was a stem cell transplant of my own stem cells. It was then that I was told that Medicare would not cover a stem cell transplant for multiple myeloma. It was not that stem cell transplants were experimental because Medicare covered them for a number of other cancers. It was just that Medicare did not cover them for multiple myeloma.

I found this hard to understand for a number of reasons. First, most large insurance companies were covering stem cell transplants for multiple myeloma, and my own insurance carrier would have covered one for me had I not been eligible for Medicare.

Second, I was told the major cancer centers considered stem cell transplants to be the first line of treatment for multiple myeloma.

Third, recent studies reported in medical journals clearly showed the need that the use of bone marrow or stem cell transplants could significantly extend the life of multiple myeloma patients, and, further, that the age of the patient was not a determining factor in their success.

And, last, I was also informed the stem cell transplants for multiple myeloma were being performed by other federal agencies, including Medicaid and the Veterans Administration.

I wrote numerous letters to HCFA officials presenting this information and asked them to reconsider their position. However, I received HCFA's standard response to the effect that stem cell transplants for multiple myeloma were not covered because HCFA considered them to be experimental.

I also wrote to a large number of congressmen and Senators with little impact. Generally, their staffs sent my letters on to HCFA, and I received more HCFA standard responses.

Medicare's failure to cover stem cell transplants for multiple myeloma was disturbing because this seems to be light years out of step with the rest of the medical community. Even more disturbing was my lack of a viable forum to appeal Medicare's decision.

I was told I could not appeal before having the transplant; that is, I would have to first have the transplant, personally pay for it, and then submit the hospital and doctor bills to Medicare for its denial. Only after receiving Medicare's denial could I appeal. This was not a realistic option for me as I did not then have the energy to fight these windmills.

At this point, my cancer became aggressive, and my cancer count started to increase. I became very concerned. I could see my life being prematurely shortened without a stem cell transplant. I felt that by the time Medicare approved stem cell transplants for multiple myeloma, that either I would be physically unable to survive a transplant or I would be dead.

After reluctantly accepting the fact that I could not expect to receive any help from Medicare for a stem cell transplant, I explored other alternatives. In doing so, I fortunately found out I was eligible for medical benefits from the Veterans Administration.

Following various tests, I was approved by the VA in Washington for a stem cell transplant for multiple myeloma and was sent to the VA in Nashville, Tennessee. It was one of the three approved VA transplant centers and a staff of doctors from Vanderbilt Medical Center.

Because my cancer count had increased, I was placed on various chemotherapy treatments until my cancer count again became low enough to perform the stem cell transplant procedure. Finally, on March 8 of this year, at age 71, I received my stem cell transplant.

I'm happy to say that I progressed through the high-dose chemotherapy and stem cell transplant

procedures without the many side effects experienced by most -- by others, most of whom are much younger. Because of this, my doctors and nurses fondly called me their poster boy. This made me feel good.

I will be forever grateful to the Nashville VA for the high-quality care given to me. I'm also grateful for its professionalism in recognizing that a stem cell transplant was appropriate for treating my multiple myeloma. I am in remission today, largely due to the Nashville VA and its dedicated staff of doctors and nurses.

I'm sad to say that it's too late for some of my friends with multiple myeloma. They passed the window of opportunity for their stem cell transplants because Medicare would not cover the procedure. Some are dead, others now have cancer counts too high and physical conditions too poor to currently obtain stem cell transplants.

It is my hope and prayer that HCFA will act promptly to cover stem cell transplants so that the lives of many other multiple myeloma patients may be saved or lengthened. When they are covered, I hope that arbitrary limits based on age are not imposed.

In closing, I would like to say that in areas other than stem cell transplants, Medicare's served me well. For that, I am grateful. I'm also thankful for the opportunity to appear here today.

MS. GEYER: Thank you. Our next speaker is Elaine Snyderman. Elaine?

MS. SNYDERMAN: Ladies and gentlemen, my name is Elaine Snyderman. I've paid my own way here. I'm from Highland Park, Illinois, and I'm here to discuss the Medicare policy that covers some patients aged 65 and over while denying coverage for others.

Now you've heard about multiple myeloma, the lethal cancer that primarily attacks bone marrow, blood, bone and kidneys, that is at present incurable. Without state-of-the-art treatment, you've already heard patients seldom live beyond three years after diagnosis.

High-dose chemotherapy followed by autologous stem cell transplant is now the most promising treatment for the longest, strong remission. It is important to note this hematologic disease is related to leukemia and lymphoma, but Medicare does cover auto-transplant for leukemia and lymphoma patients over 65, while denying it to multiple myeloma patients.

Rather than address the general problem that arises when Medicare becomes the primary insurer for such patients, I would like to refer to a specific situation.

In November 1997, a community college instructor, aged 63, was diagnosed with multiple myeloma. The oncologist, a former National Institute of Health fellow at Highland Park Hospital, recommended what he considered to be a reasonable and necessary therapy.

The patient consulted a Mayo Clinic specialist who confirmed the diagnosis and recommended the same therapy, as did the specialist at Chicago's Northwestern Memorial Hospital, and it was the treatment that she received, high-dose chemotherapy followed by the autologous stem cell transplant.

Three specialists from three respected institutions recommended the same procedure. Private insurance covered every phase of the treatment. The patient went into complete remission after completing the chemotherapy in March 1998, and the following month, her own stem cells were harvested, purified and frozen. Shortly thereafter, she received a transplant comprised of half the cells harvested. The rest were frozen and banked if she needs another transplant within a five-year limit for the durability of the stem cells.

She was an out-patient for the entire treatment which is a cost-effective way of doing it, and experienced no complications. Indeed, she was amazed at the humaneness of the procedure. She has since returned to teaching, community work, family responsibilities and a full schedule. Her quality of life and productivity are as high or higher than ever.

In November, she will celebrate her two-year anniversary of living with multiple myeloma. It is hard for her to believe her fatal diagnosis isn't just a persistent bad dream. She will also celebrate her 65th birthday. Therapy once considered high risk has become for her and others like her safe and effective.

But the bad news is the day she turns 65, Medicare will become the primary insurance server. In effect, if she relapses, and with this disease, we know there is no cure, Medicare will not only prohibit the prescribed treatment but mandate that the secondary insurance provider follow suit. This mandate will require her to seek other means, if available, to pay for the approved therapy, the transplant of her own banked stem cells. Not every patient is able to find other means.

It seems to me that to cover related hematologic cancers and not multiple myeloma is a discriminatory policy. Selective legislation in terms of both age and disease. Certainly age can be a detriment, but a specialist at a major medical center performing this procedure would evaluate the patient's condition and likelihood of recovery and recommend accordingly.

Federal law prohibits age discrimination virtually across the board. In the case of multiple myeloma, however, federal law mandates certain death for patients 65 and over with limited funds, denying them the prescribed recourse to extend their lives and the quality of their lives.

As medical researchers toil in their labs with vaccines, genetic alteration and new drugs to find the cure, every patient who can receive an extension of life buys time, buys hope, and buys the real possibility of a cure.

Ladies and gentlemen, in this narrative, I referred to myself in the third person because I've learned I am not unique in the National Health Care Profile for this disease.

Thank you.

MS. GEYER: Thank you. Our next speaker this afternoon is Mr. Robert Crawford.

MR. CRAWFORD: I'm a patient. March 27th, 1997, I got sent in for a total body bone scan. I couldn't get out of bed. They -- the radiologist said I had metastatic disease. Then in April of 1997, on my 82nd birthday, my oncologist diagnosed multiple myeloma. He gave me three standard melphalan, prednisone treatments, and I think he saved my life, and he got me on a walker, but I was turned down everywhere because of age for anything more.

My local oncologist said I was over 50, and I was over 50. Johns Hopkins said I was over 70, and a paper by Mayo Clinic said I was -- had to be under 74, but a paper in Myeloma Today by the Arkansas Cancer Research Institute said that age wasn't a prognostic variable.

I just called them up cold. They said come on out. They'll promise nothing. July '97, I went out there. They changed my chemotherapy to dexamethasone. In November '97, I had my stem cell harvest. In December '97, I had my first stem cell transplant at 140 milligrams per deciliter of melphalan, and then in April '98, on my 83rd birthday in the hospital, I had my second stem cell transplant with 200 deciliters per milligram of body weight of melphalan, and how do you explain it?

My father and mother said health comes ahead of everything else. They were non-smokers and non-drinkers. I tried to follow. I had no alcohol in later life. I never smoked, and exercising, I mainly swam the first half of my life, but the second half of my life, in 1968, Coopers Book on Aerobics came out in paperback, and I started running, and I've been running for 30 years.

Now, since my diagnosis, on exercise, during the transplants, I got up and ran around the hospital halls with my walker, and on the second stem cell transplant, I -- they had an exercise bike down in the visitors room. So, I went down there and used the exercise bike. Nobody else did. There were 40 or more patients being transplanted, and I still went around the halls with my walker besides that.

It's counterintuitive, but I thought the net result was I think I had a much easier time on the transplant than any of the younger patients. Now, I'm very beholden to ACRC and my life because their pro-active research on multiple myeloma, their meticulous reduction into practice of their research, their complete transparency as to data and papers with a patient, I could get anything I wanted, and I did, and their in-depth knowledge enabled them to risk taking a patient turned down everywhere else and to give him the full melphalan protocol for younger persons to a guy that's 83 years old, and that concludes what I want to say, and I've got a hand-out of data to prove what I've said.

(Applause)

MS. GEYER: Thank you, Mr. Crawford. Our next speaker is Mr. Jacob Sopher.

MR. SOPHER: You're my hero. I also am a multiple myeloma patient, who has been treated at the University of Arkansas Medical Center for the last two years.

My comments really have nothing to do with the statistics since most of them are very foreign to me, and from watching here today, I see that that field is really covered, but I believe that my stable good health today derives from the innovative stem cell myeloma treatment program that I have received.

Of course, I am aware of Medicare's regulations that make stem cell collection and transplantation financially prohibitive, especially for senior citizens.

It is my understanding that previous to the development of the impact myeloma treatment, the average life expectancy for multiple myeloma patients was between two to four years.

I know because I have personally spoken to other patients. Some multiple myeloma patients are now in remission for eight to 10 years or more after receiving the stem cell treatment.

While there may be discussion in the medical arena as to the merits of stem cell transplant treatment as opposed to conventional treatment, having been involved personally for the last two years and being on the scene for treatment, there is no doubt in my mind or the minds of the other patients who have received this impact treatment that the stem cell transplant treatment is the wave of the future for multiple myeloma patients.

At the very least, all victims of multiple myeloma should be able to make that choice. What is important and vital is that multiple myeloma patients be eligible for the stem cell treatment whether they can afford it or not.

People's lives should not be measured by the extent of their pocketbooks, and that is exactly what is occurring today with multiple myeloma patients. Two to three years from now, when there will be no question regarding stem cell transplantation treatment, when it is indeed established that it is the best way to keep patients in remission for years instead of months, the families who have lost loved ones because they were not financially eligible for the program will be devastated.

Just as there was a time when heart and organ transplants were considered experimental and not covered under health plans, it subsequently became routine coverage.

I respectfully submit that it is time to change stem cell transplantation from experimental to routine, so that we can not only extend the life expectancy of multiple myeloma patients but also allow them to make their remaining years productive and enjoyable.

In closing, it is pertinent to note when each patient's own stem cells are harvested, they are frozen and treated and kept in storage. In the event that a transplantation patient does relapse, they can use their

own stem cells to put them back into remission.

I assure you from my own personal experience the mental comfort that comes from knowing this is an integral part of the treatment and should not be denied to multiple myeloma patients. What can be more reasonable and necessary than that?

Thank you for your time and your patience.

MS. GEYER: Thank you, Mr. Sopher. Before you sit down, could you please tell me? Thank you.

MR. SOPHER: Would you interpret for me? No, no. I just can't hear what they're asking. Did I pay for my own trip? Yes, I paid for my own trip.

MS. GEYER: Thank you very much, sir.

MR. SOPHER: Yes. Is that the only question?

MS. GEYER: Yes.

MR. SOPHER: I paid for my own trip on Amtrak.

MS. GEYER: Cost efficient. And I'm sorry, we do have to ask this question for the record. So, thank you for your patience.

Our next speaker this afternoon is Ms. Judith Goldman, and she's up with us already.

MS. GOLDMAN: As a 66-year old, nine-year survivor of multiple myeloma, I felt that it was important that I attend this Baltimore town meeting to express my feelings.

When I was diagnosed in 1990, stem cell transplants were not an option, only allogeneic bone marrow transplants, something else, which in many instances proved to be fatal.

I did not need any type of transplant during the past nine years because I was one of the fortunate ones who went into a good remission after two years of chemotherapy. But if my luck changes, and more chemotherapy is needed but doesn't do the trick, the only thing remaining to prolong my life until a cure can be found would be a stem cell transplant.

Now that I am on Medicare, I am ineligible for one as Medicare does not cover a stem cell transplant for multiple myeloma, and, frankly, I am scared.

Many myeloma patients who belong to HMOs are already on fixed incomes. They have no means of

raising the extra money necessary to pay for quality treatment of their disease nor to see a specialist in myeloma, actions which are sometimes denied them, let alone pay for a stem cell transplant which may be the only thing left to prolong their lives.

If they manage to survive until they can apply for Medicare, they will still be denied the stem cell transplant.

Chemotherapy causes many different reactions in different patients. Many are debilitated during the period where they are on chemo and can barely function. Others do better and can function at 50 percent or more. But they are still not fully productive members of society, whether in business or taking care of their homes and children.

On the other hand, other than for the period of getting ready for and during the actual stem cell transplant, there are few debilitating effects on the patient. After a short, unproductive period of time, most are back to where they were before treatment was started.

On the other hand, those of us who underwent chemotherapy had many days of being incapacitated every five weeks or so for the duration of our treatment. More often than not, the patient ends up with some permanent disabling reaction to chemotherapy.

I, for instance, experienced nerve damage to one arm that lasted for several years after chemo was stopped, and leg cramps that are still on-going seven years later.

Unlike a prisoner who is given a death sentence and can then keep on appealing until his demise, all of us are given a death sentence upon the diagnosis of multiple myeloma without any chance of appeal. Why? Because those who are dependent upon Medicare are being denied their final appeal, a stem cell transplant.

In the United States, myeloma patients represent one percent of all cancer diagnosed, two percent of all cancer deaths as reported in 1998. Multiple myeloma is the fastest-growing hematological cancer in the Western world with between 14 to 15,000 new cases being diagnosed yearly in the United States. It has one of the fastest growth rates of all cancers. Only five to 10 percent of patients will be alive at 10 years following diagnosis. Over 35 people die every day in the United States from multiple myeloma. There is no known cure.

A stem cell transplant is one of the few tools available after chemotherapy fails to buy the multiple myeloma patient more time until a cure can be found.

There is much to be done in searching for a cure for multiple myeloma. Some wonderful things are beginning to happen in cancer cures, utilizing, for instance, gene and virus research. I really believe we may be only a few years away from some significant breakthroughs. Let's keep as many multiple myeloma patients alive as long as possible in order for them to be the beneficiaries of a cure. Please,

help get Medicare to approve stem cell transplants.

In summary, the government's health agencies have long ignored the plight of the 50,000 myeloma patients still living, writing off the 13,000 that die every year. It seems to only concentrate on paying for treatment, experimental and otherwise, for other blood cancers. Actually, there are so many undiagnosed myeloma patients, many who die without it being diagnosed, that at any given time, there could be almost a 100,000 patients in the United States.

What about us? We do not deserve to die for lack of treatment any more than the next person. Yet we are condemned to a sentence of death because the last vestige of what could prolong our lives until a cure can be found is not being supported by Medicare and is therefore being denied to those of us who must rely fully on our Medicare insurance.

Multiple myeloma is no longer a disease of just the elderly. I am now going to put on another hat and tell you about one of our younger myeloma members who has asked me to speak on her behalf.

Michelle Bayley was 39 years old when she became so ill that she was unable to function at her job and had to move back in with her parents because she could no longer support herself.

April 19th, 1994, was the last day that she was able to work. She was finally diagnosed in May of that year, that she had multiple myeloma. She had COBRA coverage that allowed her to have her stem cells harvested at Mayo Clinic for future use.

When she became ill, her COBRA insurance kept going up in cost from a $120 per month until at the end, they wanted $2,300 every quarter which was approximately $766.66 per month. At $2,300 per quarter, it would have cost her $9,200 a year which she could not afford to continue with that insurance carrier.

Because she qualified as totally disabled, she became eligible for Medicare coverage on October 1st, 1996, and then was able to get accepted by the Illinois Comprehensive Health Insurance Plan, ICHIP. In June of '98, she was told that it was time for her transplant, and that she would have to pay $10,000 up front before she could have the procedure.

Because of her youth and not being employed, she did not have $10,000. Medicare would not pay for the reinfusion of the cells but would cover the cost of all other lab work, etc. Therefore, her 72-year old father and 67-year old mother had to take $10,000 out of their retirement money in order to give their daughter a second chance at life.

On August 6th, 1998, 16 days before her 44th birthday, Michelle had her stem cell transplant, and she feels that she is truly being given a second chance at life.

Thank you.

MS. GEYER: Ms. Goldman, thank you. I believe you may have said this, and I may have missed it. Are you here on your own behalf?

MS. GOLDMAN: Oh, yes, I am a patient.

MS. GEYER: Thank you. Our next speaker this afternoon is Mr. Michael Lauro.

MR. LAURO: Good day. I see we're running about 10 minutes ahead of schedule. I'm scheduled for five minutes. I'd ask the panel for an additional 60 seconds, if that's possible.

DR. HOLOHAN: I didn't quite get what you were asking.

MR. LAURO: I said -- fine. Unfortunately, I paid for my own trip, yes. Good day.

My name is Michael Lauro, and, first of all, I'd like to say that it's a real tribute to the speakers that have come up here that they've been so polite in the face of such perverse policy choice as this.

I say that because for the last decade, I have worked as an AIDS activist with the organization Act Up Golden Gate, and Act Up as a movement is widely credited with reforming the drug approval process in this nation.

Act Up Golden Gate in particular is a treatment and policy-based organization open to all individuals with life-threatening illnesses, including AIDS, breast cancer, hepatitis C, and now, it seems, multiple myeloma.

Among -- just briefly among our accomplishments, we've been involved in numerous drug approvals. We were responsible, I believe, for only the second compassionate use drug released under the compassionate use basis for breast cancer. Last week, we had a million dollars appropriated as a line item in the California budget for liver transplants for people with hep C and HIV.

These last four months, however, I found myself in the role of the multiple myeloma care-giver as my father, Alphonse Lauro, was diagnosed with Stage 2 multiple myeloma.

I have some letters of support from various congress persons, Senators, patient advocate organizations, which I'll submit later in the record.

I'm here today primarily to speak to the public policy implications on this issue, and by example, I'd like to begin my testimony with my family's own personal experience, beginning four months ago.

That experience began in the office of a private oncologist, and we sat there, my father and I, and we

listened quietly as he related to my father Stage 2 MM diagnosis, and his recommendation, his only recommendation, I might add, that he undergo high-dose chemotherapy followed by -- combined with a stem cell transplant.

We then confirmed this initial diagnosis at an oncology department at a large teaching hospital which again for the second time recommended and only recommended chemotherapy followed by and combined with a stem cell transplant.

Our journey ended at -- when we traveled to a myeloma specialty center at the University of Arkansas, and there again we listened for the third time to the same recommendation, precisely the same recommendation.

You all know that this story doesn't have a happy ending because the chapter -- because it was only at this third institution that we were told that Medicare does not cover stem cell transplants.

So, my question to all of you is, how far must we travel, how long must we wait, where must we go to find this elusive oncologist who's going to recommend something other than a stem cell transplant because we haven't found one?

The point of this summary -- I think the point of all this is to illustrate that at least based on my family's personal experience and on the facts particular to my father, that stem cell support has, while Medicare has been slumbering, sleeping these past three years, has clearly become the standard of care across the nation.

It's widely recommended, commonly preferred, often performed, and I believe, and I hope you will come to the conclusion over these next two days that it's the superior treatment, a superior standard of care.

I can tell you -- you know, someone mentioned the word "betrayal" here today, and that was a word that resonated with me because as I held my father, who was shaking, when I had to tell him that Medicare wouldn't cover it, that was his reaction, and as you have heard today, even though my father has supplemental insurance, it's about as helpful as a confederate dollar at a Yankee affair because they won't opt in until Medicare pays something.

I think there are four brief policy points that I'm going to go over. One is the Center for Medicare Advocacy has ceased taking on new cases for Medicare appeals because of this process. So, whatever decision is arrived at, in fairness to myeloma patients everywhere who are left twisting in the wind, this -- if a favorable decision is reached, it should be retroactive from the date this committee announced that this hearing would be held.

Second. A supportive decision would help remedy the inconsistent level of access to an effective therapy nationwide. We heard how private insurers, HMOs, state Medicaid programs, CHIPs, comprehensive

health insurance programs, commonly cover this procedure. So, we'd arrive at a consistent level of access.

We also heard how multiple myeloma disproportionately affects African Americans. A supportive decision will raise the level of access to therapy parity among historically under-served communities, especially in light that we've heard stem cell transplants are approved for other diseases, like leukemia.

Finally, I ask you to remember the last time this issue was considered was four long years ago. For many Americans, you've heard it, you've heard it, you've heard it, they can't wait. The average life expectancy from diagnosis is three years.

You know, many, many years ago, a famous AIDS activist stood before a panel, and he said, please, please, please, don't let my epitaph read that I died of red tape. All of you are faced with a similar decision. The time is now to make the right decision. Anything else would simply be genocide of those over 65.

Thank you.

MS. GEYER: Thank you, Mr. Lauro. Our next speaker is Bonnie Jenkins.

MS. JENKINS: My name is Bonnie Jenkins. I'm a nurse from the University of Arkansas for Medical Sciences, Arkansas Cancer Research Center, and they have paid for my trip here.

I have been asked by two delegations to read letters to you because they were unable to attend. The first is from the Arkansas Congressional Delegation consisting of Tim Hutchison and Blanche Lincoln, United States Senators, Dick Snyder, Marion Barry, Jay Dickey and Asa Hutchinson, United States Representatives.

They have written, "As members of the Arkansas Congressional Delegation, it has come to our attention that the oncology leadership at the University of Arkansas for Medical Sciences, Cancer Research Center, the Dana Farber Cancer Research Center, the Mayo Clinic and Northwestern University have made a formal request for a national coverage decision regarding the suitability of high-dose therapy in the treatment of multiple myeloma in the Medicare population.

We support and urge your approval of the aforementioned organizations' request for Medicare coverage of high-dose therapy. With 40,000 Americans living with this disease at any one time, and an estimated 13,700 new cases diagnosed every year, we support the need to allow Medicare beneficiaries the same treatment options, including high-dose therapy, that is afforded others with this disease.

With the average age of diagnosis of 65 years, it is incumbent that these patients receive advocacy for this measure. When the median survival rate with standard therapy is only 30 to 36 months, new therapies and solutions must be considered.

When the Technology Advisory Committee considered this therapy in February of 1997, we understand that they felt the technology met their criteria for newly-diagnosed disease or responsive disease, yet no action was taken to allow this therapy to be used for this patient population.

Some of the most recently-published data appears to indicate that age is not a factor in these categories or for patients with refractory multiple myeloma.

For your additional information, we are pleased to note that UAMS was recently awarded a five-year $13.5 million grant from the National Cancer Institute, a branch of the National Institutes of Health, to study multiple myeloma, including its genetic origins and new therapies. UAMS is one of the nation's largest and prestigious multiple myeloma programs.

The scientists, physicians and staff are committed to better understanding of this disease and providing the best possible treatment for their patients. If there is anything we can do to help in this process, please do not hesitate to contact us. We thank you for your consideration in this effort to approve health care for the Medicare population of our country."

The second letter is from Dr. Ladislaw Cerney, Ph.D., Professor Emeritus, University of Minnesota, retired after 26 years of service to the university and the state of Minnesota.

He is a 72-year old U.S.A. citizen, diagnosed with multiple myeloma in December of '94, and his topic is reimbursement issues for ABMT.

"I am sorry that I cannot attend the panel meeting in Baltimore on September 15th-16th, 1999, because I am undergoing treatment at the Arkansas Cancer Research Center in Little Rock.

Following are my remarks and efforts in order to achieve an appeal of the part of Medicare National Guidelines Coverage Decision 35-30.1.B, Autologous Stem Cell Transplantation, where Medicare denies coverage for this procedure for patients with multiple myeloma.

After being diagnosed in December 1994, I went through dozens of chemotherapy which eventually became ineffective. My doctors recommended autologous transplant as the only remaining option to stop the debilitating symptoms. They all consider ABMT a proven standard, effective, state-of-the-art procedure which has been performed in thousands every year in myeloma patients in the United States and all over the world.

In spite of Medicare refusal, I went through ABMT in June and July of 1997, paying the expenses of the procedures from my retirement fund. Then I went through the steps of appeals up to the hearing in front of Administrative Law Judge Jerome Berkovitz of Minneapolis.

The following are some of my arguments. The Department of Human Services, including Medicaid, by

their decision in Minnesota of 1997, April, covers without any limitations ABMT for the diagnosis of multiple myeloma. It is ironic that if I did not have any financial resources and thus being eligible for medical assistance, I would be fully reimbursed for my ABMT.

Since I have earned my retirement and paid my social security and Medicare contributions during my 26 years of service to the state of Minnesota, I feel I am being punished and denied the same treatment.

As a citizen of the United States, I expect to have the same rights as federal employees. I feel that denial of payment by Medicare for my ABMT is discrimination of those patients with multiple myeloma like me who are not federal employees or over the age of 65, and since the time of the above decision, the majority of the United States insurance companies have been routinely paying for ABMT with multiple myeloma.

I then proceeded with the steps required to appeal in a hearing with the administrative law judge. He ordered Medicare to pay for all expenses incurred inthe hospital, except the infusion of stem cells. He omitted the cost of out-patient procedures, like collection.

Medicare quickly obliged and did not pay for these services. There was no way for this progress. I contacted Mr. Klaus Karsten from Florida who faced the same problem and sent him the decision of Judge Berkovitz. The result was a decision of Administrative Law Judge James Russell in Florida on July 26th, 1999, where he ordered Medicare to pay all expenses for ABMT.

The decision was that an ABMT at issue is covered under the provisions of Title 18 of the Social Security Act, therefore the carrier has been directed to make the appropriate payment under Title 18.

Judge Russell made some important findings. Medicare National Guidelines are not a law. They are not even a status. A judge cannot contradict the recommendations of experts in the field, and in the case of any ambiguity, the court has to act favorably for a claimant.

It seems that every patient with multiple myeloma under Medicare must go through this exhausting process, wasting precious energy and resources for lawyers and the time of administrative law judges in the United States. Resolution would be the above Medicare National Guidelines be deleted as obsolete and discriminatory.

Thank you, Dr. Ladislaw Cerney, Ph.D." Thank you.

MS. GEYER: And because we are running so well ahead of schedule, there is one addition to the agenda this afternoon. I believe Mr. Ray Getsov would like to address the panel.

MR. GETSOV: Thank you. My name is Raymond Getsov. I live in the Baltimore area. I did pay my way here.

I'm now 66 and a half and counting, and believe me, when you have multiple myeloma, every day is precious. I was diagnosed in 1993, after complaining of a lack of energy, and I went to several local physicians, including, of course, in Baltimore, you always try Johns Hopkins, and was prescribed the standard of treatment that had been prescribed since 1966.

However, after a couple months of this and finding no help, through a pharmacologist, I learned that there were a great number of protocols from the Arkansas Cancer Research Center and decided to go there, and in 1994, I got a stem cell transplant from the University of Arkansas.

It put me in remission for over four years. So, I'm still here, and it's a blessing. Dr. Barlogie and his group and the good Lord. They still have stem cells there at the ACRC.

However, here I am aged 66, and if I have to go for another transplant, you know, Medicare wouldn't take care of me. I don't know. It's hard for me to understand. Here we have one of the biggest portions, and it gets bigger all the time, of our population is over 65, and more and more people are going to get diseases, whether it be, you know, multiple myeloma or something, and Medicare has to realize this and understand that if you have hospitals like Arkansas, Dana Farber, some of the others, that prestigious hospitals that are saying they can give people extra years to live, just seems, you know, illogical that they're not doing anything.

Why is an agency of the richest, most powerful country on this earth feel it's necessary to discriminate against older population? Beyond me.

Thank you.

MS. GEYER: Mr. Getsov, I believe Dr. Bagley may have a question for you.

MR. GETSOV: Oh, sure.

DR. BAGLEY: I was just curious. Two years ago, when you were diagnosed, --

MR. GETSOV: I was -- no. I was diagnosed in '93.

DR. BAGLEY: Oh, I'm sorry. I just wondered if you could sort of -- I'm sure you were diagnosed. You went through some decision-making, and you ended up -- but could you tell us just a little bit about -- about how you ended up being diagnosed? I'm sure you were being treated here, perhaps locally, and you were referred or you ended up going to Arkansas.

MR. GETSOV: We were on vacation in Italy, and we were climbing up Mount Vesuvius. I really wanted to see what happened there, and I couldn't keep up with my wife. I said what the heck's wrong? So, I came back at the end of March of '93, and I went to my doctor, and he checked, and one of the things he did check was my urine, and, you know, said uh-oh, I think I see something, and he says you

might have multiple myeloma, and they gave me a bone marrow biopsy and found out that I did, and I called -- I don't know whether it was the National Cancer Institute or NIH, whatever it was, for a reference, and they suggested I go to Dr. Eric Seifter who is with Johns Hopkins, and both he and the doctor that I had gone to before recommended the standard treatment, and he said that at Hopkins, -- is anybody here from Hopkins? I don't know. It doesn't make them look too good.

But, anyway, they said that, you know, they said that they could take me for a transplant if I did it within a year, and I was in remission, and, luckily, the pharmacologist who was a relative of a relative, you know, checked all the protocols and found out that the University of Arkansas was doing the most research and recommended I go there, and that's what's -- a little bit of the background.

DR. BAGLEY: Okay. Thank you. That's very helpful.

MR. GETSOV: Sure.

DR. HOLOHAN: Before we take our break, I feel I owe Ms. Hill something because I kind of cut her off because at that point, we were a little behind schedule. She was commenting about letters from bone marrow transplanters and the Veterans Health Administration in support of high-dose chemotherapy and stem cell support for myeloma.

In fact, as I've stated, the VA has programs in that. They are done under the aegis of research, however, and the patients have to be part of a prospective randomized trial, usually a Phase 3 cooperative group trial.

It is not a standard covered benefit in the VA, and since three speakers referred to the VA, for whatever it's worth, I should point out that federal benefits are not uniform across all federal programs. For example, the Veterans Administration pays for all drugs for all patients. Medicare does not pay nor Medicaid, and for the most part does not pay for drugs.

The Veterans Administration provides and pays for preventive services. Medicare is by statute not permitted to do that. The Veterans Administration pays for research which the Health Care Financing Administration is by statute prevented from paying for. The VA pays for travel costs for patients who are referred from one to another center. There is no other federal program that pays for that.

Without boring everyone, the VA also pays for domiciliary care, respite care, adult home health care and long-term care, none of which are in general provisions of other federal programs.

So, I'm glad that the VA was able to provide services to patients. I'm glad the VA is able to do research in this area, but it's not a comparable federal program, and it shouldn't be viewed as that.

MS. GEYER: I think at this time, we will take a break for 15 minutes and meet back here at 3:30.

Thank you.

(Whereupon, a recess was taken.)

MS. GEYER: All right. I think that we're ready to reconvene and move into our Scheduled Commentary Section. I noticed that our audience has thinned out. I think that the hurricane must have disseminated into the audience. So, hopefully we'll get out of here, and all of you can get safely on your way today.

I think our next speaker is Mr. Greg Dean, and as a reminder again, if you would disclose if you're traveling on your own behalf.

Scheduled Commentaries

MR. DEAN: This trip has been paid for by my employer, Northwestern Memorial Hospital.

MS. GEYER: I'm sorry. I couldn't understand you.

MR. DEAN: This trip has been paid for by my employer.

MS. GEYER: Okay. Thank you.

MR. DEAN: Good afternoon. My name is Gregory Dean, and for the past two years, I have been the Financial Coordinator for the Bone Marrow Transplant Program at Northwestern Memorial Hospital in Chicago, Illinois.

It is my responsibility to coordinate the financial arrangements between the hospital, patients and the patients' insurances. When patients have limited or insufficient coverage, I attempt to make arrangements that will allow them to come to the hospital for transplant.

I am here today to speak about the injustice of the Medicare Program when it deals with multiple myeloma. I am also here to appeal to your sense of fairness and ask that you allow Medicare to provide coverage for transplant to multiple myeloma patients.

Most patients are not aware that Medicare does not cover the cost of transplant for multiple myeloma until after they have been diagnosed and are in need of procedure. They are also unaware that their supplemental insurance in almost all cases will not cover for a diagnosis that is not approved by Medicare.

In effect, these patients are punished for receiving Medicare. Even though bone marrow transplant is considered a standard of care, these patients are faced with appealing Medicare's denial of treatment,

paying for the procedure out of pocket, individual fund-raising through charitable events, or applying for Medicaid.

For almost any other transplant patient, I can provide assistance. For patients who are covered by insurances that are not contracted with Northwestern, we have been able to negotiate single rate agreements allowing them to come to transplant.

In other cases, such as in our autoimmune program, where transplant is considered investigational or experimental, our physicians have been able to speak to medical directors at the insurance companies, explain the benefits of our program, and we've been able to broker exceptions for these patients allowing them to come to transplant.

Other patients can get reduced or even free care, but these options are not available to multiple myeloma patients with Medicare coverage.

As a financial coordinator, I find it unjustifiable that a procedure that is covered by Medicaid is not covered by Medicare. I have worked with patients who have been faced with deciding between spending all or a significant portion of their retirement savings to receive a transplant just as they've reached the age to retirement.

Patients who choose to apply for Medicaid must contend with working their way through the bureaucracy of the Medicaid Program, meeting spend-down costs and facing the possibility of having liens placed against their homes and personal property while they're fighting for their lives.

Patients who attempt to obtain financing through fund-raising are reduced to begging for money from the community, their friends and family members. In either case, precious time is lost in attempting to secure financing instead of treating the disease.

Some of my patients who have been caught in this vicious cycle have simply given up while others have died as they've tried to secure financing.

As a representative of the health care community, a concerned citizen, and someone who has seen the efforts of these patients as they've struggled to survive, I humbly request that this committee vote to allow Medicare to provide transplant coverage for multiple myeloma patients.

Thank you for your time and consideration.

MS. GEYER: Thank you, Mr. Dean, and our next speaker and our last speaker for this afternoon is Dr. Kyle.

DR. KYLE: Dr. Holohan, Ms. Geyer, members of the panel, I want to thank you for the opportunity of speaking to you this afternoon about multiple myeloma and autologous stem cell transplantation in

particular.

I'm from the Mayo Clinic and have been a physician, am a physician, working in the field of multiple myeloma for over 40 years.

I'm speaking today on behalf of the American Society of Hematology, which is a professional organization consisting of hematologists and scientists in the field. The membership of this organization is over 9,000 persons. Multiple myeloma obviously is one of the diseases that is of great interest by this society.

Multiple myeloma, as you have heard a bit earlier, constitutes about one percent of all malignancies and slightly more than 10 percent of all hematologic malignancies. The rate is 4 to 5,000 persons per year in Caucasians, that would be 40 to 50 per million, and in the African Americans, the incidence is twice that in the Caucasians.

Multiple myeloma is characterized by an over-growth of plasma cells in the bone marrow as shown on this slide. Another major feature of the disease is the presence of an abnormal protein found in the blood in about 75+ percent of patients.

Involvement of bone is also a frequent occurrence and is present in about 75 percent of patients at the time of diagnosis of this disease.

Myeloma is a disease involving older persons. The median age is 66 years in our practice, and this is a group of patients, a little more than 1,000 patients with multiple myeloma seen at our institution. As you can see, 18 percent of this group of patients was between the ages of 65 and 69 years of age with 38 percent greater -- equal to or greater than 70 years of age, thus it is a disease involving the older-aged population.

I believe that patients who are 70 years of age or younger should have the opportunity of an autologous stem cell transplant. I believe that this is necessary -- is reasonable and necessary for care of these individuals.

It is important to collect these stem cells before the patient has been treated with melphalan or other alcolating agents because these drugs will damage the hematopoietic stem cells.

This is data from the French study in which 200 patients with newly-diagnosed multiple myeloma were randomized to receive either chemotherapy or a transplant procedure. The response rate was higher in those receiving the autologous stem cell transplant, and the relapse-free five-year survival was almost three times greater in the transplant group than in those who received chemotherapy.

This study has recently been updated from the survival standpoint, and at six years, 43 percent of those who received the bone marrow transplant survived for six years or more, while 21 percent of those given

chemotherapy were still alive. That is almost twice as many patients favoring the transplant group.

The InterGroup study is a prospective study chaired by Dr. Barlogie of the Southwest Oncology Group. The CALGB and ECA Groups are also involved in this study. So far, a little more than 800 patients have been accrued to the study with a mortality rate overall of one percent.

Now, all of us would like to know the number of patients, aged 65 to 70, who were accrued in this study, and the number who had received a transplant, and the mortality thereof, but since this is an on-going study, we are unable to obtain that information at this time.

I would point out that at the University of Arkansas, 49 patients, aged 65 or greater, were given an autologous stem cell transplant. Those patients were compared with age- and sex-matched group of 501 younger patients, and there was no difference in survival or relapse-free survival comparing those greater than 65 with the younger patients.

In our own experience, we have done an autologous transplant on 15 patients with multiple myeloma who were 65 years or greater, and of those patients, 11 are still alive, three died of progressive disease, and only one died of a transplant-related problem.

So, I think that transplant is viable for patients above the age of 65, and I think that all patients above that age should be given the option of an autologous stem cell transplant.

Thank you.

MS. GEYER: Dr. Kyle, there are questions.

DR. HOLOHAN: Dr. Kyle, I have a question --

DR. KYLE: Yes.

DR. HOLOHAN: -- that you may want to clarify for some of the audience. This appears in material we were sent as well. You discuss the InterGroup French myeloma study and point out that the original report showed 52 versus 12 percent survival in the high-dose and stem cell support versus the standard treatment at five years, and the numbers are now 43 and 21 percent, respectively, and you might want to clarify for the audience how a five-year survival could be 12 percent and a six-year survival could be 21 percent.

DR. KYLE: Yes. The initial numbers were those published in the New England Journal of Medicine and represent an actuarial survival, whereas now with a much longer follow-up, the numbers are better and are more accurate.

DR. BAGLEY: I was just wondering if -- has the American Society of Hematology taken a formal

position or have they adopted an opinion on this procedure?

DR. KYLE: No. The American Society of Hematology has not adopted a statement on autologous transplantation, but again I would emphasize that the vast majority of hematologists and oncologists who treat multiple myeloma would recommend an autologous stem cell transplant.

DR. BAGLEY: You stated they haven't developed a position --

DR. KYLE: Beg your pardon?

DR. BAGLEY: -- on -- you said they have not developed a position on --

DR. KYLE: A formal position.

DR. BAGLEY: -- transplant. That's for this use or for any use?

DR. KYLE: For any use.

DR. BAGLEY: Okay.

DR. FRANCIS: I have two questions. The first is you suggested at the beginning that you were making a recommendation for patients aged 70 and younger, and then at the end of your talk, you said anyone over the age of 65, and I want to know what -- what the -- what your view is 70 or younger, and, if so, why, or whether your view is the more general one?

DR. KYLE: Well, the reason I mentioned 70 initially is that the InterGroup study includes patients just to the age of 70. However, as you heard here from a patient this afternoon who was well above 70, who was transplanted, in our own practice, we have transplanted patients up to age 72 or 73, and at the University of Arkansas, there have been a number of patients who have been transplanted who are older than that.

It's obvious that chronologic age does not mean very much, and that it's the condition of the patient and whether they have any complicating diseases are very important in the consideration.

DR. HELZLSOUER: Just to follow up with the InterGroup study which has been mentioned twice now, what is that study design? Is it a randomized study? What are the arms of treatment, if so?

DR. KYLE: This is a randomized study in which all patients with previously-untreated multiple myeloma are treated with VAD, and then after four courses of VAD, the stem cells are collected, and the patients are randomized to receive an autologous stem cell transplant or alcolating agent therapy consisting of Vincristine, VCNU, melphalan, cytoxin and prednisone.

When the patient who has received the chemotherapy has relapsed down the road, that patient then receives an autologous stem cell transplant. The cells, of course, were collected prior to the alcolating agent therapy.

DR. HELZLSOUER: So, it's essentially looking at earlier versus late?

DR. KYLE: It's essentially looking at early versus late transplantation, yes.

DR. HELZLSOUER: Thank you.

DR. MINTZ: Yes. Dr. Kyle, in an article published in the Seminars on Oncology in February 1999, in which you are the sole author, and it's a very clear and comprehensive article, you state that autologous stem cell transplantation for multiple myeloma should be done ideally in a clinical trial. Is that still your present position?

DR. KYLE: Well, I think the critical word here is "ideal", and I'm alluding also to the InterGroup study. The accrual has been rather disappointing actually, especially when we compare it with the accrual that our French colleagues are able to amass.

DR. ADAMSON: Do you have any thoughts about treatment of patients who are resistant?

DR. KYLE: Yes. In our -- in my opinion, there are two different types of refractory or resistant multiple myeloma patients. The first is the patient who is treated with VAD and does not respond to VAD. That group of persons accounts for about one-third of all patients with multiple myeloma.

In our experience, going ahead with autologous stem cell transplant is a good move, and those patients will have favorable results.

There is a second group of patients with multiple myeloma who have been treated with chemotherapy repeatedly and have become resistant to the disease. Those patients, I believe, are completely different, and those patients either do not respond or respond and relapse quickly.

When we began transplanting at the Mayo Clinic, we selected patients initially who had been treated with chemotherapy and had become resistant, and patients in whom we had expected to survive for six months or less.

We transplanted those patients, and in every one of them, we saw objective response, but the duration of the response was short, the disease came back, and we also had difficulty in engraftment of those patients because of their prior alcolating agent therapy.

So, -- and we also had one of those patients who went on and developed acute leukemia which was an

end product of the alcolating agent therapy. So, we feel that patients who are indeed refractory and have had long-term treatment with alcolating agents are not good candidates for transplant.

DR. FRANCIS: I have both a -- this is really a general question and an observation. Several of the patient speakers commented on their quality of life during the transplant.

I haven't seen addressed from the scientific side the issue of morbidity from the treatment, although I have seen obviously a fair amount of data with respect to mortality, and I wonder if you could address both from your own experience and what's more generally known of morbidity as opposed just to mortality from the autologous transplant, and that's actually a question I'd like to be sure gets generally addressed during this session.

DR. KYLE: Yes. Again alluding to a French study chaired by Dr. Fermande from Paris, in which they did randomize patients to early versus late transplant, the median survival of those patients in both arms was about five years.

Dr. Fermande felt that those who had a transplant early were spared the chemotherapy and had a better quality of life than did those who had received the chemotherapy. Again, we have no data from this country on the quality of life in those individuals.

I might also add in passing that over the years, in our prospective studies of chemotherapy for multiple myeloma, that the mortality has run from three to five percent with chemotherapy.

DR. HOLOHAN: We have a couple of minutes left. Let me ask one other question, Dr. Kyle.

DR. BAGLEY: Jeff had a question, too.

DR. HOLOHAN: Oh, I'm sorry. Go ahead.

DR. LERNER: Yes. I took your point on -- that there were patients who you look at on their sort of physical age rather than their strict chronological age, but do you know, is there ever -- is there a data source that would -- that you've ever seen that does discuss really an actual cut-off, if you feel that has some scientific validity?

DR. KYLE: Well, these cut-offs have been rather arbitrary, and initially, it was 60 years for autologous transplant. In fact, when we did the InterGroup study, it was originally 65 and then changed to 70, and this is a reflection of the ability to do the autologous transplant more easily now because of improved supportive therapy for patients.

As far as deciding physiologic versus chronologic age, this is a political hot potato, I think, in anyone's hands, and I would personally object to one stating that those who are 70 and above are not eligible for certain things.

There's a great deal of difference from person to person, and I think if one asks any physician who sees patients that there are patients at 75 or 80 years of age who are more able and -- to tolerate a procedure such as this than are some others who are 55 years of age.

DR. LERNER: Can I also just ask you on the other end of the age scale, is there any age that's too young for a transplant?

DR. KYLE: No. No, no. The younger, the better, in short, because the younger patient by and large is going to be able to tolerate a more vigorous procedure than is an older person.

DR. HOLOHAN: Dr. Kyle, I noticed your letter was on -- your signature was on the formal request letter. Were you involved in selecting the materials that were forwarded to HCFA, the printed materials?

DR. KYLE: Not directly. These -- this was done rather quickly while I was away, and I did not select the material. I did sign the letter later.

DR. HOLOHAN: Okay. So, then it would be unfair for me to ask you if you could attest to the accuracy of the material that was submitted since you were not involved in selecting it.

DR. KYLE: I was not directly involved.

DR. HOLOHAN: Thank you.

MS. BERGTHOLD: I would just be interested in your opinion as to why there have not been more Phase 3 trials, studies, for multiple myeloma as there have been for other kinds of cancers, so that there's more evidence to look at, and why do you think that's so?

DR. KYLE: Phase 3 study comparing chemotherapy --

MS. BERGTHOLD: Right.

DR. KYLE: -- with autologous transplant?

MS. BERGTHOLD: Right.

DR. KYLE: Yes, that's a very, very good question, and when the InterGroup study was discussed, this was the goal of many people at that meeting, but it was pointed out that there would be many patients who would not enter a study in which they had a 50-50 chance of having chemotherapy and not having the opportunity of having an autologous stem cell transplant.

Unfortunately, there are many instances in the practice of medicine in which a new drug or therapeutic approach has been adopted without a prospective trial comparing that agent with the best available therapy.

MS. BERGTHOLD: Can I just ask one follow-up question? It seems to me that that's an issue in all sorts of randomly-controlled trials, that you, you know, have 50-50 chance of getting into the experimental group.

Are there economic reasons as well as to why you can't recruit more patients, and there haven't been more studies, do you think, or political reasons?

DR. KYLE: Well, there's no question about the fact that the numbers of patients that have entered the InterGroup study have been very, very small because if you enter a patient above the age of 65, one knows that Medicare is not going to support that, and if the patient has third party coverage, one does not know whether that will be approved or not for several months, and one needs to collect the stem cells within that period of time, and the physician does not want to collect the stem cells unless there is approval for transplant because then one is between the proverbial rock and a hard place; that is, you have the stem cells collected, and you don't have -- and the patient does not have the funds to do the transplant, and that's a very, very difficult situation to be in. So, those patients are simply not entered into a prospective study.

DR. HELZLSOUER: The previous speaker mentioned that autologous bone marrow transplant for multiple myeloma was considered standard of care. Do you agree in your opinion? Do you consider that standard of care now for treatment of multiple myeloma?

DR. KYLE: I think that consideration of an autologous stem cell transplant is the standard of care for multiple myeloma today, and that is based upon the fact that autologous stem cell transplant can now be done with no greater mortality than with chemotherapy itself. It's gone a long ways in the last decade.

MS. GEYER: Okay. We thank you very much, Dr. Kyle, and I think that this concludes our session for this afternoon, and we'll meet back here at 8 a.m. tomorrow morning.

Thank you.

(Whereupon, the meeting was adjourned, to reconvene tomorrow morning, Thursday, September 16th, 1999, at 8:00 a.m.)

Note: The language on this website comes directly from the transcribed testimony taken at this panel meeting. The views and opinions are those of each of the experts and not those of the Centers for Medicare & Medicaid Services. CMS does not edit these transcripts and makes no assertion as to their accuracy.

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The Johns Hopkins University

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Midwestern University

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ECRI

DR. PAUL MINTZ
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Consumer Representative

DR. LINDA BERGTHOLD
Researcher and Consultant

Industry Representative

CATHLEEN DOOLEY, MPA
Ortho Biotech, Inc.

A G E N D A

Welcome and Conflict of Interest Statement

Lauren Geyer, MHS

Old Business

Dr. Thomas Holohan

Scheduled Commentaries

Lori Williams
US Oncology

Dr. Ken Anderson
Dana Farber Institute

Dr. Bart Barlogie
University of Arkansas Cancer Research Center

Dr. Anne Traynor
Northwestern University

Spencer Pearlman
Legislative Assistant for Congressman Porter

HCFA Presentation

Dr. Vilis Kilpe

Afternoon Session

Open Committee Discussion

Open Public Session

P R O C E E D I N G S

8:10 a.m.

Welcome and Conflict of Interest Statement

MS. GEYER: Good morning, everyone. It looks like we've a much smaller audience today, and we'll hope to keep things moving right on time so that all of you can get safely on your way home.

If you will bear with me yet again, I have to read the conflict of interest statement. After doing that, I'll turn the microphone over to Dr. Holohan, our chairperson.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. The agency has determined that all members and consultants 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.

At this time, I think Dr. Holohan will have the panel reintroduce themselves to all of you this morning. We'll start with Dr. Adamson on the end.

DR. ADAMSON: I'm Dr. Jim Adamson. I'm the Carrier Medical Director for Medicare in Arkansas and also the Corporate Medical Director for Arkansas BlueCross BlueShield.

MS. BERGTHOLD: I'm Linda Bergthold, and I'm the consumer representative.

DR. MINTZ: I'm Paul Mintz. I direct the Clinical Laboratories and the Blood Bank at the University of Virginia Health System, where I'm a Professor of Pathology and Internal Medicine.

DR. HELZLSOUER: I'm Kathy Helzlsouer, medical oncologist and epidemiologist from the Johns Hopkins School of Public Health.

DR. FRANCIS: I'm Leslie Francis. I'm Professor of Philosophy and Law and Adjunct Professor of Internal Medicine in the Division of Medical Ethics at the University of Utah.

DR. HOLOHAN: I'm Tom Holohan. I'm the medical oncologist. I'm also the Chief of Clinical Programs and Patient Care Services for the Veterans Health Administration, Washington, D.C.

DR. BAGLEY: And I'm Grant Bagley, Director of the Coverage Analysis Group at HCFA, the group that deals with coverage decisions, medical evidence and also the group that directly interacts with this committee.

DR. JOHNSON: I'm Robert Johnson, the Assistant Dean at Midwestern University College of Pharmacy in Glendale, Arizona.

MR. JORDAN: I'm Ron Jordan, Senior Vice President at Hospice Pharmacia in Philadelphia, Pennsylvania.

MS. DOOLEY: I'm Cathy Dooley. I'm the industry rep for this panel.

DR. LERNER: I'm Jeff Lerner. I'm Vice President with ECRI Health Services, non-profit health services research organization, and I direct the AHCPR Evidence-Based Practice Center.

MS. GEYER: At this time, I believe Dr. Holohan will talk about any Old Business that we have left to discuss.

Old Business

DR. HOLOHAN: I think there are only two points to make to prevent any misunderstanding or misinterpretation of statements made yesterday.

The implication was that all Medicaid Programs paid for this technology, and to my knowledge, that is not the case. Medicaid Programs are determined individually by state. The mandated federal benefits do not extend in the Medicaid Program to these type of transplants.

The second was some lack of clarity on precisely for what disorders Medicare, the Health Care Financing Administration has made a national coverage determination for autologous stem cell or peripheral blood cell transplants, and I will read these to make sure that we all understand what the current status is.

I'm not going to read the CPT or ICD-9 codes.

Autologous stem cell transplantation is considered reasonable and necessary under Section 1862 of the Act for the following conditions and is covered under Medicare for patients with, first, acute leukemia in remission, lymphoid, myeloid, monocytic, acute erythema, and leukemia, who have a high probability of relapse and have no human leukocyte antigen match.

Two, resistant non-Hodgkins' lymphoma, and a number of ICD-9 codes follow, or those presenting with poor prognostic features following an initial response.

Third, recurrent or refractory neuroblastoma. Fourth, advanced Hodgkins' Disease. Patients who have failed conventional therapy and have no HLA match donor.

Non-covered conditions. Insufficient data exists to establish definite conclusions regarding the efficacy of autologous stem cell transplantation for the following conditions: acute leukemia not in remission, chronic granulocytic leukemia, solid tumors other than neuroblastoma. Effective May 24th, 1996, multiple myeloma.

In these cases, autologous stem cell transplantation is not considered reasonable and necessary within the meaning of Section 1862 of the Act and is not covered under Medicare.

DR. BAGLEY: That's important to note because I think lest there be any confusion over the issue we're dealing with, you know, we're dealing with the medical evidence to support a policy with regard to a specific range of indications, and as you heard, the National Coverage Policies, as previously articulated, deal with covered conditions, deal with non-covered conditions, and in fact don't deal with a great

number of conditions, and that's the case frequently in the Medicare Program, as we administer it.

As we make national decisions based on the evidence, we make determinations when the evidence is sufficient that a condition should be covered, and that is then a decision which applies to all Medicare contractors.

We may consider the evidence and feel that the evidence indicates that it should be non-covered, in which case it is a decision which applies to all Medicare contractors, and there are many times in which we have not evaluated the evidence completely and for many reasons have not made a national determination in which case a Medicare contractor in processing claims must make determinations as to whether or not it is a reasonable and necessary service, and it must do that in two ways, either by processing the claims or by dealing with the issue of developing a local medical review policy, and in fact those policies may vary from the area of one carrier to another.

So, when we make a national determination as you heard here, there are conditions which are covered. There are conditions which are not covered, and there's some conditions which are not dealt with.

Now, what we are about yesterday and today is to deal with one specific indication which at the present time is non-covered, and we should be evaluating that based on the medical evidence, and that's how we should be approaching this, and while it -- I think it is something that was pointed out frequently yesterday, and I think it's inevitable that we consider those kinds of things, that we should be focusing on the medical evidence, not the fact that another program, for example, may pay or may not pay for it in some circumstances because, after all, we should be guided by the evidence, and if the evidence persuades us that this should be a covered service, it really makes little difference if another program pays for it or doesn't.

If the evidence supports it, we should write a policy that does exactly that, and on the other hand, if the evidence does not support it or the evidence indicates that we should have a policy with certain conditions and parameters, then we should do that based on the evidence, and that's what should guide us.

MS. GEYER: And just to let all of you know, some of the staff members have nicely left copies of this actual section on the table outside if anyone here would like to obtain those.

Also, Dr. Kang, who is on the agenda for this morning, seems to be caught in the inclement weather. So, I believe we'll continue on with the schedule, and if he does come, we'll adjust as he walks in.

So, I think that means we'll start with our first presenter this morning, Lori Williams. As a reminder, please state if you're here on your own behalf or not. Thank you.

MS. WILLIAMS: Good morning. My name is Lori Williams. I work for US Oncology, an oncology physician practice management company that is a leader in cancer treatment and research. US Oncology is a network of over 750 oncologists and more than 50 cancer centers spanning 25 states and supplying cancer care for 13 percent of the U.S. cancer patient population.

US Oncology has provided the expenses for me to be here today.

I am here to speak to you today as an oncology nurse. I have been an oncology nurse for 19 years and a transplant nurse for 12 years. I have cared for over a thousand patients who are receiving transplant therapy.

I am an author of the Oncology Nursing Society Guidelines for Stem Cell Transplantation, and I work with the Oncology Nursing Certification Corporation to develop tests that certify oncology nurses at both the basic and advanced levels.

I have worked with the American Cancer Society on Professional and Patient Education Programs and facilitated support groups for transplant patients.

There are three fundamental points that I would like to highlight for you today. First, we urge the Medicare Program to keep pace with the standard of care in the rapidly-evolving field of oncology therapies. Specifically, we urge you to adopt a coverage policy similar to many private payers by establishing coverage for transplantation therapy for the treatment of multiple myeloma.

Second, we urge the Medicare Program to ensure patient access to transplantation for multiple myeloma therapy in community out-patient transplant programs.

As health plans and other insurers have realized, out-patient transplants can offer excellent treatment outcomes, shorter recovery times, and more cost-effective treatment than in-patient therapy. The use of community out-patient transplant programs also helps ensure that all appropriate patients have fair and equal access to this therapy.

Third, we urge the Medicare Program to establish eligibility criteria to enhance consistency and fairness.

Oncology nurses have played an important role in the success of community out-patient transplant programs, and we are very proud of our specialty. We feel that we bring a great deal of knowledge, expertise and compassion to our patient care.

We also have an extraordinarily strong, active nursing organization, the Oncology Nursing Society. This organization run by oncology nurses provides oncology nurses with resources and support to deliver the best patient care possible.

Through ONS, oncology nurses have access to standards of care, care guidelines, continuing education and general and advanced credentialing. Well-educated, skilled, experienced oncology nurses are involved in the continuum of cancer patient care from clinical to education to research to administration.

Through our efforts, patient care and the quality of patients' lives are greatly improved. Because of their levels of expertise, vision and commitment, oncology nurses have made it possible for cancer patients to receive more effective oncology care in the out-patient setting.

Through new models of care delivery and innovative symptom management, oncology nurses assist cancer patients to maintain a much more normal lifestyle while receiving treatment for their disease in a safe and cost-effective manner.

You have heard and will continue to hear from experts in the field of transplantation about the effectiveness of therapies for multiple myeloma. Myeloma patients are not routinely cured by transplantation, but their overall survival can be significantly increased, and they may remain disease-free for extended periods of time.

Time and again, I have seen the tremendous positive impacts that transplantation therapy can have on a patient's quality of life. Having been involved with transplant therapy in the early days when patients were hospitalized for weeks and months at a time in isolation rooms, I have seen firsthand the advancements that have taken place in care for transplant patients.

Because of the expertise of professional oncology nurses, transplant patients are now able to walk into clinics to receive high-dose chemotherapy in control of and actively participating in their treatment. Many of these patients will never have a fever, never enter a hospital, and will return to work eight to 12 weeks after they began treatment.

As an oncology nurse, I am proud that my profession has been in the forefront of making these advancements in care possible.

However, as a transplant nurse and patient advocate, I am often concerned about inequities that I observe in coverage for various therapies. Stem cell transplantation offers a prime example of this inequality.

I have had a myeloma patient's wife sitting in my office in tears saying is not my husband's life as valuable as Mr. Jones's? Why does Mr. Jones get a transplant and my husband does not? I had no answer for that woman.

I have cared for other patients who had insurance coverage for a procedure, such as transplantation, but the coverage was available only if the procedure was done at a facility hundreds or thousands of miles from home.

The additional expense, disruption of family life and burden of this travel may make the therapy impossible for patients to take advantage of. Indeed, I have had a major health plan medical director tell me that he used transplantation at a distant center as a method for controlling transplant utilization.

Fortunately, episodes such as this are becoming increasingly rare in the world of commercial insurance. Health plans and other insurance companies realize that out-patient transplants can offer excellent treatment outcomes with shorter recovery times than in-patient therapy.

Unfortunately, an even more troublesome trend is emerging. As an oncology nurse, I have observed the beginning of the development of a two-tiered system of care. Because of Medicare regulations, many older patients do not have access to therapies that are available to younger patients with commercial insurance.

Similarly, older patients may be hospitalized for therapy that younger patients receive in the ambulatory setting. This is a serious matter since patients usually prefer care in ambulatory settings which allow them more control over their disease and treatment.

Many therapies performed in well-run, well-staffed out-patient settings are associated with fewer complications than when patients are hospitalized for the same therapies.

However, the experience nationwide suggests that these benefits are not currently being enjoyed by seniors with multiple myeloma, particularly as a result of Medicare's current coverage policies.

For example, a network of 17 transplant programs received 331 referrals for transplant for multiple myeloma over a three-year period of time. Of these patients, only eight percent were over 65. Out of this group, a total of 156 patients were transplanted. Only 10 of those patients were over 65.

From this group of patients receiving transplant for multiple myeloma in community out-patient transplant programs at two years post-transplant, 90 percent are still alive. This is a very safe procedure that can extend the lives of patients.

The inability of older patients to access the same type of therapy in the same settings as younger patients has everyone unhappy, doctors, nurses, other health care providers, researchers, and, most of all, patients and their families.

As an oncology nurse who is a strong patient advocate, I would encourage you to adopt rules similar to commercial insurance and provide Medicare coverage for transplantation of multiple myeloma therapy and other new oncology therapies. Therapies with documented efficacy should be available under all forms of coverage.

Then, please take the next step that commercial insurance still often has not taken, and that is to prevent

the anxiety that many patients experience while waiting to hear if they will receive approval for therapy. Make clinical authorization automatic for patients who meet established eligibility criteria.

The transplant physicians I work with in US Oncology will gladly serve on committees with their peers to fairly determine these criteria based on scientific evidence. When establishing these rules, consider also patient quality of life issues, allow fair, adequate Medicare reimbursement for therapy in ambulatory settings, whether this is a large comprehensive transplant program or a high-quality community out-patient center, where patients may remain in control of their therapy and their lives.

Thank you for your time and attention.

DR. HOLOHAN: I'm going to take the prerogative to ask a couple of quick questions.

MS. WILLIAMS: Sure.

DR. HOLOHAN: Any of the panelists can do the same. You represent an organization that manages out-patient chemotherapy, high-dose chemotherapy and stem cell transplants, is that correct?

MS. WILLIAMS: That is part of our business, yes. We have physicians -- we manage physician practices. Many of our transplant physicians also do in-patient transplants.

DR. HOLOHAN: Do you have any data that shows that the outcomes of community-based out-patient programs of this sort have outcomes equal to those that the academic centers have published?

MS. WILLIAMS: We have data that shows that our results are as good or better than the data represented by the Autologous Bone Marrow Transplant Registry and the International Bone Marrow Transplant Registry.

DR. HOLOHAN: Okay. I ask because that was not provided to us.

The second question is, if this panel recommends to the Health Care Financing Administration that this be covered, would you have any comment on any conditions or limitations that we may choose to recommend?

As you're probably aware, transplant centers for liver transplants, for example, have to be approved by the Health Care Financing Administration. It's not enough to open your door and say we're doing liver transplants.

MS. WILLIAMS: There currently is a voluntary organization that accredits transplant programs. It has been in existence for a few years. It's called the Foundation for the Accreditation of Hematopoietic Cell Therapy.

They are accrediting programs right now. Several of our programs have already been through inspection and accredited. From a point of view of the transplant nurse, I think that their standards are very reasonable. They have recently started accrediting. The accrediting has gone slowly, the speed is picking up with which they are doing it.

I think to adopt rules that would either say their standards would be followed or similar standards to theirs, many of the cooperative groups are now going to where rather than doing their own accreditation, which they used to, are now using that accreditation, and all of our transplant programs within our organization are required to meet those accreditation standards. I think they're very reasonable.

DR. HOLOHAN: Okay. And, finally, you talked -- you asked the panel to consider quality of life issues, and I'll follow on to a question that Dr. Francis asked yesterday.

Do you have any data on changes in quality of life or improvements in quality of life with this treatment?

MS. WILLIAMS: We do not currently have that. We're in the process --

DR. HOLOHAN: Thank you.

MS. WILLIAMS: -- of collecting it.

DR. FRANCIS: Could I just follow up and ask? You said you had data on the comparative data out-patient center versus in-patient. Is there any way we could get that within, I mean, the time frames of this, and also is any of that data broken down as to age? Is there any reason to think that age is a relevant variable in your data about how patients do on an out-patient basis?

MS. WILLIAMS: We can break it down by age. I'm not sure that we've got enough data in the older population to tell you anything. What are your time frames in needing the data?

DR. FRANCIS: I guess today.

MS. WILLIAMS: My biostatistician has been in the Philippines for the last several weeks with a mother who is seriously ill and unfortunately has been my problem in having the current data here for you.

DR. FRANCIS: Thank you.

DR. JOHNSON: Mr. Chairman, the standards that Ms. Williams referred to, can we gain access to those, the accreditation standards that she mentioned? Are those available to us?

MS. WILLIAMS: FAHCT is a national, you know, organization. I would assume that you could call

their office and ask for their -- the accreditation office that we deal with is at the University of Nebraska, and they have a web site. I don't know if I have their phone number with me or not, and I'm sorry, I normally travel with a copy of their standards, and I don't have one with me today.

MS. GEYER: Thank you very much for your presentation, and our next presenter this morning is Dr. Ken Anderson.

DR. ANDERSON: If I could have the first slide, please?

I'd like to first thank Dr. Holohan and Dr. Bagley and others for taking time to address with us this very important issue, especially today given our natural disasters that are inhibiting our normal routine.

But I do think it's very important, and what I'd like to do over the next 15 minutes or so is just give you a little bit of a background but share with you, I hope, some information that will help you as you address this decision, fully respecting that in order to define something as reasonable and necessary, one does need to have evidence-based data, and I'd like to share with you that I think in myeloma, especially compared to the diseases that were read earlier by Dr. Holohan, there really is very significant evidence-based data to consider.

Anyway, by way of introduction, I just want to remind you that there are approximately 15,000 new cases of myeloma each year, 40 to 50,000 individuals affected, and this therefore represents about 20 percent in terms of causes of deaths from hematologic malignancies.

If you look in the literature, anywhere from two-thirds to as many as 80 percent of affected patients are aged 70 or less. You have heard yesterday from Dr. Bishop, and I just want to reiterate, that this disease is sensitive to chemotherapy and radiation therapy, and in spite of coming up on 50 years of research trying to improve things with combining conventional doses of therapy, there really has been little, unfortunately little progress using conventional doses of therapy. So, this disease remains incurable.

Just to further illustrate that for you, there have been two large meta analyses performed of the data published in myeloma comparing the standard low-dose melphalan and prednisone regimen with a variety of combination chemotherapy regimens.

One of these meta analyses is shown on this slide where nearly 4,000 patients who were treated in 18 different trials with melphalan and prednisone compared with a variety of different stronger combination chemotherapy regimens were evaluated as to their relative merit.

Unfortunately, the conclusion was that combination chemotherapy really did not improve upon standard melphalan and prednisone.

The rationale for high-dose therapy is shown on this slide. Unfortunately, the tumors are universally fatal, that multiple studies, including those in the meta analyses and others that I've just mentioned, have

shown that this disease is sensitive to treatment, and, fortunately, way back into the 1970s, Dr. Tim McElwaine in England was among the first to show that high doses of therapy in this disease could actually achieve for the first time significant levels or percentages of complete remissions. So, we have a sensitive tumor, not unlike leukemia in this regard.

And, so, over the last 20 years or so, high-dose therapy in myeloma has been evaluated, and I'd like to share with you four randomized trials in myeloma, three of which are complete and one of which is on-going.

This, I stress, because this is more randomized trials than exist in leukemia, refractory Hodgkins' Disease, neuroblastoma or Hodgkins' Disease, all of which we heard this morning already have been approved for compensation.

Firstly, let me remind you of the French trial that you've heard about already a couple of times, published in the New England Journal in 1996. It was published by Michel Attal and colleagues, and it was a randomized national trial in France in which 200 patients were enrolled, and as you can see here, they all received initial induction therapy with a combination approach and then received additional therapy in a conventional way or were randomized to high-dose melphalan and total body irradiation.

These patient groups were comparable in all of their features, clinical and laboratory features, and I won't go over that with you. This is the result of that trial as published originally in the New England Journal of Medicine, and I'll just point out for you, if you look at the outcome in this column of the conventional therapy versus melphalan and total body irradiation, if you look at the response rates as well as the probability of five-year event-free and overall survival, there was a statistically significant benefit in all categories for the cohort of patients that were treated with melphalan and total body irradiation.

What did this translate into? I included, and I'd like to just show you quickly, the two survival curves from their original paper. This, first of all, shows, not very clearly, unfortunately, the overall survival of the high-dose group in the upper curve versus the conventional, the cohort treated with conventional therapy, and several questions have been asked about quality of life, and really another way of looking at that is progression-free survival or event-free survival. How much time do you not have active myeloma, and this particular trial in France did show also again from their paper a significant benefit in event-free survival for the high-dose therapy arm versus the conventional arm as shown here.

Now, Dr. Barlogie will further update you with more recent follow-up on this trial, and I won't spend any more time on it.

To address the issue about quality of life because this really is very important, especially to those of us who take care of patients with myeloma which, unfortunately, is incurable, so what we need to do is provide longest quality period of life for our patients that we can.

Dr. Fermande in France fortunately did another randomized trial in myeloma, published already in Blood. Again, it was in France. They have a very good track record of doing nice randomized trials. 200 patients again with myeloma were randomized, and this time, the question was not whether or not to use a transplant, it was whether or not to use a transplant early in patients who received induction therapy and then went straightaway to transplant or, in the other group, to wait and use the stem cells and high-dose therapy later to treat patients with myeloma whose disease had relapsed after standard treatment.

So, as was mentioned yesterday, it's early versus late transplant in a randomized trial, and what I'd like to show you on the next couple of slides is just to summarize for you the outcome of that particular trial.

The overall survival for both groups, that is the 100 patients who received an early versus a late transplant, was equivalent and was roughly five years, but to directly address the quality of life issues, one can look at the event-free survival, and as you can see here, 39 months in the early transplant group versus 13 months in the late transplant group, a significant difference without events related to myeloma.

One of the scales of quality of life, and one can argue about what's the best scale, and I'm certainly not an expert in this area, but there is a scale called the "Twist", and this is not some crazy dance from the 1960s, but actually it's time without symptoms and toxicity.

I like to say it's time without the ravages of myeloma or the treatment that we use to treat myeloma, and what you can see here is there was a significant benefit for getting an early transplant versus a late transplant in terms of quality of life as reflected in this particular scale.

From Dr. Fermande's paper, again I'm sorry that this doesn't project as well, but what you can see here is for the early transplant in the left panel and the late transplant in the right panel, the Twist, the time without symptoms and toxicity, is shown in this stippled area on both slides. So, you can see here the area here is much larger than the area here when you get a late transplant.

I will just tell you from a personal experience that to have inactive myeloma, patients are not going to be cured, at least, unfortunately, at the present time, but to have inactive myeloma that is controlled, where people can have normal quality of life, performance status and perform activities of daily living is really the goal that we are achieving and striving to achieve for more and more of our patients nowadays.

I want to tell you about a third randomized trial because high-dose therapy has become the standard of practice in the United States and around the world, and this is a change since you've last looked at this issue three years ago.

One bit of evidence for this is shown here. I had the privilege of participating in a multi-center randomized trial, a third randomized trial in multiple myeloma. There are no other hematologic malignancies in which three randomized trials have been published, but this particular trial compared high-dose therapy in patients with myeloma and peripheral blood stem cell transplants.

The reason I mention that is that peripheral blood stem cell transplants, when given back to patients who receive high-dose therapy, result in the restoration of the patient's blood and immune system much more rapidly than does bone marrow. So, this procedure is much safer than it ever has been.

I think when you're thinking about reasonable, you need to think about safety, and this is very safe. This was a multi-center trial, and it happened to compare different ways of giving stem cells, and it's really not important. The only issue I'll tell you is there were a 134 patients who all received the same high-dose therapy and then got stem cells that were processed to try to remove the myeloma or weren't processed, but the point I want to make is peripheral blood stem cells.

In these 134 patients, published in Blood, one can look at all of these end points in the study which are related to how fast the peripheral blood grew, the number of transfusions, the number of infections, and in fact, they were all comparable in the peripheral blood stem cell groups, and my point that I want to make for you today is in this study, which included patients up to age 70, there was only two out of a 134 patients who had transplant-related mortality.

Plainly put, with peripheral blood stem cell transplantation, high-dose therapy in myeloma can be given as safely or perhaps more safely than conventional chemotherapy.

Now, this final randomized trial in myeloma, which is the fourth, is an on-going randomized trial in the United States. It is a multi-center trial sponsored by the Cancer and Leukemia Group B, and I'm the chairperson of this trial in that area, by the Eastern Cooperative Oncology Group, and Dr. Robert Kyle is the chairman of this trial in that group, and in the Southwest Oncology Group, and Dr. Bart Barlogie is the chairman of this trial in -- for that particular group.

My point is just to mention for you that we now have 800 patients in the United States randomized to high-dose therapy versus conventional chemotherapy. While we don't know the results because we need to fully accrue this trial, and then we need to wait a couple of years to have significant follow-up in order to have strength in our observations, what we do know is with these 800 patients enrolled, the mortality overall is one percent or less.

So, it can't be unsafe, and all of these trials have internal monitoring committees that meet regularly and would in fact alter the trial or in fact close the trial if there were undue toxicity. So, this is a fourth trial.

Now, at our institute, I've had the privilege over the years, since 1986, to treat a 105 patients with high-dose therapy and autologous transplant. As you can see here, they had a median age of only 52, but I have treated patients at our institute up to age 69. Most of them had advanced stage disease, as shown here.

I want to make two points with this next slide. In particular, the response rates are exceptionally high with high-dose therapy around the world, and our center reflects this. We had a 30-percent complete response rate, and the majority of the rest of the patients respond as you can see here.

Importantly, as you consider whether or not age is reasonable as a criterion to limit this modality, only one-percent transplant mortality again in our study with patients up to age 69.

Finally, this is the overall survival and event-free survival, and let me just show you quickly that we have patients now eight to 10 years with overall and some, albeit too few, 15 to 20 percent who still have no myeloma out at eight to 10 years.

My final comment. I've had the privilege to serve as the chairman for what's called the National Comprehensive Cancer Centers Network. This is a group that's made up of 10 different cancer centers around the country. They're the Dana Farber, the Fred Hutchinson Cancer Center, the Roswell Park Cancer Center, the University of Michigan Cancer Center, University of Alabama, Memorial Sloan-Kettering, Johns Hopkins, Stanford, Northwestern, M.D. Anderson Cancer Centers, and we have made guidelines for the treatment of myeloma, again looking at evidence-based data, exactly what you're doing, and I would just point out here that we have criterion for diagnosis. We have criterion for initial treatment, but when in fact we look at bone marrow transplantation, which is shown on this slide, autologous bone marrow transplantation, when we did exactly what you are doing in these 10 cancer centers, we were unable to limit or restrict high-dose therapy based on any criterion of age, and, so, we did not do so in our guidelines, and these guidelines have been adopted by multiple payers for provision of care at these 10 cancer centers.

Thank you very much.

DR. HOLOHAN: Questions from the panel?

DR. MINTZ: Dr. Anderson, are there prognostic variables in your practice that you use to exclude patients from transplantation?

DR. ANDERSON: Yes. I think that there are, Dr. Mintz. We need to consider when we treat patients with myeloma what their physiologic status is, and, so, for example, patients who have -- need to have, excuse me, normal cardiac function, pulmonary function, liver function, etc., in order to withstand therapy. That probably is also true for low-dose or conventional therapy, but it's clearly true for higher doses of therapy as well.

In terms of prognostic factors for outcome of high-dose therapy, I'm going to defer that question to Dr. Barlogie who has summarized that topic.

DR. HELZLSOUER: Dr. Anderson, along those lines, I'm curious then to know what the justification is for the age cut-off of 70 in the InterGroup study rather than basing it on the physiological parameters.

DR. ANDERSON: Well, it's a wonderful question, and I'm smiling because when we were sitting together with our colleagues at the National Cancer Institute and CTAP and others to design this

national randomized trial, the original age cut-off was going to be 60.

With discussion, it went to 65, and, finally, we were actually -- there were comments that we were actually discriminating against the elderly, and, so, we moved it up to age 70, but you have to appreciate this -- I don't know when this started. It's five years or six years ago now. It's quite a long time, and what I'm saying to you is we have now data that I presented to you from trials, several of which are accruing patients up to age 65 or 70, with only one-percent toxicity.

So, I think if we were designing another trial today, you know, hindsight is 20/20, we would -- we perhaps would not even limit it. We wouldn't probably limit it at age 70, but the reason that we did it was in fact that we were -- it was thought at that time that we were discriminating against the elderly. So, we raised it from 60 to 70.

DR. HOLOHAN: Let me ask a few questions, and then I'll ask you to try to be brief --

DR. ANDERSON: Yes. Okay.

DR. HOLOHAN: -- in answering. You talked about four randomized control studies. Is it the case that one is incomplete at the present time, the fourth one?

DR. ANDERSON: Yes.

DR. HOLOHAN: That's an on-going study, and that only the first study, the French InterGroup study, was actually a comparison of standard versus high-dose?

DR. ANDERSON: Yes.

DR. HOLOHAN: Okay. The others were comparisons of different mechanisms of delivering --

DR. ANDERSON: Actually, I think -- well, go ahead.

DR. HOLOHAN: Go ahead.

DR. ANDERSON: Do you want -- I think that's not quite fair. I think the -- you're absolutely right on the first trial. In thinking about it, you need to consider this. The -- you're right, the first trial, the Attal trial in the New England Journal of Medicine, was set out to be conventional therapy versus high-dose therapy.

As that trial evolved and as high-dose therapy became more acceptable and safer, that trial, as you undoubtedly can know and can read from the New England Journal paper, became, and it was mentioned by Dr. Francis yesterday, became a trial really of early versus late transplant because many of

the late patients who relapsed after conventional therapy received a transplant.

The second trial I mentioned, Dr. Fermande et al, directly set out to test that question, but when you say it doesn't really compare them, it's not quite true because it does compare initial high-dose therapy versus initial conventional therapy, and then it asks the question later of using high-dose therapy as a treatment for relapse which after all is conventional standard therapy nowadays as well.

So, it's -- if you're asking are there more trials likely to happen comparing conventional therapy and standard therapy, I think the answer is no. The standard of practice in the United States and around the world is high-dose therapy. That is going to be the control arm in future studies.

DR. HOLOHAN: Well, then I'm puzzled about the on-going randomized control trial that you described. If in fact the standard is high-dose chemotherapy, isn't it unethical to conduct this trial?

DR. ANDERSON: We -- I think you have a good point in terms of the issues that are going to be addressed by this trial.

I think the way I have looked at it, and I think I will mention a couple of different aspects, firstly, what this trial has -- the randomized trial that's on-going, not completed, in the United States is testing is early versus late transplant.

So, in terms of it being unethical, I don't think so because both arms are -- have available and will receive a transplant. It's either going to be early or it's in the randomized fashion or it's going to be late when they relapse, and they have had -- then they have the option for the transplant. So, that's why patients are still accrued.

But you can appreciate and you heard from Dr. Kyle so nicely yesterday that we had trouble in the United States accruing this to this trial. It's really unfortunate, and I think part of the problem has been that as we -- as the world has evolved, and information has come from other studies that suggest that high-dose therapy with peripheral blood to recompensate blood in the immune system is so much safer, and high-dose therapy achieves complete response rates, that patients frankly don't want to be randomized any longer or take the chance of getting either conventional therapy or high-dose or -- versus high-dose therapy, and, so, it has been hard to accrue.

Fortunately, we're almost finished, and I don't think it's -- I do think it's going to serve a useful purpose because in terms -- it will look at trials. It will add to the Attal trial. It will add to the Fermande trial. It will be a national cooperative effort in the United States, the first one, which will address this issue. So, I do think it's still important.

DR. FRANCIS: I had two questions. The first is I was puzzled by the slide that showed that the event-free survival difference between early and late transplant was 26 months, but the Twist difference was only five months, and I'm interested in what accounts for that difference which seemed huge to me.

DR. ANDERSON: Yeah. You are absolutely right, and again I don't want to pretend that I'm an expert on quality of life assays or the Twist assay, although it was developed at our institute. So, we tend to use it.

What my reading on that would be is event-free survival means progression-free survival. No activity related to myeloma. Twist is time without symptoms and toxicity. Sometimes patients have symptoms related to treatment that they have received a long time ago. A neuropathy from vincristine would be a good example, which would mean that they have -- they're still not going to make it. They're going to be counted as still having symptoms. So, it's shortening that period of Twist, whereas they're still in event -- they're still in the event-free cohort. They don't have active disease, but they still have symptoms related to prior therapy that they had had.

I think that's at least one explanation that accounts for some of the difference that you saw in that slide.

DR. FRANCIS: So, what that -- I mean maybe you could comment on this. Would you suggest that if there are advantages in terms of event-free survival, those might be less important from a qualitative point of view than the Twist measure because of the lingering effects of the earlier therapy itself?

DR. ANDERSON: Yeah. I think -- I wouldn't want to say one is more important than the other. I don't know that, and I don't think that's ever been looked at at all.

I do think -- I can tell you both from the studies and from experience that higher responses in myeloma, higher complete response rates and more progression-free or event-free survival does translate into improved quality of life.

What I think you're seeing there is the Twist, after all, in my understanding is a novel approach of looking not only at event-free survival because, as you correctly say, that's not the be all and end all. We want quality of life, and quality of life is sometimes related to the therapy that they get as well.

So, Twist is trying to incorporate both of those things. I don't know which one's better. Time will tell. I think we're going to end up looking at both and other measures as well in our future studies.

DR. FRANCIS: Go ahead.

DR. HOLOHAN: One quick question. In the chapter you wrote in Seminars in Hematology, you cited reports from the French group that indicated no greater benefit of two order graphs over one. Do you believe that to be accurate?

DR. ANDERSON: Yeah. I would -- what I would say on that, I -- a number of us in the room have just returned from the Seventh International Workshop in Sweden last week, and that trial that you referred to is a trial of one versus two transplants, 400 patients accrued, 200 in each arm, and that analysis that I

referred to there was based on an ASH abstract, American Society of Hematology abstract, that was a preliminary look at the data, meaning they looked too early and found that there was no benefit at this juncture, at the time of that ASH abstract which I think was over a year ago now, for the two transplants.

It's still premature. There is a randomized trial coming which is terrific. We have another randomized trial in myeloma, but I would not -- I don't think that we should and you should honestly consider that trial yet until it is mature in terms of looking at the relative merits of two versus one.

DR. ADAMSON: You mentioned in selection of patients normal pulmonary, cardiac, hepatic function, etc. The etc. Let me ask this. On renal function, what is your view of that?

DR. ANDERSON: Yeah. You know, I -- again I'm going to defer somewhat to Dr. Barlogie on this. In our particular experiences and in the trials that I showed you from France, the two trials from France, and the trial in the United States comparing different kinds of peripheral blood stem cells in the national randomized trial, the InterGroup trial, which is not yet completed, and in our own experience, we demand some level of renal function. It's like creatinine of two, and a creatinine clearance of 60, but it's quite arbitrary, quite arbitrary.

I think Dr. Barlogie can speak more directly because he has studied the safety, relative safety of high-dose therapy in patients who have different degrees of renal compromise, where I haven't, quite frankly. We set arbitrary standards and went forward with that.

DR. LERNER: Given your knowledge of the safety of the procedure, what's your feeling about settings in which the -- if Medicare were to provide coverage, what would be appropriate setting to provide therapy? We heard an earlier presentation which argues for providing an out-patient setting more broadly.

DR. ANDERSON: Whether it's -- okay. Let me see. I -- up until the end, I thought you were going one way, and let me -- I don't want -- I can't comment from personal experience about out-patient transplant versus in-patient transplant. I have no personal experience in that.

I will just share on that particular issue that with peripheral blood stem cell transplant, patients nowadays engraft, which means they have return of their white count and platelet count and red cell count, very quickly, eight to 10 days later, and whereas it used to be common for patients to get fever and complications because of that very short time at which they're at risk with low blood counts, they hardly ever get complications nowadays. So, that has made the out-patient transplant possible in multiple groups, including at Arkansas and other places that we heard this morning, are performing these, and I think that again they should be held to the same standards in terms of safety.

I would just add one quick thing. I have had the privilege of working with the American Association of Blood Banks on hematopoietic progenitor cell accreditation program, and we have developed standards which are the same standards that are being used by FAHCT that was referred to earlier, and what is

evolving in this country right now is in order for patients -- for centers, whatever kind of center, academic centers, other centers, to perform hematopoietic progenitor cell transplantation in the U.S., they're going to need to be accredited by FAHCT or AABB, and what that means, just to tell you in plain English very quickly, is that means every aspect from the recruitment, evaluation of the patient, phosphoresis to collect peripheral blood stem cells, processing of the product, admission to the hospital or treatment in the out-patient setting, clinical care and follow-up care, every aspect is being closely monitored, and, honestly, in some states, such as Massachusetts, where I live, if you are not FAHCT-accredited, you will not get third party payment for doing this process.

So, I think in terms of quality control that's been asked by several of you, not only in myeloma but in this field more generally, we will have rigorous quality control, and we do, and we will have even more rigorous control in the very short term.

DR. FRANCIS: This is a question that you may not be able to answer, but something in the material we've been given, something has been made of the fact that this disease has roughly twice the incidence in African Americans that it does in whites, and I'm curious to know. I've seen studies on lymphoma, for example, that African Americans receive transplants for lymphoma at roughly half the rate that whites do.

I'm interested in whether there's any race-specific data with respect to myeloma and the receipt of transplant in any of the trials or currently.

DR. ANDERSON: Yeah. I don't know of any. When we have our -- the trials that I showed you from America, the national randomized trial in particular, NIH National Cancer Institute-sponsored. So, we are obligated and are recruiting actively minority groups, but I don't think there is specific data as to the relative access or performance of stem cell transplants for minorities.

You are right about the increased incidence. We don't understand it. Radiation exposure and pesticide exposure are among the conditions that pre-dispose to myeloma, but since we don't know the under-lying cause, there doesn't appear to be a genetic cause that we've identified yet, that's about as good as I can do at this time.

DR. HOLOHAN: I think in the interest of time, we're going to have to move along. We're starting to run a little behind already.

MS. GEYER: Thank you, Dr. Anderson. Our next speaker is Dr. Barlogie.

DR. BARLOGIE: Good morning. Thank you for giving me the opportunity to present some data to you. I'm a myeloma physician who has dedicated the past 20 years of my 30-year cancer career to trying to improve the therapy of patients with multiple myeloma.

Unlike some of the other hematologic malignancies, especially some of the rare ones, like hairy cell

leukemia, where we have found a number of active agents serendipitously producing complete remissions in the majority of patients, these complete remissions have been sustained so that the long-term outcome in those patients can be equated with cure.

In multiple myeloma, despite evaluation of new agents, complete remissions have been rare with standard therapy, and as I entered the field, the entire aim was to try to enhance the incidence of complete remission from about five percent with standard therapy to the range of 50 percent which we are now at using the principle of dose escalation of one of the agents, namely melphalan, that is the most active alcolator drug for multiple myeloma, and as was pointed out, Dr. -- the late Tim McElwaine introduced this approach without stem cell support, and we then entered the field by adding growth factors in support of hundred milligram per meter squared of melphalan, which was doable, was associated with the mortality of 15 to 20 percent, and this is published in Blood, and when we entered the field of hematopoietic stem cell support, really purposefully avoiding the term transplantation, it is reinfusion of the cellular -- autologous cellular support, so that an agent, melphalan, that is an early stem cell killer, that is it targets the perimeter normally hematopoietic stem cell, so that the duration of severe malaplasia is long, and when one exceeds a certain dose level, the marrow does not recover or rarely and very late.

So, with the help especially of mobilized peripheral blood stem cells early in the disease course, the duration for a typical patient with myeloma at risk, that is where the neutrophil count is less than 500 per microliter, is only on the order of two to three days. So that even in the most tripled patient or especially in such a setting of a most tripled patient with renal failure, with hypercalcemia and what have you, this approach under controlled conditions actually is the safest because the marrow recovery can be anticipated very promptly, so that there is no long-term marrow suppression with the attendant risks of fungal disease and so forth.

I'd like to just follow up -- if I can have the first slide? Can somebody help me with this, please?

Just to follow up on the issue of renal failure, we have reported at the American Society of Hematology meeting several years ago on this analysis, where 42 patients with greater than two milligram percent of creatinine were compared with peer mates matched for pertinent prognostic factors, such as cytogenetics and so on, twice as many patients, and as you can see, the results are comparable.

This study was conducted after we found out in a pharmacology trial that melphalan given intravenously was actually not cleared through the kidney, contrary to earlier reports, and this has been published by Trical et al in clinical cancer research.

So, let me then -- this is the updated IFM-19 study, kindly provided to me by Dr. Michel Attal, showing at 90 months now with patients only beyond 60 months, that high-dose therapy is superior to standard therapy.

An update in historically-controlled report of our total therapy program versus what standard therapy

with VAD that had been published in Blood in 1998 as shown here comparing 116 patients newly-diagnosed with 116 patients receiving mainly VAD, the P value on this is less than .005, and as you can see, at about 90 months, the overall survival duration is 50 percent with the intensive treatment program as compared to about 20 percent with standard therapy.

Now, this study has been alluded to. This has been a peer mate analysis of young and old. There is now a program back in Houston and in Little Rock later on, we have not limited the high-dose therapy approach to patients in terms of age because we recognized that the -- that at least half of the patients over age 65, and we wanted to develop therapy that could be given to the typical patient with myeloma; that is, a patient presenting with renal failure, a patient with old age, and any other problems related to multiple myeloma.

As is shown in this slide, the two groups, age groups, were comparable for all of their features, and this is again the event-free and overall survival of these two sets, young and old, and as you can see, there is no difference in event-free or overall survival, and this is reported, and the only features that entered the prognostic model are a multi-varied analysis were cytogenetics, duration of prior therapy, and age in a multi-varied analysis for survival was 0.8 P value.

We have now examined the clinical outcome of the first 1,000 patients treated with melphalan-based high-dose therapy at our center. The characteristics are shown here which are typical of our referral population. Univariate analysis reveals here the numbers of months for event-free survival, overall survival and CR duration, and age on univariate analysis was not a significant variable, and on multi-variate analysis, we can see that there were many variables prior to high-dose therapy that entered the model for event-free and overall survival.

Most importantly, cytogenetics, then the Beta-2 microglobulin as a tumor mass and renal function marker, and duration of prior therapies, reactive protein and so on. Age again did not enter this model.

This is a representation of patients event-free and overall survival as well as CR duration, according to the presence or absence of Chromosome-13 abnormalities which we have recognized as the key feature, key adverse variable in this disease pertinent to about 15 to 18 percent of patients. Significantly inferior outcome with this variable.

We then looked at survival by age, overall survival on the top and event-free survival on the bottom. There was no difference. When we looked at age within the three risk groups that were defined on the basis of cytogenetic abnormalities of Chromosome-13 at Beta 2 microglobulin. So, on your left, the low-risk group where both of these features were favorable, the middle panel where one of these features was unfavorable, and on your right where both features were unfavorable, and then asking the question of age under 65 or greater than 65, you see that the curves are super-imposable and so are the -- hence the P value is -- and there are in these three panels on the left 35 patients 65 years and older or in the middle panel, 54, and the right one, 67.

When one considers the various prognosticfeatures and evaluates the long-term benefit from dose-intensive therapy aiming at durable disease controls through the initial step of achieving complete remission, then you can see on your right -- on the right panel that the duration indeed is extended, so that at seven years from the first cycle of high-dose therapy, 60 percent or so of patients continue and continue complete remission. We are seeing a plateau in the curve.

I'd like to briefly cover a recently-reported study from Torino by Mario Boccadoro and his colleagues evaluating three cycles of high-dose melphalan, hundred milligram per meter squared, in elderly patients following initial stem cell collection with cyclophosphamide, a stem cell spearing agent, and growth factor, and then these three cycles were administered, and patients received stem cell support after each of those cycles.

These 71 patients entered in this trial were compared with 71 similar patients receiving standard melphalan and prednisone. 53 of the 71 patients in both groups were over age 60. They were comparable in other criteria, and they were -- the groups were matched on age and Beta 2 microglobulin.

The clinical response to repeated melphalan, high-dose melphalan therapy which, by the way, could have been given without stem cell support, revealed a complete remission rate of 47 percent as opposed to five percent, and an additional -- or the overall partial remission rate was 88 percent versus 49 percent, and those were significantly different.

The curves are shown here for event-free survival on your left, overall survival on your right. The prognostic factor analysis revealed then that the Beta 2 microglobulin and the high-dose therapy both were independently significant markers or factors, I should say, for both event-free and overall survival when the entire population was considered.

The ABMTR provided me kindly with registry data on some 1,100 patients reported to that registry and showing again no difference in survival according to age. There were 53 patients 65 years and older, and I'm sorry, this is the most important slide, I never have this happen to me, never have. I have the slide upside down, but it says that age is not a prognostic factor with high-dose therapy for myeloma, and that the variables determining outcome are entirely biology and disease-related, and I want to stress this in relationship to acute myeloblastic leukemia, where the disease over age 50 or 55 or 60 is really different; that is, one sees more of certain cytogenetic aberrations, and this is not the case in multiple myeloma.

So, on the basis of the evidence that I have provided, that is high-dose therapy promotes a much higher incidence of complete remission of a -- in the 40 to 50 percent range, and this has been the case in other malignancies, then indeed has led to an extension of event-free and overall survival in the single report of randomized trial, and in a number of Phase 2 trials and in historically compared trials, and age when examined in all of these trials was not an unfavorable feature with high-dose therapy but was, and I omitted this slide, but it's in your hand-out, it was actually an unfavorable feature with standard therapy.

Thank you for your attention.

DR. HOLOHAN: I'm going to limit each panelist to one question and one question only.

DR. ADAMSON: Do you mind going back to your creatinine slide that you had at the very first?

DR. BARLOGIE: Can I have the first slide in the carousel? Okay. No. The second set. There's one ahead of the -- no? Yeah. Thank you.

DR. ADAMSON: Is that a typographical error? It says --

DR. BARLOGIE: It should be greater than two.

DR. ADAMSON: Yes, thank you.

DR. BARLOGIE: Yes, yes. I'm sorry. Greater than two.

DR. FRANCIS: I have two. I wonder if you could comment on the event-free survival versus Twist measures and the quality of life baton that was passed to you, and the second is, do you have any race-specific data about access in your --

DR. BARLOGIE: As the chairman of the current InterGroup trial, I have pleaded with the National Cancer Institute to have a quality of life analysis attached. This was turned down because of funding. I have tried very hard, and this would have been a unique opportunity that we will not see again.

I think Dr. Anderson addressed the issue of Twist as best as one can. In the absence of maintenance chemotherapy, those patients who have -- who do not experience relapse are indeed fully functional, and how this Twist analysis ends up with a significantly shorter duration of benefit in one versus the other, I cannot further address. I think this takes perhaps a statistician to address and look at the actual data in order to satisfy your concern.

DR. HOLOHAN: Second question?

DR. FRANCIS: Any race-specific data about receipt of care. Do you have any race-specific data that you know of about receipt of the care?

DR. BARLOGIE: What care?

DR. FRANCIS: Any data based on race about current receipt of --

DR. BARLOGIE: No. I live in a state where the Delta Region is very poor, and we have an AHAG system, and we are trying very hard to enroll patients, the black population, other minorities, and we make them as much aware as humanly possible.

They typically come to us much more advanced with their disease, and it's -- we try as hard as we can, but the population at greatest risk and with the highest incidence of this disease, unfortunately, is clearly under-represented, and that has to change.

DR. HOLOHAN: Dr. Barlogie, with regard to the question that Dr. Adamson alluded to, I have your publication from Blood, and it says that "eligibility criteria, at protocol entry, patients could have renal failure, creatinine greater than two."

However, the next sentence says, "Renal failure had to improve after VAD so that serum creatinine levels could not exceed two milligrams before high-dose chemotherapy as well as before the first and second autologous transplant."

So, in fact, all of the patients who completed high-dose treatment and transplants had to have a creatinine less than two at the time they started.

DR. BARLOGIE: You are referring to the total therapy program, --

DR. HOLOHAN: Right.

DR. BARLOGIE: -- Protocol 89001 for newly-diagnosed patients that accrued patients between 1989 and 1994, and at that time, we did not have the information we subsequently gathered.

We became aware -- we conducted studies in collaboration with Dave Alberts at the University of Arizona Cancer Center who had done the original melphalan, oral melphalan pharmacology data, and I think we found out that the pharmacology of intravenous melphalan was not altered in about 1992 or 1993.

We reported on this in clinical cancer research, Trical et al, and then have created a special high-dose therapy program for patients with renal failure, and that is what the data are based on.

DR. HOLOHAN: Was that publication that you referenced supplied in this package to us?

DR. BARLOGIE: I was about to say that it'll be there. Dr. Trical's, I think it's in -- I can get this faxed and distributed, if it's not there. I have not scrutinized your package.

DR. HOLOHAN: I don't recall having seen it.

DR. BARLOGIE: Okay.

DR. LERNER: May I ask a question? You referred to the Boccadoro study. Is there -- he has about 36

patients, if you broke it down, who actually are over 65. Do we -- is there any sort of more individual data so we can look at those patients who actually are above 65? The way it's presented, you can't really tell.

DR. BARLOGIE: Right. Not today, I don't think I can get this. I have the cellular phone number, but I could try, but I doubt this will be realistic to accomplish today.

We have actually a program for patients over age 70 that starts with a cycle of 140 milligram per meter squared with the first cycle, and then according to tolerance, the second cycle will be identical or escalated to full dose. 24 or so patients have been enrolled. There's been one early death, and otherwise this program has been well tolerated.

We submitted this as an abstract to the American Society of Hematology meetings later this year. I wouldn't have a copy of that abstract. That hasn't been accepted yet.

DR. LERNER: Because I really think, you know, it would be great to have his data for the over 65 given the controversies and, you know, other studies that would argue that age is -- it's not a prognostic variable.

DR. BARLOGIE: I think in our publication in Blood, we split this out over 70, if I'm not mistaken, in the Blood paper by Dr. Siegel. I think there are three columns. It's under 65, 65 to 70 and over 70.

DR. HOLOHAN: I think we're going to have to move along. We're starting to fall behind again.

DR. LERNER: Maybe we can come back.

MS. GEYER: Thank you, Dr. Barlogie.

DR. BARLOGIE: Thank you.

MS. GEYER: And actually at the beginning of your presentation, I was trying to find out what that noise was. I'm sorry, I didn't hear if you were here today representing ACRC.

DR. BARLOGIE: I'm representing -- I'm traveling on myeloma centers support, and I'm representing, I think, the myeloma investigative community. I have been asked by Drs. Champlain and -- from M.D. Anderson and Carl Bloom from Stanford to represent them as well.

MS. GEYER: Thank you. Our next speaker this morning is Dr. Anne Traynor. I believe I saw her. There she is.

DR. TRAYNOR: Good morning and thank you. I wanted to thank you very much for the time to speak

to you, and we'll try not to over-simplify what's obviously a complicated issue.

We've tried as much as possible to design our talk so as not to overlap our information or perspective too greatly so that we wouldn't waste your time or those of the audience.

I am going to try to present a summary of the slides that are available, and obviously neither in the Blood paper nor in the slides will all of the details that might be requested be available with regard to the Torino study.

We present this information to you in that obviously from this country, the greatest repository of information of older myeloma patients lies with the Arkansas group. You've seen most of those publications and heard the presentation.

There is, of course, a single prospective randomized study of which you're well aware that has a fairly low compliance with the high-dose therapy arm in the older patients which is the Attal study, and the perspective, I think, of the Torino investigators was not to perform a prospective randomization but rather to allow a high rate of compliance with high-dose chemotherapy in the older age group, and to evaluate the outcome in a median age 64 population with respect not just to enhanced -- potential enhancement of survival but also of the brunt of toxicity in this age group.

You've probably heard to a large extent the remission durations achieved typically with conventional chemotherapy of 18 months, and the overall survival of 36 months upon which these and all of us as investigators have tried to improve.

For the purposes of this study, a complete remission was defined, and you probably appreciate that that's defined variably now in different studies as an end component reduction greater than 95 percent by densitometry or quantification. Normal bone marrow, no evidence of new bone disease, and pressure remission as an end component reduction of greater than 50 percent.

The perspective of Torino and, I think, many of us is that most commonly currently patients diagnosed with multiple myeloma under the age of 55 are most commonly not randomized but are actually treated with high-dose chemotherapy as either allogeneic transplant recipients or autologous transplant recipients, usually depending on the availability of an HLA-matched donor, and if you look at the convention now in myeloma centers in the age 55 to 70-year old age group, that is where the greatest degree of variability lies, partially because of the reimbursement issue but also because of the changing concept of toxicity in the older age group.

In the greater than 70 age group, the convention is very much to treat with conventional chemotherapy. Realizing this, the investigators targeted the 55 to 70-year old group, which they felt was the age group in dispute.

As it turned out in their study, 30 percent of the patients, of the initial 100 that they looked at over this

set period of time, opted for conventional chemotherapy, and 70 percent with the high-dose chemotherapy. Because the patients' agreement with the treatment arm, choice of the treatment arm was a part of the study, the rate of compliance with the high-dose therapy arm in this age group was excellent as I'll present soon.

So, essentially this was the design, as you probably are aware, of the Torino study that targeted this age group, and of the 100 patients initially registered from 1994 to '98, 71 ended up being treated with intensified chemotherapy with stem cell support, and 29 with conventional chemotherapy.

Then for the purpose of analysis, they compared those 71 patients treated with high-dose chemotherapy, in this case melphalan 100, which I'll elaborate on soon, to a 160 patients treated with melphalan and prednisone. They selected 71 patients from 160 treated with melphalan and prednisone for age and disease match controls.

If you look at the rate of compliance, therefore, in this study, the study essentially included induction therapy with VAD followed by high-dose cytoxin and stem cell harvest followed by two consistent cycles of high-dose melphalan with a third high-dose melphalan cycle to be added in close sequence at complete remission as we defined it for this study had not been achieved after the second cycle, and even out to the third cycle, the compliance rate was 91 percent, whereas you can see it was in the range of 93 percent with the second cycle in this age group of high-dose melphalan.

Once again, this was the design of the study. The two or standard, if you will, high-dose melphalan treatments were applied to all patients or were supposed to be applied to all patients and were applied with about a 93-percent compliance.

The close intervals between these high-dose melphalans was consistent throughout the study, and you can see the days and the intervals between them. So, patients re-evaluated after the Day 90 high-dose melphalan who did not fulfill complete remission were asked to proceed to one additional cycle.

The comparison of 71 disease and age match controls from the same institutions shows an event-free survival that is statistically significantly different for the high-dose chemotherapy arm, and an overall survival that is as well.

I think that in some studies recently, criticism has been made that the conventional therapy arm fared relatively poorly compared to historical controls, but I think that most of us would agree that in the Italian study, the conventional therapy arm has failed quite well and quite comparably to how most of us see our conventional therapy patients fare at myeloma centers.

The immediate survival, as you can see, there's a plateau at about 55-percent survival between the period of 30 and 38 months, and then at about 40 months, we seem to be achieving the 50-percent survival whereas, of course, the median survival for the high-dose chemotherapy arm has not been reached at the time of this study. Close to 70 percent of patients were still surviving at 40 months follow-up.

If you look at the effect of high-dose chemotherapy on achievement of complete remission, you can see that there was in fact an impact of additional cycles of high-dose chemotherapy, and this has been corroborated at the basic science level by evidence that high-dose melphalan can overwhelm the capacity of the nucleus to remove melphalan and prevent its activity in a much more effective way than conventional dose melphalan can do, and, so, it's interesting to note that not only does high-dose melphalan in the standard one or two cycles continue to increase complete remission seen, but that even out to the third cycle, complete remission achievement, which, of course, is correlated with enhanced survival, has been seen to increase substantially.

The other major issue, of course, is hidden in the decision analysis with regard to this age group as potential toxicity with regard to age. I think that the toxicity of these 71 patients in the high-dose melphalan arm was very comparable to that that is seen in younger age groups treated with high-dose melphalan 200 days with an AMC less than 500 intrasingly did not seem to increase after the third cycle of melphalan compared to the first, and likewise days of thrombocytopenia also did not seem to substantially change with the third cycle of high-dose melphalan.

With regard to extra hematologic toxicity, again the mucositis incidence and the fever in hospital stay all quite -- compare quite favorably with regard to younger age group publications as I think you're aware.

With regard to the Chicago population that I serve, which is a combined large group of myeloma patients that are combined VA and Northwestern University faculty foundation patients, we simply tried to get them the best care that we can. I'd say that roughly 40 to 50 percent of our myeloma patients are African American. They are all extremely varied in terms of their financial status and their prior access to health care.

We have tried what mechanisms we can within the given insurance and health care systems to deliver them the most innovative and effective drug therapies available.

At times, patients have chosen to exercise their ability to be treated through the VA system because they feel that they have access to more. Needless to say, anyone familiar with the Veterans Administration system knows that the majority of patients who are by age or by having served in the Armed Services eligible for VA benefits are not necessarily benefit-eligible for payment of medications and other benefits because their income or what income they have in retirement may still place them outside of a range that makes them eligible.

The major bone marrow transplant centers, of course, are located in San Antonio naturally associated with Vanderbilt, and, of course, Seattle is associated with Hutch, and there obviously isn't consistent policy within the VA of denying transplant to the over 65s.

So, it's not at all uncommon for our lymphoma patients to travel to those sites for autologous bone marrow transplant, and with that precedent, it became not uncommon for our myeloma patients likewise,

if they were eligible for benefits through the VA program, to travel to those sites for transplant.

The directors of those programs say that they quite regularly perform bone marrow transplants for patients over 65 for this disease with good results, and that they generally use the age -- not the age but the overall well-being and organ function of the patient as a parameter in deciding eligibility.

Currently, in Chicago, the patients have a large and very well-educated patient support group, and they've asked me a question which seems obnoxious posed to you, but many of them have paid, you know, for four decades into social security, are well aware that those sitting among them who are on Medicaid as well as the more indigent of the veterans are -- have this care available to them, whereas the large majority of Medicare recipients and disabled patients who are not Medicaid recipients do not, and the question that they pose is, is this a disparity in federal coverage, and we have tried to explain to them the difference with regard to Medicaid and Illinois coverage.

But it does feel, I think, as you probably heard from the testimony of patients yesterday, it does feel to them sitting in groups, large groups of patients, that at times, they have been penalized for being middle class.

I think that I would venture to say this is a proven therapy that can benefit Medicare patients and disabled myeloma patients. There are certainly faults to the Torino study, and there are faults to every study that we can bring in here that isn't a prospective randomized study with a 99-percent rate of compliance in each arm.

I know that. I only wish to emphasize to you that I think we've seen substantial data here today and yesterday for the efficacy and the tolerability of this procedure in this population.

Thank you very much for your time and attention.

DR. HOLOHAN: This isn't a question. It's a comment. Dr. Traynor, I presume you weren't here yesterday when the issue of what's available in VA came up.

DR. TRAYNOR: No, sir, I wasn't.

DR. HOLOHAN: The -- just to clarify for the people who were not here yesterday, this came up in the comments of three patients who -- or patient advocates who presented.

The Veterans Administration provides treatment beyond the level that is provided by Medicare because of statutory requirements. Included among our statutory requirements are to provide clinical care, to provide education, to provide research, and then to act as a back-up for the Department of Defense in time of a national emergency.

So, the autologous transplants for the most part in the VA are provided through a research venue and

funded out of central headquarters. They're not funded out of the facilities' budgets where they exist.

Secondly, you had a slide that said veterans are excluded if they are of middle class, and that is not accurate. The eligibility reform legislation of 1996 made VA patients essentially one class.

If you are enrolled, you are eligible for benefits. If you're not enrolled, you are not eligible for benefits. There's not a dividing line in terms of your taxable income at the present time and hasn't been for three years.

DR. TRAYNOR: Well, that's good for me to know because I'll just tell you the experience we've had. Many of our patients who want to explore the VA benefit and actually go into our intake section at the VA Lakeside are asked immediately what their income is and then are told if it's above 20 something thousand that there's no use in their filling out the paperwork.

Is that --

DR. HOLOHAN: Well, that's contrary to the eligibility reform law.

DR. TRAYNOR: I realize that with regard to receipt of medication, that income -- there may be a sliding scale and a dis-eligibility for --

DR. HOLOHAN: That's correct.

DR. TRAYNOR: But are you saying that for in-patient cardiac and lung and bone marrow transplant, income is no factor?

DR. HOLOHAN: That's correct.

DR. TRAYNOR: Thank you very much.

DR. HOLOHAN: If a veteran is eligible, they can be enrolled. Eligibility is a different issue. The simple fact that you've been in the military doesn't mean that you're eligible for veterans --

DR. TRAYNOR: Right. No. I know that. A patient of ours who had had a service-related injury as well as all of our patients who have war-related injuries seem to have no limitations on their benefits whatsoever, but what I've had more difficulty with is patients who are just in the military with honorable discharge but didn't have any history of injury during the time that they served.

Are they less likely to be eligible?

DR. HOLOHAN: We could probably spend an hour --

DR. TRAYNOR: Right.

DR. HOLOHAN: -- discussing all of the legal aspects, and I'd have to turn to my counselor here. Suffice it to say that there are new eligibility rules passed by statute by Congress in 1996, if a veteran is eligible and enrolled, they get the full package. Your income is not a factor, at least until the last time we had that argument with OMB.

DR. TRAYNOR: Great. Thank you.

DR. HOLOHAN: Could I ask two quick questions about the Palumbo study? One is, they reported in the multi-variate analysis that a complete response rate was unrelated to overall survival, and that seems to be different than some of the other papers and some of the other presentations.

DR. TRAYNOR: I think that it would be -- I think that that's -- that's true, and I think that it is contrary to what is observed in most papers. I think in this particular case, where the median overall survival of the high-dose therapy arm has not been close or reached, it would be a little bit preliminary to make that statement.

Of course, you're well aware that papers, different papers and analyses have defined complete remission in different ways, and many define complete remission as disappearance of monoclonal protein by immuno-fixation, no detectable disease for six months or a year post-transplant or a designated time point.

So, I can say that the achievement of CR as you see it in the 46-percent range in this group is an over-estimate by those standards, and it's certainly conceivable that if they had defined CR by an immuno-fixation of serum and urine as well as radiographically and by bone marrow biopsy, they would have found a closer correlation.

DR. HOLOHAN: Okay. Just one other question. Do you want to comment on the median survival of the matched group of patients treated with melphalan?

It appears that the median survival is significantly higher in that group than the historical data would suggest, higher by anywhere from 33 to almost 40 percent.

DR. TRAYNOR: I think just as an informal observation, that that's probably true, and for myself as a reader of this manuscript, I trust the analysis because of the excellent survival in the control arm.

I think many of us know that patients monitored carefully in a myeloma specialty center and seen reasonably early in the course of their disease probably do have a survival in excess of two and a half years median by conventional therapy, and that's probably closer to three and a half years.

There are -- and I think that there may be incremental increases in survival associated with antibiotic therapy and injections and different subtle maneuvers that are available to us to enhance by minimal increments the survival of these patients in this decade.

I think that it is of the order of magnitude that you're describing, but I think that most of our patients feel that they see that.

We always wonder if the catastrophic cases that Bart was sort of alluding to, the patients that present in very advanced disease with multi-organ failure, having had their diagnosis unmade through progression of their disease are calculated into those median survivals because if they were, they might substantially bring it back toward the older figure, and I think sometimes they're not in those figures.

But -- and they obviously make a significant impact on overall survival.

On the other hand, when you look at patients electively begun on melphalan and prednisone, I would say that their figure is more comparable to what I and others are seeing now for control group.

MS. BERGTHOLD: We have heard that Medicaid in some states covers this treatment, and I'm wondering if you have any idea how many states or what states do cover it, and whether or not any of those -- I'm sure you don't know the answer to this, but I would -- I'll ask it anyway.

If any of those states have done sort of evidence-based analysis before they covered it or what the process was.

DR. TRAYNOR: It's a good question, and I only know for my surrounding states because I'm up in the northeast corner of Illinois. I know the case for Indiana and Michigan. I don't believe I know the case for Iowa, but there's a good chance that Dr. Kyle would.

The -- in Illinois, evidence-based analysis is done in conjunction, I think, if I'm not mistaken, there's a private contract with analysts from BlueCross BlueShield, but they say they do choose evidence-based analysis, but then they also have a policy in Illinois of choosing transplant centers, and, so, in a sense, this is a little bit more like what was alluded to for the VA policy which is if a transplant center has an active protocol, in most instances, it is reimbursed if it is one of the Medicaid-defined transplant centers.

With regard to the state of Michigan, I have been told that evidence-based analysis is done for Medicaid, and I know this predominantly from appealing for transplant for other diseases other than multiple myeloma, where the evidence is less -- where there's less of a history.

In the -- I know that Medicaid in the state of Michigan and Medicaid in the state of Indiana do cover, but the exact policy of data analysis and how much is according to creditable transplant centers and their policies rather than a fair analysis of data with regard to each individual transplant, I couldn't tell you.

MS. GEYER: Thank you, Dr. Traynor, and just for the record, are you here representing Northwestern University?

DR. TRAYNOR: I am, and also representing the Chicago area myeloma patients which is a support group of myeloma patients. Financially, I funded myself to come here.

MS. GEYER: Thank you very much, and our next presenter is Mr. Pearlman. I don't know if he is here with us this morning, and I do see him coming towards the front.

We have a question slightly off the record for you. How is the weather and traffic getting back to D.C.? We have a few panel members concerned.

MR. PEARLMAN: It's been better. It's a little wet out there, obviously. I didn't realize I was next. I thought there was someone else.

Good morning. As you know, my name is Spencer Pearlman. I'm a legislative assistant for Congressman John Porter from Illinois, and I will be rather brief in my comments.

Mr. Porter regrets that he wasn't able to be here. We are unfortunately embroiled in some rather contentious appropriations process right now which actually involves HCFA. I'm actually not used to being on this side. I'm generally on that side when people are testifying. So, this is truly what goes around comes around.

I actually would like to say I'm humbled to be here. I took a brief glance at the people who are testifying today, and I saw lots of M.D.s and Ph.D.s and myself and thought what have I gotten myself into here.

Essentially the reason that I'm here is a woman who testified yesterday named Kathy Hill is a constituent of Mr. Porter's. I have worked with her in the past, and she has met with Mr. Porter on several occasions, and she has -- she was the reason -- she was essentially the person who brought this issue to our attention and made us aware of what was going on, and her passion for this was truly inspiring, and that is the reason why I'm here today and why Mr. Porter asked me to come here.

Obviously I cannot contribute anything of scientific value to the dialogue here today, but where I think I can be of help is to speak briefly about the human side which I understand you also heard yesterday, but also Congressman Porter's views in terms of health care in general.

As you know or as you may not know, he is chairman of the Appropriations Subcommittee that funds the Departments of Labor, Health and Human Services, and Education, and within that is, of course, the National Institutes of Health and the National Cancer Institute, and biomedical research and health care in general is something that's extremely important to the congressman.

He has -- he was the one who spearheaded the effort to try and double the funding for the NIH over a

five-year period of time through annual 15-percent increases over the next five years, and actually last year, we were able to provide the first 15-percent increase.

The reason that he set about doing that is essentially because investment in research saves lives, and it produces advances in the treatment for cancer and other fatal diseases with the ultimate goal of hopefully one day eradicating disease.

One thing that Mr. Porter speaks of on many occasions, and we hear from many constituents as well about this issue, is how you transfer the knowledge that you get through research and apply it to real world situations in trying to help patients who have diseases where essentially it feels to them like it's a death sentence, and how do you provide treatments to them that give them some sort of hope?

Obviously this is of the utmost importance to make sure that these advances are made available to the public. Mr. Porter's also received constituent mail, obviously not a lot because fortunately many people do not suffer from multiple myeloma, but occasionally it does trickle in from people who are suffering from the disease and feel the pain and the heartbreak of having the disease, and as I said, having spoken as well with Kathy Giusti who I believe testified yesterday, the idea of having hope when you have a treatment such as stem cell transplantation which is obviously an exciting new advance, and essentially I'll wrap up.

The main reason why I'm here is because I'm supporting Kathy Hill in her efforts as is the congressman. Obviously we do not -- the congressman doesn't want to influence anything that he has no jurisdiction over. Essentially what his hope is that this town meeting will enlighten some people and hopefully allow them to seriously consider the information that was presented at the town meeting and perhaps ultimately provide coverage for what seems to be a life-saving treatment, and with that, I guess I'm finished.

DR. HOLOHAN: Does the lawyer on the panel want to get a shot at a congressional assistant? No?

MR. PEARLMAN: Thank you.

DR. HOLOHAN: Thank you.

MS. BERGTHOLD: Actually I do have a question for him.

DR. HOLOHAN: Hold. Not free yet.

MS. BERGTHOLD: This is a little bit facetious, but is the congressman also willing to increase support for Medicare funding as well as support for research?

MR. PEARLMAN: Oh, yes, absolutely. Health care, that's his baby. So, he -- despite the budget caps, he wants to increase spending which is why we're in the contentious situation actually.

DR. HOLOHAN: Just as an aside, and I don't mean this in a humorous sense, the former director of HCFA, Bruce Bladock, wrote a paper published in the New England Journal that described the conduct hearings and conclusion of the latest Medicare Reform Committee. If you haven't read it, you should, and if you leave your fax number with the people here, I will make sure you get it. It's incredible reading.

One of his phrases was in Washington, where no truly bad idea ever dies.

MR. PEARLMAN: I can vouch for that.

DR. BAGLEY: I just wanted to thank you for bringing up one thing which is important, and I think as we talk about individual cases, and then we move on and talk about scope of research, I think the one point you brought up is very important, and it's the one we're really here talking about, and that's how do we make that transfer from research to practice because I think Dr. Traynor mentioned earlier, made the allusion, that we were talking about a methodology here, a treatment here that simply because of various kinds of funding may be more available to the poor than to a Medicare beneficiary, for example, and I guess the implication of that would be that perhaps we've moved too slow.

On the other hand, I think the other implication from that which I don't suggest is the case here, but the other implication is that perhaps through our funding mechanisms, the poor are bearing the burden of medical research which I would hate to think is the case either.

So, I think you pointed out, I think, the issue which is really in front of us, and I appreciate the fact that you did that, is that we're really talking about when do things move from research and into medical practice. That's the question we're here about, and thanks for focusing us on that.

MS. GEYER: Thank you, Mr. Pearlman.

MR. PEARLMAN: Thank you.

MS. GEYER: And just for the record, I want to read in that Dr. Karen Fields from the Moffitt Cancer Center, which is in Florida, was unable to get out of Florida to be with us today.

So, I think at this time, we will conclude this morning's session and go to a 15-minute break.

Thank you.

(Whereupon, a recess was taken.)

MS. GEYER: Dr. Vilis Kilpe will be providing the presentation for HCFA this morning. Dr. Kilpe?

HCFA Presentation

DR. KILPE: Good morning, everybody, members of the panel, distinguished clinicians, ladies and gentlemen. I will attempt to summarize this massive amount of information here before the panel. I'll try to focus on the newer studies relating to stem cell transplantation in multiple myeloma.

I will start with a basic description of the clinical characteristics of multiple myeloma. I will then proceed to some of the Phase 2 studies, and I'll finish with one randomized trial, the Attal study.

I would also like for you to know that I am not an expert in multiple myeloma, and I will be quoting many of the clinicians sitting here. In case I make a mistake, please feel free to correct me.

I will start with the clinical characteristics of multiple myeloma. Multiple myeloma is a disorder of malignant plasma cells which accumulate in the bone marrow and produce an immunoglobulin, usually of the IGA-IGG variety.

Complications of multiple myeloma include osteolytic lesions, anemia, bacterial infections, renal insufficiency. The cause of multiple myeloma is unknown.

These are the malignant plasmablasts which are responsible for the manifestations of the disease, and, in general, the greater the number of these -- well, my pointer doesn't seem to work. The greater the number of these cells, the worse the outcome.

Could I have another pointer maybe? You've heard these numbers before. The incidence of multiple myeloma is four to five cases per 100,000. It's more common in African Americans. Thank you. And -- sorry. Median age is about 65 years.

The minimal diagnostic criteria for multiple myeloma are that there's more than 10-percent plasma cells in the bone marrow or a plasma cystoma at one of the following, N protein in the serum, N protein in the urine, or osteolytic bone lesions.

There are a couple of variants of multiple myeloma, and this one actually happened to be described by Dr. Kyle in about 1980. Small grain myeloma, these patients tend to do well over time. It's characterized by low monoclonal protein output. Bone marrow infiltration approximately 10 to 20 percent. No anemia or renal failure hypercalcemia and no bone marrow lesion. As a matter of fact, Dr. Kyle suggested that these patients should not be treated.

Another variant of multiple myeloma is intuit multiple myeloma, slightly higher monoclonal protein output, bone marrow infiltration of approximately 20 to 30 percent, two to three small osteolytic lesions,

no compression or collapse, no hypercalcemia, mild anemia, no symptoms. Again oftentimes these patients are not treated.

Now, a bit about disease course over time. Drs. Anderson and Traynor have provided wonderful diagrams of the disease course of multiple myeloma. As you can see, multiple myeloma may start as a monoclonal neuropathy of unknown significance or intuit myeloma. As the cells proliferate, the disease becomes symptomatic. Disease can be treated. Treatment may result in remission lasting a year or two. Eventually there's a relapse. A relapse is practically universal. Eventually the disease progresses and becomes more difficult to treat.

So, when you -- when looking at the studies, it's important to know what phase of disease the patient is in when they enter a study.

Now, a bit about staging and prognostic factors in multiple myeloma. The classic staging system for multiple myeloma has been the staging system. It basically has four components. Hemoglobin levels, serum calcium, whether or not there are bone lesions, and the level of monoclonal protein output.

Stage 1 is said to be characterized by low myeloma cell mass. Stage 3 is characterized by high cell mass. The survival of patients in Stage 1 is approximately five years median survival, and in Stage 3, there's approximately 15 months.

Over the years, a number of risk factors have emerged in multiple myeloma. These are the high-risk factors. Cytogenetics, Chromosome-13 deletion, an indeed greater than two percent, LDH two times normal, hemoglobin less than eight, Beta 2 microglobulin greater than four, CLP elevations greater than four, hypercalcemia or excess protein production, protein secretion greater than 10 grams percent.

Recent studies from the Mayo Clinic show the survival of advantage of having a low monoclonal protein -- I'm sorry -- a low Beta 2 microglobulin. I'm sorry. The pointer doesn't seem -- this one works. As you see, the survival in patients with low Beta 2 microglobulin is substantially higher than those with a high Beta 2 microglobulin.

If you look at the labeling index, the same is also true. Patients with a low level of labeling index tend to do much better, and if you try to interpolate that, the survival at five years is approximately 60 percent, whereas those patients with a high labeling index, the survival at five years is only maybe 10-15 percent.

Low mass myeloma is characterized by absence of onset of favorable cytogenetics, plasma labeling index not exceeding one percent, LDH within normal range, hemoglobin greater than 12, Beta 2 microglobulin less than 2.5, CLP less than 2.5, serum calcium, marrow plasma cytosis not exceeding 20 percent, normal serum albumin.

Now, a bit about therapy for multiple myeloma. For years, the treatment of multiple myeloma has been melphalan and prednisone. Dr. Bataille in his review of the subject states that "melphalan,

cyclophosphamide and glucocorticoids are the most effective drugs against multiple myeloma. Combinations of other drugs, including vinca alcaloids, are no more effective than melphalan and prednisone."

An important aspect of the management of multiple myeloma is support and care, and I just want to focus on a few. The use of bisphosphates for bone disease, radiation therapy for localized lesions, management of hypercalcemia and anemia, most important of all, management of the infections. These people tend to be susceptible to infection, and this may be fatal.

Now, a bit about prognosis. With no treatment, prognosis is progressive course with median duration of survival approximately six months. With chemotherapy, fewer than five percent of the patients achieve through complete remission. Remissions induced by standard chemotherapy do not exceed 18 months. Median survival does not exceed 30 to 36 months or about three years. About five percent survive 10 to 15 years.

The next curve I will show you, I'd like to sort of make a mental image because this is an important baseline when looking at patients with multiple myeloma. What it says here on the bottom is that this is a survival plot for newly-diagnosed patients with myeloma receiving standard dose chemotherapy under the auspices of the Southwest Oncology Group.

A few points about this slide. If you look at the five-year survival, again it's somewhere perhaps 25-27 percent. But you also notice that 10 to 15 percent of the patients survive longer, 10 to 15 years, and if you look at the 50-percent mark, the median survival here is about three years.

Now, a bit about some Phase 2 studies. Phase 2 studies using autologous bone marrow transplantation or stem cell transplantation suggested that this therapy improved complete remission rates and overall survival for multiple myeloma, and here is a summary of some of those studies, and I would just like for you to focus on a few things. Focus on the complete remission column.

You notice that in the mean studies, complete remissions ranged from about 24 to 75 percent, substantially better than the five percent with chemotherapy. You'll notice that the overall survival is also greater than 36 months.

It's also important to note that we have a heterogenous group of patients here. There's varying prior treatment. There's varying disease status prior to treatment. There's varying regimens, and some got stem cells, some got bone marrow. So, it is difficult to interpret those results.

The age in these studies is mostly late 40s, early 50s. This therapy is also associated with some degree of mortality. Early death ranges from two percent to 25 percent, and the other numbers are similar.

Now, in 1994, Dr. Alexanian published this study indicating that limited value of myeloblative therapy for multiple myeloma. In this study, the utility of myeloblative therapy supported by autologous blood

progenitor cells was assessed in 49 patients with multiple myeloma. Outcomes were compared with those similar patients who did not receive intensive treatment primarily for socioeconomic reasons, and here is the outcome. Small number of patients, comparing 23 to 33 patients, and here you see that transplant didn't help much, and this is what's called late myeloma.

There were various subgroups of late myeloma, and basically the outcome is essentially the same.

Here is another subgroup. Transplant did not appear to help in these patients with late myeloma. When you read the test of this article, you find that in the resistant-relapse group, median remission time was only five months, median survival time was eight months, and the primary resistance group median remission was 17 months, treatment rate of death in two patients, and in the late remission group, median remission time was 12 months, as compared to seven months in the chemotherapy group.

They concluded that current myeloblative treatment supported by autologous bone marrow or blood stem cells were useful in very few patients with multiple myeloma after the first year of chemotherapy.

Then in 1999, an interesting report came from the Mayo Clinic again, indicating that plasmablastic morphology is a powerful independent predictor for survival rate after an autologous stem cell transplantation for relapse of primarily refractory myeloma, and plasmablastic morphology is set to be present when two percent or more plasmablasts are present in the plasma cell population.

And here is the outcome in these patients. As you see, the patient's non-plasmablastic morphology have a substantial survival advantage, and the survival advantage is the area between the two curves, and if you actually look at the survival advantage, the median survival time for the plasmablastic group here is given as five months, median survival time for the non-plasmablastic group is given as 24 months. So that the survival advantage here at the 50-percent point is about 19 months.

If you look at again the five-year survival, five-year survival in the non-plasmablastic group is about 30 percent, whereas it is only about 10 percent in the plasmablastic group.

Here's a table of the results, and as you can see, complete response rate was 21 percent in the plasmablastic group, and 35 percent in the non-plasmablastic group. Median survival times were considerably shorter in the plasmablastic group, five as opposed to 24. Progression-free survival was also substantially shorter in plasmablastic group.

This is a table looking at relative risk, the risk of death. You see that age here is not very significant, and whereas all these other factors have substantial impact on the outcome of the disease.

Dr. Vesole in his review of this subject has a table indicating the effect of pre-transplant disease status on transplant outcome, and here you see the patients who have sensitive disease do substantially better than those who have refractory or resistant disease. Overall survival is 52 months in sensitive disease, whereas it's 39 months in the refractory disease, only 25 months in the relapse category.

Now, a bit about tandem or double transplants. In 1997, Dr. Barlogie published this study indicating the superiority of tandem autologous transplantation over standard therapy for previously-untreated multiple myeloma. He compared a 116 patients on total therapy with a 116 patients from small trials, and here are the basic results.

Dr. Barlogie was able to achieve 40-percent remission, complete remission, where that number is not available in the small trial. Event-free survival was 49 months in Dr. Barlogie's hands versus 22 months with the chemotherapy group. Overall survival was 62 months in total therapy group as opposed to 48 months in the chemotherapy group, approximately a one-year advantage.

These are the results. I only wish that Dr. Barlogie had fixed this table a little bit so I could figure out the numbers of it better, but what this shows is that in a chemotherapy group here, if you look at the five-year survival, you have to estimate it here, the five-year survival appears to be about 45 to 50 percent -- I'm sorry. He has it here. The survival group, pull it up a little bit. Yep. Okay.

The chemotherapy group appears to have five-year survival, about 45 to 50. The total therapy group appears to have survival of approximately 60 percent. So, the gain here is about 10 to 15 percent at five years.

Then Dr. Barlogie published another study in 1999 where he described what happened to all of his 231 patients on total therapy. The median age of these patients was 51. They have symptomatic myeloma, and these are newly-diagnosed multiple myeloma patients.

He was able to achieve a five-percent complete remission rate after DAD, 15 percent at the end of induction, 26 percent after the first transplant, and 41 percent after the second transplant. The median survival was 68 months, and event-free survival 43 months, and you can see that these are substantially better than chemotherapy.

The actuarial five-year survival here was 58 percent, close to the number I report on the previous graph.

Now, what were the characteristics of Dr. Barlogie's patients? You see again mean age is 51. Hemoglobin, 34 percent, less than 10. Beta 2 microglobulin, 30 percent, greater than four. Cytogenetics, abnormal 21 percent. Mostly IGG myeloma.

Now, what happened to these patients? As you can see in this graph, survival, five-year survival here is 58 percent. The treatment had a mortality of approximately seven percent, and that's listed here. 55 percent of the patients did progress by end of five years.

Dr. Barlogie also published another remarkable finding. The impact of abnormal cytogenetics and Beta 2 microglobulin on outcome, and here you see the median survival in patients who don't have these bad characteristics at seven plus years was only 2.1 years in the patients with the abnormal Beta 2

microglobulin and abnormal cytogenetics. You notice that this curve is much steeper than the other.

Again if you estimate the five-year survivalhere, here in the poor prognostic group, the survival is about 20 percent, whereas it is about 60 percent in the better prognostic group.

Now, here is a complete analysis of all the prognostic factors, but I'm not going to focus on all of them. I'll just focus on one because I know sooner or later, I have to talk about age. Let me focus on the age column here.

We have a 181 patients less than 60. Their overall survival was 84+ months, and there were 50 patients greater than 60. Their overall survival was 50 months, and apparently the older group did slightly worse, and this appears to be statistically significant.

Now, the French have also done single versus double transplant studies, and here is that randomized trial that was mentioned earlier of 400 patients. One arm got a single autologous transplant, the other arm got a double transplant. In French hands, the outcome is here.

What they basically state is the double transplantation was not found to improve response rate event-free survival or overall survival, and complete remissions are listed about 30 to 33 percent. They give a two-year survival. I don't think that's very meaningful in multiple myeloma.

Now, a bit about age and stem cell transplants. Again, in 1999, Dr. Siegel and colleagues published this study, that age is not a prognostic variable of transplants for multiple myeloma. They had 49 patients, aged greater than 65 years, and 49 younger than 65 years. They were matched for prognostic factors.

Here is the outcome. You see that in terms of overall survival, the median survival is 4.8 years in the younger, 3.3 years in the older. The curves are somewhat lower in the older, but these were not statistically significant differences, and if you look at duration of complete remissions, they appear to be equivalent, but please note there are only 21 patients here and 10 patients here. That's not very many.

Now, the issue of toxicity from this therapy arose yesterday. This is toxicity in Dr. Siegel and Dr. Barlogie's hands. What you see here, that patients get diarrhea and pneumonia sepsis. There are differences in the various columns, but those differences are not statistically significant.

It's worth noting that early death is eight percent in the older age group, and two percent in the younger age group.

Upon multi-variate analysis, the only factors that turn out to be significant were the cytogenetics and the Beta 2 microglobulin and not age.

Now, various criticisms have been lodged against these so-called uncontrolled or Phase 2 studies. Here is one from Dr. Bataille's review of the subject. He states, "Uncontrolled studies in patients with newly-

diagnosed disease have found that combinations of conventional induction therapy and high-dose therapy followed by autologous stem cell transplantation produce a 30 to 50 percent rate of complete remission, and it's defined as the appearance of M component as determined by standard electrophoresis and prolonged survival. However, all of these studies are marred by selection bias."

Now, what is selection bias? Again, the folks from May Clinic will help me out. In the article in bone marrow transplantation in '99, they discussed this issue, and they do it better than I could say it.

Because transplantation in multiple myeloma is off-limits at larger medical centers, there is a selection of bias for patients who are able to travel to these centers. Some patients who go on to transplant have been selected by their initial ability to survive to the point of transplant, making this an inherently more favorable group.

In non-randomized studies, it's difficult to determine whether achievement of a complete response reflects superior therapy or whether those patients would achieve a complete response with inherently more sensitive tumors and are ultimately destined to do well because of favorable biology and sensitive diseaserather than treatment intensity.

Another comment by Dr. Lockworth in his review of stem cell transplantation. He states, "Although response and survival in these Phase 2 studies appears to be better than the historical control groups of patients who were treated conventionally, one should be careful to draw definite conclusions about so far published non-randomized trials."

This is illustrated by historical comparisons performed by Dr. Attal et al and Arksani, who showed that patients who did not receive high-dose chemotherapy but were eligible, younger-aged chemo-sensitive disease, had the same prolonged survival, greater than five years, as patients who received an autologous transplant.

And now we come to the one important randomized trial. The French study. I think it is important to read what they say in the introduction. "For the past 30 years, combinations of melphalan and prednisone has been the standard treatment for multiple myeloma. Extensive trials of other drug combinations have not led to major improvements in clinical outcome. Myeloma remains an incurable malignant tumor. Median survival does not exceed three years. Although high-dose therapy and transplantation is promising in patients with myeloma, selection bias hinders direct comparison of the important results of those with conventional therapy. Prospective randomized trials are needed to compare conventional therapy with transplantation." And, of course, they did the study.

200 previously untreated patients with myeloma, under age 65 years, were randomly assigned at the time of diagnosis to receive either conventional chemotherapy or high-dose therapy and autologous bone marrow transplantation.

What were the patient characteristics? Here you see that age again is 58, 57, mostly Stage 3 disease,

mostly IGG myeloma, hemoglobin was 11, plus or minus two, lactate dehydrogenase was elevated, bone marrow plasmacytosis ranged from 36 to 39 percent, Beta 2 microglobulin was elevated slightly higher in the conventional dose group.

Now, what was the conventional therapy? Conventional dose therapy consisted of altering cycles of VMCP and BVAP administered at three-week intervals for 12 months for a total of 18 cycles. The VMCP stands for vincristine melphalan cyclophosphamide, prednisone, BVAP stands for vincristine, carmustine and prednisone.

The high-dose therapy group received four to six alternating cycles of VMCP and BVAP, preparation of melphalan 140 milligrams per meter squared, and total body irradiation, followed by unpurged bone marrow transplantation. What was the outcome? I think you've seen this picture before.

22 percent got a complete remission, 25 percent in the conventional dose group got -- had progressive disease, and five percent got complete remission. So, the numbers are within the range.

What was the outcome in terms of event-free survival? You see there appears to be a survival advantage to high-dose therapy, but if you calculate it out at the median -- the median survival for the conventional group here is about 18 months. The median survival for the high-dose group is given as 27 months. So, the survival advantage here is approximately nine months.

The other aspect I wanted to mention on this is that the confidence intervals here are wide.

Now, in terms of overall survival, what happened? Here you can see that nothing happened for about 30 months or two and a half years. The outcome is identical. Then the curves begin to diverge. Now, the five-year survival here is said to be -- I'm going to give it to you. It's 52 percent in the high-dose group and 12 percent in the conventional-dose group.

Please note that the confidence interval in the conventional-dose group is one to 40. That basically means that with 95-percent certainty, the truth lies somewhere between one and 40. In the high-dose group, the interval is 36 to 67, and again the truth lies somewhere between 36 and 67, and those intervals tend to overlap.

Now, what actually happened to the patients who got transplanted? Only 74 patients in the high-dose group underwent autologous bone marrow transplantation. 37 patients in the high-dose group died, 30 died because of progression of the disease, seven died because of toxic treatment. So, if you tried to calculate mortality, seven out of a hundred is seven percent. If you calculate seven out of 74, that's about 9.5 percent.

One thing here. 26 patients in the high-dose group did not undergo transplantation, five died prematurely, six had poor performance status, five had abnormal renal function, and 10 had insufficient amount of bone marrow collected.

What did the authors conclude? The authors concluded that high-dose therapy combined with transplantation improves response rate, event-free survival and overall survival in patients with multiple myeloma, and they published a follow-up study as an abstract, and that abstract states -- let me start with the median survival.

Event-free survival in high-dose arm was 28 versus 18. So, 28 minus 18 gives one a 10-month survival advantage in terms of event-free survival. In terms of overall survival, median survival in the high-dose group was 57 months, and in the conventional group, 42 months. So, 57 minus 42 equals 15 months. That's the survival advantage.

It is also worth noting here, do you remember the last curve I showed you? Oh, that's right. The five-year survival was 12 percent in the control arm. Now, it is beyond my comprehension how a survival curve can go upwards from 12 percent to 21 percent if we're dealing with the same patients.

Now, this trial has not been without criticism. Shortly after its publication, letters to the editor appeared, and here's one from Dr. Atkins. "Conclusion high-dose therapy improved both event-free and overall survival in patients with multiple myeloma is not supported by the data. The comparison of overall five-year survival between the conventional-dose group and the high-dose group, 12 percent versus 52 percent, is also misleading since at Attal et al do not mention the wide 95 percent confidence intervals, one to 40 and 36 to 67."

Dr. Atkins further continues. "In addition, the authors failed to consider the difference may have been due to detrimental effect in the conventional-dose group and benefit in the high-dose group therapy."

DR. HOLOHAN: Could you leave that up for a second?

DR. KILPE: Yes, sir. I planned to. Oops.

DR. HOLOHAN: I just wanted to see the table.

DR. KILPE: Okay. I'll read it. I was rushing a bit. "Although they note that drug combinations other than melphalan and prednisone have not led to major improvements in clinical outcomes, they chose to use vincristine melphalan cyclophosphate prednisone and alteration with vincristine, carmustine and prednisone for a total of 18 cycles in the conventional group."

The patients in this high-dose group would have received 270 milligrams of both --

DR. HOLOHAN: Standard dose group, right?

DR. KILPE: No. This is the high-dose group. That's what --

DR. HOLOHAN: No. Conventional.

DR. KILPE: I'm sorry. Conventional. I apologize. My apologies. Conventional. Get mixed up standing here. The patients in that group would have received both VMCP and BVAP per square meter of body surface area, whereas those in the high-dose group would have received only 60 to 90 milligrams of each drug per square meter. These higher doses may have impaired both the bone marrow and cardiac reserve of the patients in the conventional dose group with no concomitant benefit resulting in worse survival.

Had the patients in the conventional-dose group received only melphalan and prednisone, perhaps they would have fared better.

Another critic. Dr. Oyvonan states that the conclusion is premature. From the overall survival curves, Figure 2, it is obvious that the survival of patients in both treatment groups was almost identical during the actual period of observation were two years. The difference appears only later when the curves are based more on projection than on observation.

Here is a comment by Dr. Lockworth in his 1990 review of stem cell transplantation. He states, "There has been only one randomized study to demonstrate autologous bone marrow transplantation improved the outcome of newly-diagnosed multiple myeloma patients when compared with conventional chemotherapy. Therefore, it seems premature to conclude that the intensive therapy is a standard approach to the younger multiple myeloma patients."

Now, I'd just like to summarize, and for what I have said, basically the outcome of stem cell transplantation depends on the phase of disease, the stage of disease, the prognostic markers, and whether or not the disease is sensitive or resistant.

Now, here is a sort of estimate of what can be achieved with stem cell transplantation. Complete remissions are said to increase from five to 50 percent, but if we compare this to the one randomized trial that's available, this number is 22 percent here, and if you look at the Phase 2 studies, that number may be 75 percent. So, perhaps 50 percent is a fair number.

If you look at the event-free survival, it is said to be improved from 1.5 to three years. Again if you look at the randomized trial, the event-free survival only enters at 2.3 years. If you look at overall survival, it is said to improve from three to five to six years. If you look at the one randomized trial, the overall survival was 4.8 years. So, it's in the range.

Now, what is the mortality of the procedure? You've heard all kinds of numbers, one percent, two percent, 10 percent. Dr. Barlogie indicates in his answer about seven percent. I think that was also reported -- a similar number was reported from the Mayo Clinic in a study you showed earlier, about seven percent. Some of the European trials are about seven percent. Perhaps that's a fair number.

However, the ultimate fatal outcome of multiple myeloma has not changed. So, this concludes my presentation.

Thank you very much.

MS. GEYER: Any questions? Any questions from the panel?

DR. HELZLSOUER: I would just like to make a comment that the common misconception of confidence intervals. The confidence intervals -- there's not an equal distribution of probability across the interval where you might expect to see the effect, and in fact, it's more like a bell-shaped curve.

So, while confidence intervals may be wide, and it's highly dependent on sample size, the point estimate and the probability -- the more likely probability is that it's surrounding that point estimate that they have.

DR. HOLOHAN: Could you turn on the light?

DR. KILPE: Yes, sir. I apologize.

DR. HOLOHAN: I feel like I'm at a congressional hearing.

DR. KILPE: I apologize.

DR. HOLOHAN: I think we actually did get to the issue in a previous question. I raised the issue of the regression toward the median, if you will, in comparing -- in autologous comparing their first paper with their second, and the earlier estimates on survival, where it appeared that it actually increased, were actuarial predictions which again raises the issue of the confidence that you can have in predicting survival on the basis of a fairly short observation period and fairly small numbers.

So, it appears as best as I can understand from reading both of those articles that the 21 percent represents more of an actual observation, the 12 percent predicted survival in the standard treatment groups was a predicted survival.

DR. KILPE: Perhaps that's so, but I can't tell it from the material at hand.

DR. MINTZ: I would just make the comment for the panel that the Attal study used bone marrow and not peripheral blood as its source of stem cells, and in that regard, one would expect a higher complication rate than from the contemporary use of peripheral blood.

DR. KILPE: Any more questions? May I sit down? Thank you.

MS. GEYER: Thank you.

DR. HOLOHAN: Yes, actually. Would you care to make any comments on the technique of matching patient groups, historical versus treatment groups, on the basis of known prognostic factors?

DR. KILPE: I don't know of any good study that compares those. I really don't have any comment on that.

DR. HOLOHAN: Does our School of Public Health person care to --

DR. HELZLSOUER: Well, I mean clearly, historical data are often used and are not the best comparison. There's lots of things, as was pointed out, I think, in one of the presentations that change over time that you cannot control for, such as supportive care primarily.

So, within -- I think it's -- gives you some information, and within the major factors, you can control somewhat, but it will never be the same level as a randomized trial.

DR. HOLOHAN: Right. I guess in summary for the great unwashed non-statisticians among us, that's one of the reasons why matched trials fall fairly far down on the evidence ladder.

You may be able to match for known prognostic factors, but we don't know what all of the prognostic factors are. So, there's an intrinsic or inherent flaw in that kind of an experimental approach. Is that fair? Have I missed it?

DR. HELZLSOUER: Known prognostic and known treatment factors that may not have been collected at the time.

DR. HOLOHAN: Correct. The other comment I should make, this isn't a question, but in response to your comment about bone marrow versus peripheral stem cell, another variation on the theme in the Attal study, the anti-group Neolone France, if you will, was -- the fact that they used TBI as a conditioning regimen, total body irradiation, which many investigators do not use because of the predicted and predictable ill side effects on more elderly patients. So, that could be another explanation.

DR. LERNER: Can I just ask? In Attal, do you see any issue with the fact that I think its cells are unpurged, if that makes a difference?

DR. HOLOHAN: I think we'll get to that later today.

DR. LERNER: All right.

MS. GEYER: On that note, are there any more questions?

(No response)

MS. GEYER: Then I believe we'll take a break for lunch at this time, and lunch was scheduled from 11:30 to 12:30, and I think we'll come back at 12:15 in the interest of ending earlier today, if possible.

(Whereupon, at 11:20 a.m., the meeting was recessed, to reconvene this same day, Thursday, September 16th, 1999, at 12:15 p.m.)

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

12:50 p.m.

Open Committee Discussion

MS. GEYER: Okay. I think we're ready to reconvene this afternoon, and this is the first time we're doing this. So, I am going to take some time to explain to the panel how we will proceed this afternoon.

Right now, we're going to move into the open committee deliberations portion, at which time Dr. Bagley will reframe those questions that the committee will be discussing this afternoon. The committee will then discuss the questions amongst themselves and have the opportunity to question anyone who has presented throughout the course of the last two days.

After these discussions have concluded, a vote -- a motion to call a vote will be called, at which time voting will proceed. The voting members of this panel are Dr. Paul Mintz, Dr. Kathy Helzlsouer, Dr. Leslie Francis, Mr. Robert Johnson, Mr. Ronald Jordan, and Dr. Jeffrey Lerner. Ms. Cathy Dooley, Ms. Linda Bergthold and Dr. James Adamson are non-voting members of this panel, and Dr. Thomas Holohan will vote in the instance of a tie, and a vote will be done as a yea or nay to each of the eight questions.

So, I think we will open right now with Dr. Bagley reframing the questions.

Does the panel have any questions at this time?

DR. HOLOHAN: One of the panelists will have to rephrase the question as a motion, and the vote will be yea or nay on the motion. The motion has to be seconded and then subject to a vote.

DR. MINTZ: So, these are not as yet motions? A motion will have to be made?

DR. HOLOHAN: Correct.

MS. GEYER: Correct.

DR. HOLOHAN: And it is not unlikely the question will be remade slightly, but you'll see.

MS. GEYER: Okay. At this time, Dr. Bagley will look at the questions which I believe are up on the computer.

DR. BAGLEY: Now, if it seems like we're stumbling along a little bit, it's because we're going through this process for the first time, and, so, I'm sure you'll bear with us.

But, you know, the important thing is that we evaluate the evidence, that we give everyone an opportunity, that we have a public hearing of the evidence, and that we're then able to translate this committee's recommendations into Medicare policy, and that's the important thing.

Now, Medicare policy, as we discussed a little bit earlier, does have some restrictions on what we can and can't do, you know. We could have a panel meeting on the value of preventive services and health interventions, and we could all come to agreement, but Medicare would be unable to implement those benefits because there are things in the Medicare law which prohibit payment for certain things, and in the same light, we could all argue about the way a certain benefit ought to be provided, and it might be a benefit in which Congress has already decided how it ought to be provided, and it wouldn't be something we would be free to do.

So, what we have done as a staff is to evaluate this issue, to put it together in such a way to present it to the panel. We have provided certainly not all of the information available but what we thought was -- represented relevant information, and we have relied on the experts in the field who have presented to the panel to present additional information, and based on this information, we're then going to get panel recommendations which will allow us to formulate Medicare policy.

We framed the questions in such a way that we are dealing with the issues that we need to put this into a policy, and I'll go over the questions again to try to put this in -- to frame the discussion and give you some indication of why we have done this.

The first and foremost question has to do with medical evidence. What we're all about is translating medical evidence into coverage policy. So, we have asked the first question. Is the medical evidence that's been presented considered by the panel, and it's been presented and considered in the panel's discussion, sufficient that we can make a determination for the Medicare beneficiary population?

Let's see. I'm going to have to get to the keyboard here, I guess.

The second question is one that's going to be very important for us as we look into the issue of policy, and I don't think by any means the fact that there's a Question 2 presumes what the answer to Question 1's going to be. But Question 2, depending on the answer to Question 1, is that if we were to develop a policy, what kinds of things should we put in there?

You know, as we develop a policy, we don't generally have a policy which is cover it/don't cover it and that's the end of the story. We have to talk about the conditions and the ways in which we implement this policy and the way we put it out, and an important distinction here between Medicare and other kinds of health plans is that Medicare isn't the kind of a plan where we could say we could -- we ought to cover it, and we ought to cover it for patients that are in good health and need it because Medicare isn't a plan where people submit medical records, and we review them and say yes, this looks okay for this patient.

We need to write a policy which tells our carriers how to do this. So, specifically, if this became a covered service, should it be a covered service for everyone with multiple myeloma, for patients with multiple myeloma who don't have other co-morbidities, who meet certain criteria, who have certain risk factors or don't? That's the reason why this question is framed around how would the criteria be written.

I think the third question is very much something that is going to be dealt with as the whole discussion goes on, and that is what is the appropriate measure, and how should we be looking at the evidence? What's the appropriate outcome to be measuring?

We've heard some discussion about survival, about event-free survival, about quality of life, and I think we would like the panel to tell us what the appropriate measures are when we consider technology like this.

The question of single transplant, tandem transplant, has been brought to the fore, and if we write a policy, I think if we were to cover this as a covered service, we would need to deal with the issue of whether or not it should be a single service or whether or not in some circumstances it should be a repetitive benefit.

I think an important issue for Medicare coverage policy, and we talked briefly yesterday about what the evidence should show us, not just that this is an efficacious treatment or technology, but in what way should it be implemented, and what kinds of limitations?

The first -- the earlier question had to do with what are the appropriateness criteria in terms of patient selection? Should we look at co-morbidities, other conditions in making the benefit available?

Similarly, are there limitations that should be brought to the fore in where the service ought to be made available? Is it a service which ought to be generally available or not? And one very important caution here. Just like it's very difficult for us to write criteria for patient selection, unless they are very concrete and can be applied generally, it is also very tempting in many ways to look at new technology and say

this is a technology which appears to be promising. It ought to be available, but we ought to restrict it to providers or institutions which have shown expertise in that.

This is something that Medicare has done in the past. It's something that was done with heart transplants. It's something that's been done in some other limited circumstances, but it's also something which is very difficult to do and is very resource-intensive, and it is not an answer to providing services which are early in that transition from experimental to mainstream practice, and, so, while we would be interested in the panel's observations on this, it is usually not a practical way to implement a benefit in a specific kind of institution or a specific institution or to specific places, that Medicare should start to cover technology when it is ready for diffusion into general medical practice, and if it's not ready for that, then it's a very difficult benefit to implement.

MS. BERGTHOLD: Could I ask a point of clarification? Since Medicare doesn't cover drugs offered in the out-patient setting, then it really isn't appropriate to deal with sort of out-patient/in-patient setting for this particular question, is it, on that?

DR. BAGLEY: I think in terms of the answer to this question and the applicability, I think if the panel thinks there are relevant factors about how this service should be implemented, if at all, I think that if there are limitations that the panel thinks are important, they ought to be expressed.

You know, for some technologies, that could be out-patient versus in-patient. For some technologies, it could be institutions withdemonstrated expertise. But as we get more and more restrictive in policies or as we get more specific, it becomes increasingly difficult, sometimes impossible, to really apply the benefit.

So that, in general, you know, Medicare benefits are benefits which we can craft a policy for, and we can write down specifications which are applicable to the general medical community, and that means any hospital, any provider, that can provide the kind of service that we've defined.

And should there be specific protocols? As you've seen from the studies presented, there are lots of ways to provide what sounds like the same kind of service, and, so, based on the evidence, because again we're all about evidence, based on the evidence, as we implement a coverage policy, should we restrict it to certain kinds of protocols, to -- should we restrict new treatments to a certain ischemia of things? Should we say it should only be done before or after other kinds of treatments? Should we restrict it to people who have been through certain kinds of diagnostic procedures?

I mean are there protocols which the evidence would tell us are the appropriate way to implement the benefit? And, finally, based on current evidence, and we haven't talked a lot about this, but there's certainly been discussion about the different studies we've looked at, is that it may be that the committee will want to deal with the issue of the source of the donor cells, and are there any other questions?

I mean based on the discussion, are there other questions? This is the opportunity for the panel to bring

up other issues, to say was the scope of the questions presented adequate, and are there other issues we should consider?

Remember, the way we have framed these questions, and we've asked the panel to consider each of these questions and provide us with an answer and a discussion around those questions, because they're ones that we need to answer in order to implement a Medicare policy, and, so, we've tried to frame the discussion around those very practical things which we need to consider in putting together a policy which our carriers and our contractors can use to administer a benefit, if in fact the committee, you know, feels that this is a benefit that we should turn in to policy.

So, with that reframing of the questions and that little bit of a background on why the questions were presented to the committee in that fashion, I'll turn it over to Dr. Holohan.

MS. GEYER: Just as a reminder, we ask that especially during this open deliberation part, any time a panel member speaks, if they could please identify themselves, both for the record as well as the people in the audience to know exactly who you are.

DR. BAGLEY: Because I hope you all realize that this will be taken down, and the transcript of this entire committee hearing will be available to -- for your future reading and your future deliberation.

DR. HOLOHAN: Dr. Adamson had some material that he wished to present to the committee. I think that this is the appropriate time to do so.

DR. ADAMSON: I have two issues.

DR. HOLOHAN: You have to identify yourself.

DR. ADAMSON: Oh, I'm sorry. I'm Dr. Jim Adamson. I'm the Medical Director for Medicare in Arkansas, and I have two issues, and I would like to address this to Drs. Barlogie and Anderson and Kyle.

You perhaps have gleaned from some of my earlier questions, we have reviewed the claims for 63 patients that were billed to Medicare in Arkansas for patients with multiple myeloma who had high-dose chemotherapy and either bone marrow or stem cell support. These patients range in age from approximately 33 to 77 years.

The transplants were done between 7/25/94 and 4/26/96. The significance of those two dates are that as Andrea Argabrite mentioned yesterday, Medicare -- HCFA had said that prior to 1996, it was carrier discretion as to coverage for bone marrow transplants and high-dose chemotherapy.

We -- Dr. Barlogie very kindly provided me all of his data, and I sent that information to the other carrier medical directors and asked them to ask the bone marrow transplant facilities in their regions to

tell me whether or not this was investigational for patients with myeloma. I received a response from 46, and all 46 said that it was investigational. This was 1993 now.

We then published a local medical review policy which did not cover high-dose chemotherapy, bone marrow transplant for myeloma. We received these claims after that publication, and, so, we have investigated these claims fairly thoroughly, and also we have now followed them through 9/1/99 using the Social Security Administration data as to whether or not these patients were still alive.

This is a group of patients, 63 patients, that basically represent every stage of myeloma. Some were very critically ill, some were very newly diagnosed, some had had multiple therapies, some had had no therapy.

It would not serve as a scientific study, I don't mean to say that, but the average survival for the entire group was 27 months with a range of zero to 62 with the median survival of 27 months. There were 38 patients who were equal to or greater than 65 years of age at the time of the transplant.

There are 12 survivors or 31 percent -- about 12 survivors -- I mean there are 12 people still alive with an average survival of 52 months, and for that group, the average survival for all of the Medicare patients, all of the 65-year old patients or older, was 24 months with a median survival of 27 months.

There were 12 that were 70 years -- excuse me -- that were over 70 years of age at the time of the transplant. There's one survivor at 58 months. The average survival was about 15 months, and the median survival was less than that.

Now, this average and median survival was severely affected by three who died very shortly after the transplant, and the three were very critically ill. 17 people have survived more than four years.

I present this data as information provided to the carrier of a conglomerate very disparate group of patients. What it brought to my mind was that there probably are limitations on the type of patient for whom this therapy should be offered.

All that said, I would like one other comment. The question has been raised over the last two days about out-patient versus in-patient. We have looked at that, both on our private side and our Medicare side. We have covered on the private side treatment for myeloma for several years, and this is primarily in the under-65 population.

What we found on the patients who had been treated at Dr. Barlogie's institution is that those people who were selected and thought to be capable of undergoing out-patient transplantation had done just as well as those who had the transplant within the hospital.

DR. HOLOHAN: Any questions from any of the panelists?

DR. MINTZ: I may have missed this. Did you say that these were -- how many of these were bone marrow and how many of these were peripheral blood? Do you distinguish those?

DR. ADAMSON: I have not distinguished that. I have reviewed most of the charts but not all of them, and I would say that most of them in '94 and '95 were bone marrow transplants, whereas those later were stem cell.

DR. HOLOHAN: What I would like to do is to go around the panel sequentially, and let the panelists raise any questions or concerns, speculations, suggestions, whatever, of the other panelists or of any of the presenters who are still here in the room.

MS. GEYER: And I see Dr. Barlogie in the audience would like to make a comment. There will be a session from 3 to 3:30 for you to make any comments you would like to.

DR. HOLOHAN: No, no. She said 3 to 3:30.

DR. MINTZ: I'll make a start.

DR. HOLOHAN: Dr. Mintz?

DR. MINTZ: I'll make a comment and then ask some questions of our presenters. I think that the practice of oncologists worldwide attests to the reasonableness of this procedure in most -- the reasonableness of harvesting peripheral blood or bone marrow stem cells in most patients with newly-diagnosed multiple myeloma of any age.

The question for me turns on the necessity. I would ask the oncologists who are present to help me understand those patients for whom they see this as a necessity.

I think we've seen a lot of data that suggests there are many patients for whom it would be very difficult to argue that this is a necessity owing to their high risk, but could they help hone for me some constellation of factors that would suggest that the evidence provides sufficient preponderance of proof that this is a necessity.

MS. GEYER: Any one of you may address the question.

DR. BARLOGIE: I think one needs to recognize in this kind of a setting, we have the failures to high-dose therapy, early relapses. That's the problem. The safety, I think, is established with stem cells collected early, superior to have durable disease control. This is related to the proliferation rate of the tumor and related to the features.

When one applies this kind of melphalan-based high-dose therapy in transplants, one cannot give cycles frequently enough like one does in Burkitt's Lymphoma. Those patients, I think, who have those high-

grade features, hyperproliferate of disease, they need treatment on time, effective therapy on time, that is, every two and a half or three weeks, and I think this is something that one recognizes, and a single agent, melphalan approach, where one has to allow for enough recovery of other organ sites is probably not the ideal approach for those patients.

Otherwise, if it's an issue of tumor burden, renal failure of recent onset, those patients who have renal failure of recent onset due to past neuropathy really revert to normal renal function with the most effective therapy, and we report it, and others have as well, on the use of high-dose therapy in this setting to achieve normal renal function.

DR. HELZLSOUER: Excuse me. Are you saying that there are no patients for whom this is not problematic? I didn't understand the answer.

DR. BARLOGIE: I pointed out one disease or a number of disease features related to the myeloma that make this procedure suboptimal. I did not say that it was worse than standard therapy. I only stated that it was not sufficiently effective so that other approaches have to be taken.

The -- I think patients need to have adequate cardio-pulmonary functions. Renal failure in my view is not an exclusion criterion, unless the renal failure has been longstanding and is an indication of systemic immunoglobulin deposition disease, either amyloidosis or immunoglobulin deposition disease involving multiple organs, gut, heart and the like.

DR. HOLOHAN: Does that satisfy your question? Because I'm not sure that I understood for which patients it was necessary. That was the specific question asked. Not the exclusion criteria. For whom is it necessary?

DR. MINTZ: That is the way I phrased it. You're right.

DR. BARLOGIE: Necessary for what? If I can get some clarification on that?

DR. MINTZ: We are in the same situation in which you find yourself. I mean we saw Section 1862's language which I believe is what's directing us which is whether there is evidence that the procedure is reasonable and necessary. Am I correct in that?

And in that regard, I concluded that it is reasonable. What I need to help me here is to try to decide whether or not it's necessary, is to try to identify a group of patients with multiple myeloma for whom there is sufficient or a preponderance of evidence that this is a necessary procedure because that's the way I'm being directed to vote, if you will.

DR. BARLOGIE: I hear you. I think one -- I could -- I'd like to answer it in two ways. One, if long-term complete response is the treatment objective with this procedure, then it is necessary.

In more general practical terms, I think patients who have failed to respond to initial VAD-based therapy, high-dose therapy has been reported to be exceedingly effective in the setting of primary refractory disease. So that a patient who is otherwise well, who has not responded, this is the only best-examined modality to help those patients.

DR. MINTZ: That's clear. On the other side, --

DR. BARLOGIE: And this also applies to renal failure.

DR. MINTZ: All right.

DR. BARLOGIE: It is -- since it is the -- since the renal failure is related to the -- most of the time, it is therefore important to reverse this process and to reduce the paraprotein production to a minimum level, so that renal function recovery can ensue.

DR. HOLOHAN: Can I ask a follow-up question since you brought up the issue of renal function? I presume this abstract and this article from Clinical Cancer Research is the -- are the data to which you've referred.

I note that the sample size in this study was 20 patients, is that correct?

DR. BARLOGIE: We have now more. We have some 70 patients now.

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

DR. HOLOHAN: Sure.

DR. MINTZ: Certainly your data suggested that those patients with both the cytogenetic abnormality and the high Beta 2 microglobulin levels did not fare well post-transplant.

Are you continuing to provide transplants to those patients, and are those data, you know, still what we have?

DR. BARLOGIE: Well, I believe -- in my view, the melphalan-based high-dose therapy is the first step to reduce the tumor burden safely and maximally. It is the equivalent of induction chemotherapy for AML in my view because it is the only therapy that gets you the initial rate of complete response.

So, we are now administering consolidation chemotherapy after high-dose therapy every two or three months in order to sustain that remission and preventing relapse, and the data have been reported at ASH a couple of years ago and will be updated this year.

DR. MINTZ: Do you have any comments on the conclusion of Dr. Alexanian regarding the limited benefit that --

DR. BARLOGIE: I was a co-investor. I was the principal investigator, I should say, of this work, and this actually was a study of 55 patients who had been reported in Blood with me as the first author.

Dr. Alexanian picked 23 patients. I don't know how they were picked. There were 23, and then some pyramids were identified. I do not identify myself with that publication. It was very selected, if that is allowed to say.

DR. MINTZ: Thank you.

DR. HELZLSOUER: This is Kathy Helzlsouer speaking. Just a comment, and I guess I would like some clarification on the current InterGroup study.

One issue we're facing is generalizability. There's one randomized control trial out there under the aegis of patients up to age 65, and I think one of the issues we're facing is can we generalize those results to the Medicare population, and I think the panel will have to think about that issue, and when we can generalize, and also sometimes that generalizability is an issue that's drawn to extremes, and I think we have to keep that in mind with cut-off, 64, 66. We've heard testimony regarding that. So, that's a big issue to consider.

The other issue is what is the standard of care now, and I would like to have clarification again, if somebody could review for me the current arms of the InterGroup study.

I've heard this is early versus late, but then I've heard that there's a standard arm that essentially is chemotherapy, that if standard now is the high-dose, then I would agree that that's unethical to have -- that should be the standard if it's unethical.

So, that would help me in posing this to see what the current study arms are.

DR. BARLOGIE: As the chairman of the InterGroup trial that includes the three cooperative groups that you mentioned, the study was designed in late 1992, and the formulation process and approval process took probably over 18 months, and it carries a 9321 number as the SWOG number.

There were representations from all over the country, from academic institutions and cooperative group affiliates in private practice, CCOTs and CCOPs, and also from the transplant world outside of myeloma, and it was clearly felt at that time, based on the available data then, that all patients should have the option of high-dose therapy with stem cell support.

It was for this reason that we chose not to repeat or perform an IFN-90 type study because we had demonstrated in enough Phase 2 studies that high-dose therapy was a much more effective salvage

therapy in patients with relapsing disease than had ever been shown previously.

So, therefore, the design of the trial was to give everybody up front the opportunity to eventually receive and benefit from high-dose therapy. So that in all patients, after four cycles of induction therapy with VAD, had peripheral blood stem cell collection, and then the assignment to standard or high-dose therapy was done in a randomized fashion with stratification for recognized prognostic factors, and then the -- upon relapse, further registration on the standard treatment arm, further registration is done so that these patients can formally be evaluated where this is essentially an early versus late high-dose therapy approach, and then there's further randomization for responding patients to Interferon or no maintenance therapy.

DR. HELZLSOUER: What is the target accrual for that trial?

DR. BARLOGIE: Over 800 patients.

DR. HELZLSOUER: And what's the target? That was what you --

DR. BARLOGIE: 1,000.

DR. HELZLSOUER: 1,000.

DR. BARLOGIE: 500 evaluable patients in each treatment arm.

DR. HELZLSOUER: Okay. And this was open again when? It was designed in 1992, but opened for accrual in --

DR. BARLOGIE: The study carries a 93 number, and I think the first accrual was -- happened in the Spring or Summer of '94.

DR. HELZLSOUER: Okay. So, the results of that are still a few years --

DR. BARLOGIE: Yes.

DR. HELZLSOUER: Thank you.

DR. HOLOHAN: Anything else?

DR. HELZLSOUER: No. Are we going to address these questions or I don't know what to bring up. There are several issues.

DR. HOLOHAN: Just trying to clarify things before we get --

DR. HELZLSOUER: Okay, okay.

DR. HOLOHAN: -- to the specific questions. Dr. Leslie? Dr. Francis. I'm sorry.

DR. FRANCIS: I'm Leslie Francis. I want to be sure I understand what I've -- this may be repetitive, but whether there is evidence of a significant increase in either event-free or long-term survival for patients with the high Beta microglobulin -- Beta 2 microglobulin or patients over 70 or patients with the adverse cytological -- cytogenetic characteristics, and I'd like it on each of those because when you say it's necessary, I mean the response I heard you give to Dr. Mintz was roughly there's nothing else we can offer, and I wanted to know whether there's evidence that there's in that group an increased survival or event-free survival rate than what you get with any kind of conventional therapy.

DR. BARLOGIE: I guess if one had the knowledge we have today, collectively, one would go about designing these things differently.

The high-dose therapy approach in the randomized trial turned out to be for the overall group when analyzed in this fashion, that is, when all patients were considered, high-dose therapy was an independent favorable prognostic feature and not in addition to Beta 2 microglobulin.

In our experience, Beta 2 M is an important feature as are other features, but independent of this high-dose therapy always entered the picture, whether analyzed in a time-dependent co-variate analysis in our non-randomized setting or whether one used a landmark technique as the second best approach to judging this issue.

So, we do not have -- I had -- we have evidence in the cytogenetically-unfavorable group, favorable and unfavorable, that, for instance, a second cycle and a timely application of dose-intensive therapy makes a difference, significant difference for event-free and overall survival. This work has been submitted to the New England Journal, and it's currently under review.

DR. JOHNSON: It appears to me at least, my observation, based on what we've heard that I tend to go along with what Dr. Mintz has said. I think the treatment does meet the test of reasonableness, and it seems like what we are struggling with is it may not be necessary for all, and how do we make those determinations of who should or should not necessarily receive the treatment.

Do we know, based on those states in which Medicaid patients receive this treatment, do we know if they have determined or established limitations on what patients may or may not be available for the treatment?

DR. HOLOHAN: At the risk of objection, I would answer that we do not know, and what we would get, if we polled the audience, would probably be opinion and not necessarily data. We really don't know what the individual state Medicaid Programs, either separately or together, approve.

We probably all know about Oregon because they've been in the news a great deal.

DR. HELZLSOUER: Dr. Holohan, I believe, and Andrea Argabrite can correct me if I'm wrong about this, but I believe we do have one protocol from the state of Illinois. Andrea, is that correct? If the panel would like to look at that, if you find that to be necessary, and for the record, the prior speaker was Robert Johnson.

DR. JOHNSON: Sorry about that.

DR. HOLOHAN: Any other -- do you want to digest that and have us come back to you?

DR. JOHNSON: That's fine for now. Thank you.

DR. HOLOHAN: Okay.

MR. JORDAN: I'm Ron Jordan. I would agree with what Dr. Johnson and Dr. Mintz have both said related to my current perception of what we've heard today, that there is enough evidence to presume that this procedure is reasonable certainly, and that I also believe it's clear to me that it's necessary for some patients, and that it's just a question of how many patients, and whether Medicare should get into dictating those kind of decisions through complicated policies and procedures, and I'm a little caught up in what an analogous type of Medicare requirement might be if we structured a very complex exclusionary/inclusionary type policy.

Is there something like that in Medicare currently that would help me get by trying to make those kind of decisions? Because I'm of a mind to believe that the expert clinicians that presented today and the worldwide standard of care that's going on is doing the best possible thing for patients in this area, and that there are a lot of thoughtful people working very hard to provide benefit to those patients where it is necessary, and that there are clearly some patients that are receiving benefit from it. How much benefit, we could debate, but I'm not sure I want to weigh the value of nine months or 18 months for any individual patient.

I'm not sure I want the Federal Government weighing the value of that for me at any particular point. I had a couple of minimal questions only because I'm interested in this issue of the procedure further down, the questions further down, because I'm already by some of the earlier ones, about whether the panel could explain further some of the standards that were talked about, the fact standard and the AAPP, I think, standard that was used for accreditation of these transplant centers.

I wondered whether because I'm also interested in the issue of quality of life and whether these things are really being monitored appropriately so that adequate signals would be provided if there was something wrong with the type of treatment that was being approved, are those standards and do they in fact include a requirement that quality of life be measured?

DR. MINTZ: I can begin to answer that. This is Paul Mintz. In my capacity as a member of the Board of the American Association of Blood Banks, and, so, it's the AABB standards, there are two sets of accreditation standards. Those of the American Association of Blood Banks, and those of what is called FAHCT, F-A-H-C-T. I believe it's Foundation of the Accreditation of Hematopoietic Cell Therapy, and they are in the process of being made compatible, such that accreditation with one is comparable to accreditation with the other.

They do not -- clearly, the AABB standards do not -- which I'm most familiar, do not address issues of quality of life or survival. These are standards that are directed at the management of the process and not the outcome.

Ken, correct me if I'm wrong, but I believe that's also true of the FAHCT standards. They address clinical and laboratory processes but not outcomes.

DR. ANDERSON: I would just echo that. I think, though, that there should be some reassurance that this is a terrific advance, and we were worrying about quality control, and in terms of both, the reason it's fallen under the purview of the AABB is, after all, what you really heard about over the last day and a half is transfusion of hematopoietic stem cells. That's really what we're talking about.

This is high-dose therapy, but it's supported by a transfusion, and, so, the folks who are very able and capable for many years to quality control blood cells are the American Association of Blood Banks.

The FAHCT agency has come along and derived from the transplant community, and there is, as Paul correctly mentioned, a nice union that's now currently -- it does control the primarily processing, but it is in detail looking at every aspect, meaning what you do to recruit patients, making sure they are appropriate patients for appropriate treatment plans and protocols, making sure that collection is done under certain standards, making sure that the processing is standard, making sure that the actual performance of the "transplant" is done under particular qualities of standards by individuals at each step who have met certain qualifications, so they're able to do what they do.

It's quite a detailed inspection and quite -- I think in terms of assuring quality of who should or who should not do these --

MR. JORDAN: A requirement for adequate follow-up, and to me, I thought that the Twist measure and the quality of life measures might reasonably be required as an adequate follow-up requirement.

DR. ANDERSON: There are requirements for -- they don't require particular outcomes. There's no demand for a certain response rate or they can't be that specific, but there is assurance. They inspect medical records. So, they follow -- they examine in detail how you look before, during and after the transplant at what you have done at each step in terms of follow-up as well, and part of that is a quality of life that has been achieved.

I don't think there's a specific measure that's demanded in either of these standards.

MS. GEYER: And if I may just add for purposes of the record, that was Dr. Kenneth Anderson speaking from the audience. Thank you.

DR. MINTZ: This is Paul Mintz. I just want to follow up about the standards and then complete that. But I used the word "process" not in the sense of processing the product but in the entire process of the procedure, and I'm familiar with the standards from the AABB, and I would like to reassure my panel members that they are rigorous and give me great assurance in the quality of the institution and physicians who are performing these.

MR. JORDAN: I think someone wants to add something. I have another couple questions.

DR. TRAYNOR: I just wanted to come back to addressing both that and also the issue of necessity. I think that Dr. Barlogie replied by necessary in what sense. You know, we have an appreciation of how difficult and how nebulous it must be in federal finance determination to be faced with terminology like reasonable and necessary and have to make some sort of an assessment of what fills those criteria.

When you have a treatment that is non-curative but is life-prolonging, how do you determine who qualifies or for whom it's necessary and for whom it's not, you know. For example, dialysis is an example of something that is certainly life-prolonging in many situations but does not result in cure of the underlying pathology.

Is it necessary for the Medicare population, and, if so, which ones? Is it the most profoundly ill or the ones that have less co-morbidity and are therefore likely to appreciate a longer survival?

So, likewise, if you select for adverse prognostic factors, be it Beta 2 microglobulin or Chromosome-13 abnormalities, do you say those are the patients for whom it's most necessary because their survival otherwise would be more limited or do you say it's the patients for whom it's not necessary because the incremental increase in survival is less?

Fortunately, you all rather than we are faced with decisions of that kind and determining for whom it's necessary. Ethically, as a provider, it seems to me that if you have a life-prolonging intervention which you feel results in little suffering and an improvement in the quality of life in your patients as you've known them repeatedly, your ethical obligation is to try to ensure that you can offer that to all of them on an equal basis.

We appreciate, I think, very much the fact that there are getting to be more regulatory guidelines, and that we'll have the FAHCT accreditation as well as the Blood Bank accreditation in terms of provision of stem cell technology which will be evolving rapidly over the course of our practice in the next 10 years, but even within that framework, I would only emphasize for us in our experience with Medicaid in the state of Illinois, that Medicaid looks at the records of patient survival and patient outcome and for each

institution in deciding whether to reimburse that institution as a bone marrow transplant or stem cell transplant provider, and then having determined designated providers in the state of Illinois, it asks me, for example, for each Medicaid patient of mine that undergoes a transplant in my institution that I provide timely reports on outcome and long-term disease-free and overall survival on that patient, so that they can update their records with regard to my institution and its eligibility for their reimbursement, and it is conceivable that Medicare would want to cross-reference that information.

MS. GEYER: That was Dr. Anne Traynor. Thank you.

DR. HOLOHAN: This is Dr. Holohan. Can I ask you for a clarification, Dr. Traynor? We've been discussing accreditation of stem cell harvest centers in the community.

Earlier, you said -- you gave reference in passing to the fact that the patient needed to be seen at a center with expertise in myeloma or a myeloma center or words to that effect, and now I believe you've explained that in the state of Illinois, a center of excellence approach, if you will, in quotation marks, is used by the Medicaid Program.

So, the question then becomes to what degree of confidence do you have that the results that you or Dr. Barlogie or Dr. Anderson report can be reproduced in the community hospital setting?

DR. TRAYNOR: I think that they can be reproduced at the designated centers of excellence of Medicaid quite reliably. I think that there is room for abuse, as you all well know, of Medicare reimbursement for any procedure, and therefore I think that long term, all federal reimbursement will have to endorse certain criteria for stem cell collection and processing and even patient outcome.

And just to go back to the data to which Dr. Adamson alluded earlier with regard to outcomes in older populations in Arkansas, it is one of the bugaboos of large referral centers that, of course, they see some of the most advanced disease patients, but I think that most of us have written protocols that go through the different -- one of the things that distinguishes academic centers and major referral centers from community practice or some centers where there may be greater degrees of Medicare abuse is that there are institutional review boards that are devised for patient protection and review every treatment protocol, including every stem cell transplant protocol, in each of our institutions, as patient advocate groups, to guarantee that experimental approaches are not abusive of the recipient, Number 1.

Number 2. If there is -- you will usually find within the eligibility criteria of written protocols patient performance status, and if patients are designated to have a certain performance status to proceed into transplant, usually that significantly diminishes the early mortality associated with the high-dose therapy.

Unfortunately, if a patient is placed on to a study at the initiation of chemotherapy before their responsiveness to conventional chemotherapy is known, they may be a very high-risk individual by appearance at diagnosis and turn out to be very responsive and their performance status markedly

improved by the time they head into high-dose therapy.

So, if you all in choosing to condone a patient proceeding into high-dose therapy are asked to make that decision before the person has been initially treated, based on performance status alone, you may deny the procedure to patients who would have an excellent performance status within three months.

So, I'm afraid, I think, the decision would have to be re-examined or made best immediately prior to transplantation.

MR. JORDAN: Just a couple other quick questions that I may be just unclear on. Is there a consensus among the clinicians that are here that we're basically talking about peripheral blood stem cell support as the preferred method, and that bone marrow is not state-of-the-art?

DR. BARLOGIE: Yes.

MR. JORDAN: Okay.

DR. BARLOGIE: There has been as part of the IFM-1994 trial, there has been an analysis of peripheral blood stem cells versus autologous bone marrow in the randomized fashion, and that trial or this part of the trial was clearly in favor of peripheral blood stem cells because of more rapid neutrophil and platelet recovery and shorter hospitalization, and by all criteria, this is now -- I think there's nobody that I know of who performs autologous bone marrow transplantation anymore.

DR. MINTZ: May I ask a follow-up question? For patients from whom it is difficult or impossible to harvest a sufficient quantity of stem cells, would the clinicians then consider that they might be able to harvest them from an autologous bone marrow?

DR. BARLOGIE: Well, one has to examine the cause for the insufficiency, and if this is related to chronic alcolating agent therapy, then one just has to give patients time, and what we do typically is giving those patients glucocorticoid-based therapy, even risking some further progression of disease, so that eventually one does get enough stem cells, and this is typically possible, I would say, in 85 percent of patients who have some problems initially. If one waits long enough for recovery, then this can be accomplished with blood stem cells.

MR. JORDAN: And one last one, and this may have been answered previously by what Dr. Traynor was saying, but is -- am I correct in presuming that this cell morphology, the Beta 2 M morphology level of a patient on presentation might be a reasonable prognostic indicator to include in a protocol, if Medicare goes to such detail?

MS. GEYER: Dr. Barlogie will respond to that, I think.

DR. BARLOGIE: I think Dr. Traynor made a very important point. It is difficult for us to judge -- we do

not have any evidence that I'm aware of in terms of randomized or historically-controlled trials that high Beta 2 M level patients do not benefit as much as do low Beta 2 microglobulin patients.

Beta 2 M is sometimes elevated because of renal failure at diagnosis or when renal function recovers, then Beta 2 microglobulin levels go down and normalize.

So, I think as in cancer in general, it is this dilemma one deals with that those who have the least risk are the ones who have the greatest -- the most to gain long term, and in terms of palliation in myeloma, the ones with the highest risk clearly benefit as a whole group but not as substantively and to this degree as low-risk patients would.

MR. JORDAN: Thank you.

MS. GEYER: Cathy, do you have anything to add?

MS. DOOLEY: Actually, I had one question, and Dr. Traynor just answered it. So, I defer.

DR. LERNER: I'd like to stay with Question 1 for a moment just to get some clarification on it.

MS. GEYER: And this -- I'm sorry.

MS. GEYER: I'm sorry. This is Jeff Lerner. And, so, it's actually a series of questions that go to the article "Age is Not A Prognostic Variable", and, so, I guess I'm really asking probably Dr. Barlogie this question as well as the panel.

It seems that there are age differences in event-free survival and overall survival that are not significant according to the article. But if event-free survival in the younger patients is 2.8 years, and in the older is 1.5 years, and for overall survival, the younger was 4.8 years and the older was 3.3 years, and what I'd like to know is, first, wouldn't these differences be significant with more power?

In other words, if it were larger sample sizes, and then that's part of a series of questions I've got.

DR. BARLOGIE: They might very well be more significant with larger sample sizes. I'd like to comment on this by saying that I have provided you with additional information on the age factor by giving you the data on thousand consecutive patients treated at the center and looking as carefully at patients who were uniformly staged, age really was not an independent variable when one looked at the entire group.

When one looked at age as a continuous variable, as a dichotomous variable, when one cut it any way you want, age was not a feature. With standard therapy, however, in the Southwest Oncology Group experience, age was an important feature. This may relate to the fact that oral therapy sometimes was not taken by those patients who are more forgetful perhaps when they are older, and it's always better if you

actually give intravenous therapy. One is certain that the therapy is administered.

I think the other point is people in the early phases of high-dose therapy evaluation limited to this modality purposefully to the younger patients because with autologous bone marrow support, the time to recovery was still long, and, so, most people therefore wanted to go for success in a way and ignoring the important issue of including the bulk of the patients who had the disease.

We haven't done this, and the reason why we have data is because we did not subscribe to this policy, and we had data to indicate that if the duration of significant neutropenia is sufficiently short, we can get a patient through.

So, I think it's terribly important to open this modality maybe like there have been some of the studies. I recognize Medicare is not a research organization, but maybe some approach could be found where by design, the issue of early versus late high-dose therapy in this elderly patient population could be addressed because if you don't ever wish to give this to a patient, aged 65 and older, you will never have the answer.

So, the paucity of data really relates to that pre-conceived notion that this treatment cannot be tolerated and might not be effective in elderly patients.

DR. FRANCIS: Can I just follow up that quickly? I want to be sure I understand. Leslie Francis. Sorry.

When you say that age is not an independent variable, are you saying that all the way across the age range or only for the age range from 65 to 70 or were you making that claim above 70, and I'm interested in linking that to the Arkansas data.

DR. BARLOGIE: Okay. I stated that when age was examined, and Dr. Paula Roberson from our -- chairman of the Statistics Department at our university is actually here, and the data are continuously reviewed and updated. So, this is all done with expertise.

When one looks at the data with age as a continuous variable, age on a univariate analysis is significant, and age is also significant when one looks at various cut-offs, but as soon as you enter the biologically most relevant variables, be they Beta 2 M, if you were even -- exclude cytogenetics because it's not done everywhere. So, if you just look at Beta 2 M and see reactive protein or duration of prior therapy, that places age immediately out into the .3 or .5 range.

So, once one accounts for the disease variables and the history of sensitivity and so on of the disease prior to treatment, then age disappears no matter how one looks at it.

DR. TRAYNOR: I think -- I'm sorry. Anne Traynor. There was a publication that we alluded to in our initial meeting with HCFA, which I didn't bring with me today, that was published in the American Journal of Hematology about a year ago, looking at age in relationship to outcome in myeloma, not with

respect to high-dose therapy but with respect to conventional therapy, which stated what is, I guess, in a sense obvious but showed it statistically, which was that for any given prognostic variable, and for any given intervention within a set of prognostic variables, older patients with myeloma fared more poorly than younger patients.

Therefore, any increment probably for any intervention is less, but what the multi-variate analysis, of course, is telling you is that the relative increment remains the same.

DR. LERNER: I'd like to follow my line of reasoning a little bit more. This is Jeff Lerner.

I'm wondering if -- well, let me do it this way. If overall survival for the older patient in again the age of prognostics article is 3.3 years, I'm wondering what is the overall survival for older patients treated conventionally, and because that might well be about three years, in which case there wouldn't be a significant advantage for older people.

So, in other words, you might see a table with conventional therapy and transplants in older and younger and see that the only real difference would be for the younger people on the auto transplant.

So, what I'm really wondering is, is there any way to look at the data so that you just -- if you take out the way we've been looking at age -- in other words, don't look at whether older people do as well as younger people, put that aside for a moment, and just say so what? Suppose older people don't do as well on it, but that they do better with transplants than they do with conventional therapy, and if we just went through that line of reasoning, would that -- is that a reasonable way to look at it, just to match that conventional --

DR. BARLOGIE: That's a very reasonable way to do, and we have not -- you know, I mean it takes resources. I think somebody asked me this question after the last American Society of Hematology meetings. I forgot with which organization this person was affiliated, and we actually had discussion with -- discussions with Dr. John Crowley, who is the chief statistician of SWOG and also the chief statistician of the Myeloma Committee in SWOG, and this kind of analysis can be readily performed in that one peer mates.

The recent basically contemporary chemotherapy under the auspices of SWOG with high-dose therapy in properly-matched patients.

DR. LERNER: See, here's where my thinking is going, is when I look at things like Attal and so on, you know, which, despite any criticisms, do seem pretty reasonable to me, I was trying to think, well, how can you extend that to older patients, and I was worried about this age as a prognostic variable because in Attal, when he took out his older patients, the people did better, you know, in the analysis.

So, I'm trying to now look if there's a way of getting the data that's not very burdensome. Okay. I have just one more thing I wanted to bring in to that, which was to go back to the Torino study, which is why

earlier in the day, I asked the question about the patients who were over 65 because, you know, the way they reported the data, you couldn't really tell, except we know there are 36 patients over -- at 65 or older, and I was wondering if it's not too burdensome an analysis if we could get that individual data from them and look at that and look for significance because then if it turned out that high-dose chemotherapy was better, you might very well answer your question, that it's fine for the over-65 group.

Now, of course, if it doesn't turn out better than, we don't know what that means.

DR. TRAYNOR: Just as a point of clarification, you all know that in the Torino study, the median age was 64.

DR. LERNER: 64.

DR. TRAYNOR: So, exactly half of patients were older.

DR. LERNER: Yes.

DR. TRAYNOR: Okay.

DR. LERNER: Yes. I'm trying to get to older patients. I was looking at Chart 3 in Torino, under the age. You can see how it's divided with the under-60 and the over-60, and I was trying to get to this older group, that people were 65 to something. Are you asking where this is? I have it right here.

Again, you know, I'm trying to find a pretty simple way of doing this, you know, not --

DR. BARLOGIE: While Dr. Traynor is looking, in the -- in our article published by Siegel, we have even the beyond-70 population in there, and I would like to say that when we did analyze in young and old the 40 pertinent prognostic features, these were -- these are the very same variables in young and old that were critical.

It was the cytogenetics. It was the Beta 2 M. So, it was totally consistent, and I think the data you are asking in terms of using and taking advantage of cooperative group trial data is something that can be done, but it's not available right now.

DR. HOLOHAN: I'm going to take my prerogative as chair to enforce the 2 p.m. 1400 hour break, and we will resume.

MS. BERGTHOLD: Can I make just one comment because I didn't -- now I've thought of something I'd like to say. One minute, one minute.

Just for the -- Linda Bergthold. One minute. Just for the sake of sort of the audience and the non-

technical people here, just so that you understand, there is no consensus in the medical community, I've spent the last year researching this, about what necessary means. So, when we come back after our break, I think it would, you know, make a lot of sense for us to talk specifically and concretely about what we think necessary means since there really is no consensus. It is a state of mind.

Thank you.

DR. HOLOHAN: With that state of mind, we will adjourn for 15 minutes.

(Whereupon, a recess was taken.)

MS. GEYER: I think we are all back, and I think we're going to reconvene with the committee deliberation section.

DR. HOLOHAN: Let me begin by pointing out that we will get back to the question of necessary.

My personal belief is that this panel is unlikely to arrive at a logically-defensible and legally-defensible definition of necessary in the time allotted to us, but I don't think that that's a reason we should avoid the issue.

I'd like to raise some kind of general philosophical points, and if any of the panelists wish to comment, they should feel free. If people from the audience want to comment, I'd ask you please try to limit your remarks.

First, a personal comment. As an American and as an oncologist, I'm disturbed by the fact that it is the French who have done the only prospective randomized control trial of this technology. I don't think I have to comment further upon that.

But it is, I think, an indication of perhaps the seriousness of purpose of clinicians in that country with whom, fortunately for my own benefit, I'm very familiar.

We've heard a number of comments and statement, some of which I have to confess leave me a little bit uneasy. We've heard that there is general belief, if not universal belief, among the cognizanti in bone marrow transplant and in treatment of myeloma that this is standard therapy, and yet the advocates, and I don't use that term in a pejorative fashion, the proponents of this technology provided us with two papers that were forwarded.

One was Dr. Kyle's paper, where he says in referring to the French study, "However, additional prospective studies are necessary to confirm this finding."

They also provided us with a paper by Dr. Lockhart -- Lokhorst, I'm sorry, published in the British Journal of Hematology, and Dr. Lokhorst remarks that "there has been only one randomized study to

demonstrate that ABMT improves the outcome of patients", and his sentinel sentence to me is "Therefore, it seems premature to conclude that intensive therapy is the standard approach for the young myeloma patient."

Because of this and some other material that has been cited previously, I am perhaps a little more of a devil's advocate as to whether in fact this is widely believed by all practitioners to be standard therapy.

In the letter that was sent to Medicare asking them for consideration of payment, the statement was made that "by comparison, Medicare pays for this treatment for high-dose chemotherapy and autologous bone marrow transplantation for breast cancer", and that perhaps frightens me more than any other concept here, and the reason it does is that as I'm sure we all know, we've spent considerable resources and treated large numbers of patients in studies that were for the most part uncontrolled, and ABMT has been widely accepted in conjunction with high-dose chemotherapy as an appropriate treatment for breast cancer, to the point where the Office of Personnel Management mandated this as a covered benefit for the federal employees' benefit health program, and notwithstanding that, in May, at the ASCO meetings, five abstracts were released, one might argue, more because the Wall Street Journal was inquiring than for scientific reasons, but five abstracts on trials of high-dose chemotherapy and stem cell support in breast cancer were released, and the fact is the studies were not uniformly but almost uniformly negative.

They were negative to the point that the director of the National Cancer Institute, Dr. Klausner, stated publicly that the evidence is not in on the utility of high-dose chemotherapy in bone marrow or stem cell support for breast cancer, and the director of the Division of Cancer Treatment, Dr. Bob Wittes, made the flat statement that the evidence indicates that it is not effective in prolonging survival.

We can argue and debate about whether we will ever find out whether or how effective high-dose chemotherapy and ABMT is for breast cancer, but it certainly does not appear to be the best way of making the transition that we talked about before of translating research into practice.

Having provided those caveats, if you will, I'll now ask if you want to go into a further discussion of the definition of necessary?

MS. BERGTHOLD: No, but I think --

DR. HOLOHAN: If you would identify yourself each time.

MS. BERGTHOLD: Linda Bergthold. I think it would be helpful if we could simply -- you know, each speaker give specific examples of -- as Dr. Mintz was doing, say necessary for whom, under what conditions, so that we just don't use this term without an anchor. That's all.

DR. HOLOHAN: Well, Dr. Bagley has offered to provide the definition currently in use by the Health Care Financing Administration, and I'm putting him on the spot, as you can see, I'm putting him on the

spot to do so.

DR. BAGLEY: The definition of reasonable and necessary has been the operable set of words that Medicare has used for 35+ years. That was the command given to us by Congress, and I think Congress understood that it was difficult, and that there should be deference to a scientific and a medically-focused agency to make that determination, and that's what we've done.

Now, having said that, you know, I've not been at HCFA for 35+ years, far less than that, and I think before I came to HCFA, there was little doubt in my mind what reasonable and necessary meant.

In fact, when I was in practice, it was crystal clear to me. It's just that I was the only one that knew what it meant, and I could never convince my colleagues that I was a hundred-percent right, and I couldn't understand why they didn't see it the same way.

But in the practice of medicine, it's exactly what we do on an individual basis and in dealing with patients day-by-day. We have encounters with patients. We evaluate clinical conditions. We consult with patients. We present options, and we then, based on what's reasonable and necessary, in consultation with the patient, decide on treatment. That's clearly what we do.

Now, from an agency point of view, we have to write policies which also can make a service available or not available based on that same command, reasonable and necessary.

Now, the issue, and as uncomfortable as it makes those of us from the clinical community, we need to have ways to process claims which not only allow for the reasonable and necessary practice of medicine but also further the issues of program integrity and eliminate the fraud and abuse in the Medicare Program.

Now, I like to think that if we wrote the right kind of coverage policies, then the practitioner making reasonable evidence-based judgments and delivering reasonable and necessary care would be inconvenienced ever so slightly in meeting those requirements and following those guidelines, but that when practice was far outside the mainstream and fell into those areas we call over-utilization and fraud and abuse, that it would be hampered, and it would be hampered a lot.

Now, that's the way policies ought to be written. It may look like a lot of rules. It may look like the Federal Government getting in our way, but we learned a long time ago in Medicare that simply saying the practicing medical community knows what's right, and if they make a decision that it's reasonable and necessary, we ought to pay for it.

Well, it turns out that's true the majority of the time. It's true the vast majority of the time, but, you know, that small amount of the time it's not true can consume an incredible amount of resources, and it's not just about money. This is about patient or beneficiary protection.

We do not want people not only paying their own money because this isn't free. People pay money out of pocket for Medicare services. 20 percent of the cost of a service comes directly from the beneficiary. So, it's not just protecting beneficiaries for things which don't benefit them in terms of cost, but it's also preventing them from treatments which will do them harm, and relying on evidence is that.

The next slide in sequence. Because, you know, Medicare has been struggling with this definition of reasonable and necessary for all of those years, and in fact, over 10 years ago, we proposed a regulation, published a notice of proposed rulemaking, outlining the criteria we would use to make the evidence-based decisions that we're here talking about today. That was 10 years ago.

It's been controversial. It's been controversial since then, and that rule has never been promulgated as a final rule. In fact, after trying for 10 years to revise that rule and put it forward, we finally in April, when we outlined this process that we're going through now, said we're going to withdraw that rule, we will issue a new proposed rule to define the criteria. That proposed rulemaking process is one where we propose a rule. We get comment from everyone, including you, the public, and we then issue a final rule. So, this is going to be an issue which we will have public debate about and public discussion about.

We'll see if this slide is in here because I think it is.

DR. HOLOHAN: Eventually you'll be right, Grant.

DR. BAGLEY: Yeah. Now, 10 years ago, we proposed roughly these criteria, and we said, you know, these really are the things we ought to be looking at. When we look at a new technology, a new device, a new drug, a new way of doing things, Number 1, it ought to be safe and effective, and those words, just like reasonable and necessary, are ones that we would carry a wallet card with if we worked at HCFA.

This is what the wallet card for the FDA says, safe and effective. The FDA determines drugs, devices and biologics are safe and effective, and they do that with clinical trials, and I think we're all familiar with that process.

But, Number 1, when we look at a service for Medicare, we say is it regulated by the Food and Drug Administration because they don't regulate everything? If it is, it has to be approved by the FDA, first criteria. If it's approved by the FDA, then we've already had a measure of safety and effectiveness. If it's not, then we need to look at that as a threshold question. Is it safe, and is it effective, and we've talked a lot about that issue today. Is it safe? Is it effective?

Number 2. Even though it's safe and effective, does it have a clinical benefit because it really is an important second question. Is there a demonstrated clinical utility? It doesn't mean you live longer. It might mean you live better. Is it quality of life? Is it survival? Is it improved clinical condition? That's a different measure depending on what we're talking about, and you'll note that's one of the questions we asked. What's the appropriate measure that we should be using in talking about this therapy?

So, safe and effective. Is there a clinical benefit, and what, of course, is the proper measure of clinical benefit depending on the technology? Can we determine the appropriateness? And again this goes to some of the questions we asked.

Is the evidence that we have to evaluate about this technology, is it sufficient that we can determine which patients? Is this a service which is appropriate for this patient and not in excess of their needs? Can we determine from the evidence, is there -- should there be a provider limitation, and which providers are appropriate to provide this service, and what's the proper setting, and does the evidence tell us whether it should be in-patient, whether it should be out-patient, whether it be restricted to specialized centers? So, the appropriateness is an issue.

And is there sufficient evidence that we can make a determination of the risks and the benefits and therefore make a determination as to for which patients the risks outweigh -- the risks and benefits come out on the positive side?

These are the questions that we've asked ourselves, you know, for 35 years in determining what's reasonable and necessary. They're the ones we proposed 35 years ago. They're the ones that in a similar forum will be proposed again, and I'll just point out there was one other criteria which was the most controversial which was proposed 35 years ago and talked about ever since, and that was one that's not on this list, but it was cost effectiveness.

Cost effectiveness. Should that be a consideration for reasonable and necessary? Well, there's been a lot of debate, and it will go on about whether or not cost effectiveness should ever be considered. Of course, we've acknowledged that limited circumstance where we think it is appropriate, and that is where we're talking about very comparable outcomes and very comparable technologies.

If a new test tests for the same thing as an old test, and the sensitivity and the specificity are almost the same, should we consider them if the price is considerably different?

So, should price enter into it at all? Should cost enter into it at all? And whether or not it should be that limited circumstance in which there is comparability or whether it should be more broadly-applied, I think, is a matter for debate. We've not heard that. We've not heard that discussed today or yesterday. That hasn't been on the table for this discussion. In fact, cost is not something that we have had presented nor have we discussed it nor did we as staff ask the panel that as one of the questions.

So, these are the things we should focus on in terms of what is reasonable and what is necessary. Is it safe and effective? FDA hasn't ruled on this. I mean we need to look at the evidence anew and determine is -- can we make that determination? Is there a demonstrated clinical benefit? I mean is it clearly demonstrated by the evidence, and what is the proper measure of that clinical benefit?

Can we determine the appropriateness in terms of patients, providers and settings, and are the risks and the benefits when taken on balance and demonstrated by the benefit sufficient that we can make a

determination for that service, and while this will eventually make its way into federal regulations, this has been our operative definition for many, many years, and it's the one that we would propose that you focus on in this discussion.

DR. HELZLSOUER: This is Kathy Helzlsouer. I take your point, Dr. Holohan, about wishing that we had more clinical trials, but I think what we are faced with today is given the level of evidence we have, what judgment can we make because it's obvious to me that, unfortunately, we do not have another trial repeating the French trial. Even the trial that was designed before those results were published felt that they could not avoid having a comparison at some point include autologous stem cell transplant.

So, I think the fact we have to face is that given what's out there, can we make some judgment, and I will express my opinion now. I think that this issue of generalizability is the one we're facing. Can we take results from this trial that was done, because that's the Category 1 level of evidence we have, which is the one randomized clinical trial, can we generalize that to the Medicare population?

I think there's good evidence to say that we can. I don't think we're faced with any strong evidence to say that it's a dramatically-different disease once you turn 65 or 66. In fact, most of myeloma occurs in that age group.

I think that the other question of can we define subgroups, I don't think we have good enough data to define subgroups if we're defining necessarily those that will respond. I think this trial did not look at subgroup analysis. Any subgroup analysis is based on observational data which has selection criteria problems.

So, I think we have evidence that in the case of multiple myeloma, that there was evidence that benefit is measured by a survival benefit, and that in my opinion, I think there's good -- there's reasonable evidence to say that it should apply to somebody who's older than 65 or somebody who's 64 or 68 that was in that trial.

I guess I want to maybe focus the discussion and maybe make a motion for the table for consideration.

DR. HOLOHAN: Well, what I was going to do is ask if any of the speakers had terse short comments to make before we address the issue of voting on the questions, if that's what you were going to bring up.

DR. HELZLSOUER: Yes, I was going to make a motion, so we had point of discussion, but whatever you --

DR. HOLOHAN: I'm not sure what you're saying.

DR. HELZLSOUER: No. I assume after the motion, there's time for discussion on that motion.

MS. GEYER: Correct, correct. But before we have that motion, I believe we have to have the open

public session one more time.

DR. HELZLSOUER: Okay. So, at this time, if anyone would like to come forward from the public, please identify yourself, and we will limit you to five minutes, so that the committee has enough time to discuss.

Open Public Session

DR. KYLE: I'm Robert Kyle, and it's obvious that there is a paucity of hard data as far as transplant is concerned in this situation.

I think that we need to take into consideration the role of the physician when seeing the patient and evaluating the total picture; that is, the physician must be experienced and knowledgeable about multiple myeloma and about transplantation.

One must take into consideration the patient's physiologic or biologic age. Also important is the patient's performance status, the function of their organs, particularly the kidney, in multiple myeloma, and then very, very importantly and was brought out yesterday, is the desire and wishes of the patient.

We must always take that into consideration. In my experience, I find patients who are very aggressive, shall we say, from a therapeutic standpoint and want to go all out and do the extra procedure, whereas there are others who say, well, you know, I want to just take a little oral medication and not do anything else, and I think that one needs to take that into consideration and to realize the desires and the wishes of the patient.

Finally, I would say just a word about our French colleagues. I, too, have been concerned about that, Dr. Holohan, and I think there might be two answers.

One, in the 1960s, when I first started practicing, we would see the patient with acute leukemia, the 6 mp was no longer effective, and we'd say to the patient, we have a new drug from the National Cancer Institute, and the patient would look at you and say okay, fine, doc, go ahead, give it to me, and no consent forms, no nothing, and everything really worked out as well as could be considered under those circumstances.

I think the French are very similar to that at present. The patient looks to the physician to tell them what to do. In my practice, patients come and many, many times, the patient has already decided that he or she does or does not want to have a transplant, and we get back again to the patient.

Now, the second reason, I think, that the French are much more successful than us is that in this country, we have a large number of oncologists who are in practice, trained in very good institutions, very

capable, very able people, and they are seeing the patient and treating the patient, and the patient doesn't get to the tertiary centers and entered on to the prospective trials in the way that we would like to see.

Thank you.

DR. HOLOHAN: Thank you. You didn't add, although my guess is you were thinking of the fact that in France, you get paid to do clinical trials. That is virtually always a covered benefit.

DR. KYLE: Well, yes, yes. The medical care of the patient is completely taken care of. The patient is seen at the transplant centers, and they go ahead.

DR. BARLOGIE: I was told I'm actually French. There was an accent on the e, and it seems to be Barlogie. But I did grow up in Germany, and I relate very much to what Dr. Kyle just said, and I think this has been an important force in conducting the trials in France.

I'd just like to say that as I came to this country in 1974, after my mentor, Dr. Fraurich, presented at the German Society of Hematology on the topic "The Curability of AML in Adults", that I was very impressed with that, and it was something that was not possible in the country I had trained, and as I then came to M.D. Anderson, and we developed in the '70s the many effective therapies for a number of diseases, I was involved in the early adriamycin trials for lymphoma, for breast cancer, the trials for testes cancer and the like, it was just a God-send in my view that in myeloma, we ended up with a tool, with a cellular support device, that allowed us in the absence of more specific therapy that would be effective even at very low doses, allowed us in the absence of that to give more of a standard agent in a very -- in the context of high degree of safety, and it allowed us to reach the first threshold, and that is achieving a considerably higher incidence of complete remission.

In newly-diagnosed patients, just for those who are not familiar with this, and it's not reported in the literature widely, it takes about nine months to achieve a complete remission with what we have currently available under the best circumstances. In AML, it's typically, as you know, a cycle of complete response, and then the issue is how to maintain this.

I believe that the high-dose therapy approach is the one approach that allows us to optimally try to reduce, to reduce the tumor bulk in a patient, and it puts us in a position from thereon to further explore other avenues.

I recognize that the number of randomized trials, unfortunately, has been limited, and I guess because of the frustration of myeloma investigators in this country and elsewhere, where the battle had raged for 30 years whether melphalan/prednisone was inferior or equivalent to combinations of drugs, I think on the backdrop of that, one then for the first time with high-dose therapy measurable increase in one end point, in a critical end point, that is complete remission was obtained, that people then jumped on this bandwagon, and I feel that the evidence is there from randomized trials and from other clinical trials.

They may be different in statistical design, but they are evidential, I think, and they do provide evidence. There is data to indicate that the greater dose intensity is associated with prolongation of event-free and overall survival, and there are no data to indicate that age per se is an unfavorable factor, and with this in mind, I think we do -- we should consider taking advantage of the tools that we have developed hard, those of us who have been committed to making a difference in this disease, not to now -- not being able to apply it to the many who would benefit.

I thank you.

DR. TRAYNOR: If you step back from this individual study, you know, --

MS. GEYER: I'm sorry. Please identify yourself.

DR. TRAYNOR: Anne Traynor, Northwestern University. If you step back from this individual issue and this individual hearing and try to view the reimbursement process and the state of medicine, you know, at large, which I'm sure many of us are intermittently doing while we're sitting here, I hear quite clearly Dr. Holohan's concern regarding the possibility of touting of a more aggressive therapy as necessarily being the more effective one.

Having witnessed years of stem cell transplant for breast cancer in a disenchanted way, and as I'm sure many of us did, your biggest fear, I think, even graver than your fear that you won't be able to deliver an effective therapy to your patients in a timely way is your fear that you will be practicing under some allusion or perpetrating some allusion not only that puts them through suffering but that really slows down the progress of the science as a whole, and, you know, I hear you saying not only how can we not waste a tremendous amount of resources and patient -- limited patient -- patients' limited lifespan in a less than useful treatment.

How can we somehow be certain that we're not, but also saying however, if this is allowed to happen, that as Dr. Kyle says, a person comes in or a patient comes in as they so often do now with a pre-conviction which is the better treatment and a strong desire to get it.

So, as much as I respect that desire in patients who, I think, are on the right track, I have to admit that I quite often hear a similarly strong conviction in patients who are making a very uninformed or perhaps erroneous decision about their own life and their own utilization of resources, and, so, there must be ultimately a way in which, as Dr. Bagley said earlier today, the Federal Government, among other agencies, finds a way to facilitate the transition from research into accelerated progressive practice.

If those centers offering procedures which appear by preliminary data to have a significant benefit are obligated to register patients, to treat their patients through the investigational review board, at a minimum to be registering their outcomes and their toxicities with the International Bone Marrow Transplant Registry, for example, and the ABMTR, and preferably to be participating in InterGroup trials and therefore making their data publishable, that at least smooths the transition from preliminary

observation into verifiable practice more easily.

If we had the outcomes and the toxicities for the large number of patients that underwent stem cell transplant for breast cancer in this country earlier, it would have been much easier to come to an analysis earlier on than was done of the apparent lack of benefit, and I would suggest that one thing the government must be able to do is to facilitate, if you will, translational research projects of a clinical nature, not just of a basic research nature, but to allow observations that are being made clinically to come to fruition and therefore to become policy as quickly as possible.

Right now, those of us treating Medicare patients are in a little bit of a quagmire, though, you have to admit, because it's not as if it's easy to randomize a 67-year old to autologous transplantation in this period of time in this country.

So, I think that with time, the government is going to have to facilitate the ability to make those observations at academic centers and to maintain the control of the process and the accuracy of the information that's relayed to them in order to either verify or deny the original decision, and they're going to have to make it mandatory that the funded centers or the centers receiving governmental reimbursement for these procedures are relaying their outcome measures directly to the government.

DR. ANDERSON: This is Dr. Anderson from Boston, and I'll be very brief. I just wanted to echo very quickly the reason that I think you're seeing the clinical representation here that you are is that we are involved in translational research in this disease, and that simply put means laboratory and clinical research designed to move new treatments to the bedside, and in that definition, our job is not done until we assure that advances that are made are actually made available to patients and can be used in the clinic.

And I -- in that spirit, I know that this is not an enviable job that you all have, and just to -- it becomes necessary to have a definition of necessary to complete the job, and for me, Dr. Bagley really clarified things very much in the last comments that you made because when I go through, you know, is this safe or effective, is there clinical benefit, is it appropriate, and what is the -- what are the risks versus benefits, I think that notwithstanding the limited data that one can point to, that there is the one randomized trial, there are other randomized trials, but if you want to look at the Attal study and focus on it, if you look at those kinds of issues that were mentioned and really clarified for me and gelled what the definition is of reasonable, I think there is a sufficient database on which to judge this issue, and I hope you'll agree.

Thank you.

DR. HOLOHAN: Prior to your making your motion, I had had a request from the co-chair to do the same. So, she will get precedence for now.

DR. FRANCIS: Leslie Francis. I wanted to make a motion that we start with Question 3 which is, as it's

phrased for us, it is what is the most appropriate measure of successful outcome with autologous stem cell transplantation?

I'm translating that into what are the measures of benefit that we're interested in looking at, and I would suggest that we treat that one first and would so move because I think all the other questions follow what we might want to say about that, follow from what we've decided or the goals that we want to be looking at.

DR. MINTZ: So, is your motion that we treat Number 3 first or are you making a motion restating Number 3?

DR. FRANCIS: Well, I would move that we treat Number 3 first.

DR. HELZLSOUER: Second. Kathy Helzlsouer seconded the motion.

DR. HOLOHAN: Any opposed?

(No response)

DR. HOLOHAN: So moved.

DR. FRANCIS: And I actually also have a suggestion about what the answer is on Number 3, that the two things that I would be most interested in looking at are overall survival and quality of life with probably the best surrogate data we have for that is event-free survival, and we have rather limited data on measures like the Twist information.

If there's no -- I was stating a position, but I would be happy to move that those are the two measures that we should be focusing on, overall survival and what we have with respect to quality of life.

DR. HOLOHAN: Is there a second? Is there an objection?

DR. LERNER: Just a clarification.

DR. HOLOHAN: Well, you either agree or you don't agree. If you agree, you second it.

DR. LERNER: One clarification on the quality of life. Did you say -- I couldn't distinguish whether you were saying an event-free survival was the measure or you're now expanding it to other measures of quality of life as well.

DR. FRANCIS: What I was suggesting is that we don't have a lot of direct data on quality of life. As I'm reading the stuff, the closest surrogate we have for it is event-free survival, and what limited things we

have with respect to Twist.

DR. LERNER: So, could you really restate -- could you restate the motion?

DR. FRANCIS: What I would move is that the two -- that the two measures that we focus on are overall survival and what data we have with respect to quality of life.

DR. HOLOHAN: Those are the definitions of a successful outcome. Those measures.

DR. LERNER: I would second it.

DR. HOLOHAN: Any opposed?

(No response)

DR. HOLOHAN: So moved.

MS. GEYER: And for the record, the first -- Jeffrey Lerner.

DR. HOLOHAN: The ball remains in your court now, Leslie.

MS. BERGTHOLD: Can I ask a question? I can't vote, I know. Could I ask a question?

DR. HOLOHAN: Yes.

MS. BERGTHOLD: Okay. Linda Bergthold. Is mortality -- isn't that usually transplant mortality or something, a measure that you would include in something like that? I mean do you want to exclude it or I mean I just -- I would --

DR. HOLOHAN: Well, let me clarify what I think was meant. Treatment-related mortality or, in this case, peri-procedural mortality is, of course, included in overall survival. Every mortality that occurs at any time detracts from overall survival measured at some point in time.

DR. HELZLSOUER: This is Kathy Helzlsouer. The purpose of Number 3 and how this is used, and maybe Grant Bagley can help clarify that, and I think there are two -- we have a motion that the two measures of outcome or survival -- that's what we have available, but if we were answering this as to what we would like to have, I think that we would ultimately like to know mortality. We would ultimately like to have measures of quality of life, that, you know, nothing that we have really do measure quality of life issues.

So, I guess the -- what I'm not -- what I'm a bit confused about is, is this an issue of what we would like

to have in the future or just what are we going to judge the data that we have now in answering Number 1?

DR. BAGLEY: I think it's a little bit of both. Being presented with a certain amount of evidence today, I think it was recognized that this is an appropriate first question because we really need to look at that and say can we evaluate the evidence?

I think we will look to the answer to this question to help us in the future because I don't think we're through with this issue because whatever recommendations for policy, this is going to be, you know, a disease with continuing research that will need new policy as new treatments become available.

So, I think it will guide us in the future not only on this issue, what is the appropriate measure of outcome, as we present ourselves with new data, but in similar situations, what should we be looking at as the evidence of outcome?

So, I think if there are significant deficiencies in the measures of outcome in the existing evidence, we'd like to know that, and if in fact they constitute fatal flaws to the evidence we're looking at, that's worth knowing, too.

If, on the other hand, there are appropriate measures of outcome, no matter how limited, but that we can use those, then we ought to use those. So, I guess the answer is -- I guess I should have answered by saying both.

DR. HOLOHAN: Let me try to encapsulate this and summarize it if I can. The question at issue upon which the panel -- the voting members will vote is the suggestion that the appropriate -- the most appropriate measures of successful outcome for stem cell transplantation in support of high-dose chemotherapy are overall survival and appropriate measures of quality of life acceptable to general health services research community, of which at the present time we are essentially limited to event-free survival and the Twist data. But the panel would prefer to express its intent that this is insufficient for the future.

Have I accurately captured what -- well, then you may vote.

MS. GEYER: Again, to redirect, everyone in favor, please say aye of the motion. We could go around the table. It's easier for the record, I think.

DR. MINTZ: Paul Mintz, aye.

DR. HELZLSOUER: Kathy Helzlsouer, aye.

DR. FRANCIS: Leslie Francis, aye.

DR. JOHNSON: Johnson is aye.

MR. JORDAN: Jordan, aye.

DR. LERNER: Lerner, aye.

MS. GEYER: And that is everyone in favor. So, do we want to make a motion to go to the next question?

(No response)

MS. GEYER: Then someone who makes that motion must be one of the voting members, and it cannot be Dr. Holohan. That's narrowed our field. Anyone?

DR. HOLOHAN: That's not why I was picking up the microphone.

DR. HELZLSOUER: This is Kathy Helzlsouer. I guess I'll take the plunge. I would then turn to Number 1, which I think then will focus the rest of the questions. So, I would -- do you want a motion about what order we do this or just want a motion?

MS. GEYER: A motion as to what your opinion is on this subject, and then someone can second that.

DR. HELZLSOUER: Okay. So, I'll make the motion that there is sufficient evidence expressed in the form of an evidence -- benefit and survival to support autologous stem cell transplantation for the treatment of multiple myeloma in the Medicare population, and evidence to say that this is reasonable and necessary.

DR. MINTZ: I'll second.

MS. GEYER: And you are?

DR. MINTZ: Paul Mintz.

DR. HOLOHAN: Any opposed?

(No response)

DR. HOLOHAN: Okay. We can vote. No one is opposed to the motion. Now, if you choose, even if you don't choose, you can vote.

MR. JORDAN: So, we're not -- is there discussion? You're asking whether we're opposed to her making

the motion?

DR. HOLOHAN: Yes.

MR. JORDAN: I see.

DR. MINTZ: Oh, okay. We're voting that we're considering Number 1 next, not voting on the motion.

DR. HOLOHAN: And what we're considering is what she has phrased. Is there sufficient evidence -- there is sufficient evidence in the form of survival data, and that's how she --

MS. GEYER: Kathy has turned it into an affirmative statement, a positive, and by agreeing to that, you're saying yes.

DR. MINTZ: We are voting on the motion? Yes?

MS. GEYER: Yes.

DR. MINTZ: Okay. Paul Mintz, aye.

DR. HELZLSOUER: Kathy Helzlsouer, aye.

DR. FRANCIS: Leslie Francis, aye.

DR. JOHNSON: Robert Johnson, aye.

MR. JORDAN: Jordan, aye.

DR. LERNER: I think I know what I'm doing here. I'm just voting to consider the motion. Positively there is that evidence.

MS. GEYER: Correct.

DR. LERNER: Well, I'm trying to -- I guess I have to abstain.

MS. GEYER: I could take a moment for clarification sake. Dr. Lerner, you have the opportunity to express your view on this subject, and I believe you have the opportunity after the panel meeting, Sharon, please correct me if I'm wrong, to submit a position paper on your view, if you feel strongly about it, yes. Would you like to make a comment at this time?

DR. LERNER: Yes, I would.

MS. GEYER: Okay.

DR. LERNER: Well, I think this issue goes to the burden of proof, and the role of the panel, you know, whether if you have reasonable proof for a younger population, whether it's the job of the advocates to convince us that we need to extend it to the Medicare population or the opposite, that it shouldn't be the burden of Medicare to say, you know, no, you haven't shown enough evidence.

Since I guess I see this as a continuous process without any sort of hard cut-off, I can't see any age at which, you know, this becomes ineffective or less effective than -- either by itself or in comparison to conventional chemotherapy.

That puts me in favor of the motion. I'm a little concerned. I would have liked to have seen the data that I requested or that I discussed earlier; that is, the analysis of the Torino study or perhaps some recalculation on the age as not a prognostic variable.

So, I'm a little uncomfortable. I don't know how burdensome it would be to get that data, but if it could be presented, and it looked anywhere near reasonable, then I would be happily in favor. That's my --

MS. GEYER: Okay. Opinion noted. I believe we can now proceed to the next question. Again one of the voting members will need to make a motion as to their opinion on one of the questions. No one's making eye contact with me here.

DR. FRANCIS: I am Leslie Francis. I will make a suggestion. This is to open it for discussion, which is that we consider Question Number 2 which is what factors should be considered insofar as the -- I take it that it's still open to discuss a limited policy rather than a complete open door policy, and I'd like us to focus there on the various prognostic factors and also the issue of age 70.

The question is whether there should be any limits.

DR. HELZLSOUER: This is Kathy Helzlsouer. I guess one of my issues for discussion, I think my basic -- I'll take the age 70 question comment first. I'm reluctant, I guess, to draw another arbitrary age cut-off to do that, and I think I would rely on judgment based on other physiologic parameters that would be determined, and maybe we'll address that later, if there will be protocols or whatnot to make the determination based on those factors rather than a strict arbitrary chronological age cut-off would be my viewpoint.

The other -- the concern I would have getting to the other issue of subgroup, I guess with the exception perhaps that I'd like to hear more discussion on the issue of refractory multiple myeloma, where we don't have the same level of evidence, I guess, -- the trial was based on those with newly-diagnosed multiple myeloma. That may be initially resistant to treatment but not in its refractory category.

So, I would like to have more clarification of that group, but with the exception of that, I'm not convinced that we have enough evidence on specific subgroups to say what we would like to say, is that who would clearly benefit from this treatment regardless of age and who would this clearly not improve their outcome no matter what you would do, and I think the information that's been provided is very limited and probably not enough to separate out those subgroups with any certainty or level of evidence, but I think that would be the discussion.

So, my only question would be in this group that's sometimes referred to as refractory, and maybe we need to have a little better definition of that, and we can have some comment from the experts.

DR. MINTZ: I just think we heard a difference between primary resistance and resistant relapse, and where I would like -- my sense is that Medicare to consider for coverage is that the problem with no data for efficacy and resistant relapse, which is what I heard Dr. Kyle and others say. So, that would be helpful to hone in on what you were saying.

DR. HOLOHAN: That may be useful. I'm not certain. Is the sense of the panelists discussing this that although, first, that we -- we may or may not have data available to us right now today to be able to make a rational and clinically-justifiable cut somewhere or is it the sense that the panel is -- would consider recommending to Medicare that these be developed and implemented as the evidence becomes available or is available?

DR. HELZLSOUER: Kathy Helzlsouer. That's an option. I mean I think we have to --

DR. HOLOHAN: I'm not trying to lead the panel, but what you -- what I heard you say was that you didn't believe that there were data sufficient presented here in what you've read that would enable you to make -- draw any kind of a rational clinically-defensible line between categories or even subcategories of patients today.

DR. HELZLSOUER: That's correct. I don't think what's been presented from that clinical trial was not adequate to do -- to make -- to select out prognostic groups who would or would not benefit.

DR. HOLOHAN: Well, it would seem then to me, maybe not to anyone else, but to me, that there really are only two choices. One is that you believe that expert opinion available to us today is an appropriate guide for drawing that line, and we should do so right now, or that alternatively, we should recommend to Medicare that these be developed in a more data-driven -- I hate to imply a more data-driven thoughtful way, but as opposed to off-the-cuff, so to speak.

DR. HELZLSOUER: Hm-hmm.

DR. HOLOHAN: I can't make a motion.

DR. HELZLSOUER: I was just going to formulate the motion. I would make -- I would make a motion

that the policy statement regarding who would be eligible for this be developed by HCFA, that there is no evidence available to us today to determine that with any degree of certainty of any subgroups that should be included or excluded.

DR. BAGLEY: I just want to observe that -- and caution you from presenting us with an impossible dilemma.

DR. HELZLSOUER: That was my concern.

DR. BAGLEY: Having decided that the evidence is sufficient that Medicare should cover this, but that the evidence is insufficient to determine how to cover it, --

DR. HELZLSOUER: Well, --

DR. BAGLEY: No.

DR. HELZLSOUER: -- I mean it's not a matter of --

DR. BAGLEY: I mean it's -- I think we've heard -- we've heard the evidence, and we've had the best evidence available to date on this disease presented to us, and I think that it's going to be important to decide that -- that if we cover this, we do it in such a way that if there are rational, you know, ways in which we define the policy, we should be able to do it based on evidence, and I would tell you that based on our experience in other areas, that given a paucity of evidence for promising therapies, that it's best to move cautiously rather than to move too far because it's hard to move backwards in coverage policy, and, for example, --

DR. HELZLSOUER: Let me --

DR. BAGLEY: -- if we were to cover the procedure with very little restriction and say, but as data becomes available, we can narrow it, it's very difficult from a policy point of view to narrow things, and the second piece of this is that if this becomes a broad coverage policy, the research by which we would answer the questions that are unanswered will probably never be done.

DR. HELZLSOUER: Let me retract my motion then. Let me make another motion for -- that we have an opportunity then to discuss this here. My motion is that for considering for policy that we address the issue as a subgroup, those with resistant relapse, that is sometimes referred to in the literature, I think, also as refractory leukemia, and my motion -- refractory relapse, and that we discuss that as a subgroup for potential consideration of coverage or non-coverage.

DR. JOHNSON: I will second that motion.

MS. GEYER: And you are?

DR. JOHNSON: Johnson.

MS. GEYER: Kathy Helzlsouer made the first motion, Bob Johnson has seconded it. Anyone else? Or should we go around now and say who's in favor and who is not?

MR. JORDAN: I would like to hear from the clinicians present whether they feel that kind of exclusion places them in a difficult dilemma in handling patients presenting to them on a daily basis, and if there's objection to that or whether that sounds like a reasonable exclusion to them.

DR. HOLOHAN: Short comments, please.

DR. BARLOGIE: Barlogie. The definition of resistant relapse is one that has to be based on a patient's response history and being tested with appropriate dosing of drugs, and this is done by history that -- of the patient's treatment by the primary physician, and this is not very black and white situation.

I would be able to achieve another response by testing certain things when the patient comes with a, quote unquote, resistant relapse, and this patient becomes responsive.

So, I just want the panel to recognize that this is not -- this is a vague definition.

MR. JORDAN: Jordan again. Is that administerable then? Is that something that the system, HCFA and the Medicare carriers, could administer easily? Is it creating a useless barrier that is not going to really protect that many people anyway or that many resources?

DR. MINTZ: The way I read the -- the way I hear the motion is that Medicare is being asked to consider this. It's not drawing a boundary. It's being asked to give it consideration.

I would defer to Dr. Bagley to answer your question directly, but my instinct is that it does not create such a problem.

DR. BAGLEY: In terms of program administration, I can guarantee you that anything we do, someone will object to it. So, you get used to that.

If we're to create some boundaries around coverage and say that the coverage becomes available under some situations, but there are -- need to be some boundaries, we would have to define the boundaries in terms of policy statements that could be administered, and it's not unlike many clinical areas in which there is not a bright line, but we would have to come the closest we could to at least coming to a definition of where that line occurred which would allow for flexibility where flexibility was justified, but at some point, there would have to be a boundary beyond which the evidence did not yet support, you know, that as a treatment option, and, so, yes, we would have to develop a boundary, and we would

have to do it based on best available evidence, and we would have to find in that gray area where the best place was to delineate a line.

DR. HOLOHAN: Dr. Traynor, I'm sorry that when the panel is voting, no -- even if the panel requests a comment, that is not kosher, as they say.

DR. MINTZ: May I comment on the motion then? Because I may well have missed this, but I did -- I'm delighted to be corrected by my co-panelists, but I did not see evidence to support the necessity of this transplantation in patients who were so defined as having resistant relapse by the presenters. So, I support the motion.

MS. GEYER: That is Dr. Mintz in support of. Would the panel like to discuss this more or take a formal vote at this point?

DR. LERNER: Just for clarification, what are the other categories that you would see now? That's the only thing that we're excluding or how would you characterize --

DR. HELZLSOUER: The motion isn't to exclude. The motion was to discuss this as a category, and I -- to consider this as whether or not we consider this as a category. Personally, from the literature I reviewed, I would hesitate greatly to define other categories based on the evidence.

So, the only thing -- the only category that I think would be reasonable to consider are those that have had disease that has been proven to be resistant to other resistant-relapse definitions.

I searched actually for a good definition of this literature, and I think it is a problem. We had in our packet additionally an assessment that was done, and it had this category also. This was not the group that was in the trial.

For the first motion that we approved for the level of clinical evidence based on that trial, this was not the population that was in that trial.

DR. FRANCIS: This is a comment from Leslie Francis. I have a lot of trouble discerning from the data appreciable evidence of benefit in the classes of plasmablastic morphology and Beta 2 microglobulin, and I'd like your comments on those two, and I need to add I'm not a clinician. So, I would like to be enlightened from that point.

DR. HOLOHAN: Yes, the chair can comment. Let me again attempt to rephrase what I believe you've proposed. You wanted to discuss crafting a motion that basically stated that for autologous stem cell transplantation for multiple myeloma, the panel is unconvinced that all patient categories appear to benefit equally or perhaps benefit at all, and you raised the question about patients with relapse refracting myeloma, which did not appear to benefit from the material that was provided to us, and Dr. Francis has raised the additional issue of patients with significantly-elevated Beta 2 microglobulin and

plasmacytoblastic morphology as being equally poorly responsive or unresponsive to treatment.

You could, in my opinion, Dr. Bagley's comments notwithstanding, I'm sorry, make a recommendation for Medicare to consider at least in the absence of compelling evidence or future evidence on excluding those categories of patients from the recommended coverage under Question Number 1, and I think that's what the general sense was leading up to.

If I've misphrased something you've said or Dr. Francis has said, I'm willing to be corrected.

DR. HELZLSOUER: I'm hesitant. This is Kathy Helzlsouer again. I'm not sure that's the motion I made, but I think we're faced with -- these are questions that have come from HCFA to us, which is what factors should be considered, and we could say that there are no factors that should be considered or there are some.

So, maybe one factor is this resistant relapse and the other one brought up is Beta 2, which are prognostic factors. I'm not sure that any prognostic factor, if it's a poor prognostic factor, then considers that they don't benefit. I don't think -- it's just a prognostic factor for disease outcome, and they may still have some incremental benefit, but clearly not as much as others, and I don't think we can define all those subgroups with possibly the exceptions of those because the chemotherapy, for example, you were using, if they've already proven to be resistant to, which is a resistant relapse group, putting them through a high -- even though the mortality may be reasonably low would still associate mortality with this.

Do they have any benefit? Are they faced with all the risks? I think this is the area we're talking about, and this is reasonable and necessary, and I think probably our hesitancy is making this judgment here today based on this evidence, if we have -- if we -- I guess in the panel, we could have more discussion.

Do we just feel comfortable that it should be an open-ended policy? What decisions made elsewhere? Do we even need to give any guidance at all? Maybe hear from the panel members regarding that, that there should be an exclusion beyond the diagnosis of myeloma.

DR. MINTZ: As I understand what we're being asked to do in this question, it's not to set the limits, it's to suggest what variables HCFA should use in setting limits, correct? This is Paul Mintz.

DR. BAGLEY: Well, I mean I think it's -- there are two dimensions to that. I think we're obviously interested in what variables are appropriate to set limits because I think there's been a lot of discussion about whether or not age is an appropriate variable or perhaps it's a surrogate for other things that are -- that should be more explicit.

Maybe there are other things we should use, and I think that's right. I think that in terms of crafting a policy, it would take us far more than the rest of today to try to set the explicit limits of the policy, but I think given the direction that we tried to find the appropriate way to separate categories of patients in

terms of a non-refractory relapse or not, we could develop those measures and do that, if we're given the direction that that's an appropriate place that we should put a boundary, and, similarly, if in fact we should be looking at other factors, we can do that, also.

So, I think you can't determine the details perhaps, but giving us the direction, we could do that.

DR. HOLOHAN: This is Dr. Holohan. Let me make a summary statement as the panel chair and see if the voting panelists would agree or disagree.

It appears that a significant portion of the panel has some reluctance to give, as they say, carte blanche to this for all categories and classes of patients. At the same time, there remains uncertainty, based on the limited data that has been made available to us, to be able to draw the line with any degree of certainty, and we believe that that is best approached by an appropriate group convened by HCFA specifically for that purpose.

I'm not making a motion. I can't make a motion. But have I captured -- is there -- are there any panel members who believe that this should be provided as a covered benefit under any and all circumstances? I'm not trying to use emotional terms, but that's basically what we're talking about for all patients.

Is there anyone who feels comfortable doing that?

MR. JORDAN: I'm not -- this is Jordan. I'm not sure that I don't feel comfortable doing that. I can understand people's reluctance based on some of the things that Grant has said that, you know, we have to be careful about going too far, but I am more confident in the medical professionals out there to do the right thing maybe than some others on the panel, and I'm not totally uncomfortable with leaving this coverage decision more open, although I could certainly live with, if the rest of the panel's consensus was that it has to be tighter than that, I could certainly live with --

DR. HOLOHAN: Okay. Jeff?

MR. JORDAN: -- a group establishing those guidelines.

DR. LERNER: I would go with your original statement. I'm comfortable. I'm not comfortable leaving it with carte blanche.

DR. HOLOHAN: Okay. Dr. Johnson?

DR. JOHNSON: I really think that the motion Dr. Helzlsouer has offered is adequate. I would hope we don't start trying to define more factors. I think she's appropriately defined the one, and we can leave it at that.

DR. HOLOHAN: Dr. Leslie -- Dr. Francis?

DR. FRANCIS: I am going to abstain on the additional factors, but I think she's right on the one about refractory-resistant relapse.

I also think it's worth saying because I've been asking the other question, that I think we should say to HCFA that we don't want an arbitrary age cut-off, that we think the other clinical variables are what matter.

DR. HOLOHAN: Okay. Dr. Helzlsouer's made a motion, and I suggest before we all die of starvation we vote on the motion. I can't restate the motion.

DR. MINTZ: I see the motion as that Medicare is directed to consider whether or not the patient has resistant relapse in establishing its coverage decision, and I vote aye. Paul Mintz.

MS. GEYER: And I believe at this time, we're ready for the rest of the panel to go and say in support either aye or nay. Dr. Helzlsouer?

DR. HELZLSOUER: Kathy Helzlsouer, aye.

DR. FRANCIS: Leslie Francis, aye.

DR. JOHNSON: Robert Johnson, aye.

MR. JORDAN: Jordan, aye.

DR. LERNER: Lerner, aye.

DR. HOLOHAN: Congratulations, and now --

DR. MINTZ: May I make a motion?

MS. GEYER: Thank you. Yes.

DR. MINTZ: Okay. I hope the hour permits this. I move that providers -- let me start over.

I move that centers performing autologous hematopoietic stem cell transplantation under coverage by Medicare be accredited either by the American Association of Blood Banks or the Foundation for the Accreditation of Hematopoietic Cell Therapy.

MR. JORDAN: Second.

MS. GEYER: If I just may, for the record, it's Paul Mintz, and you are addressing Question Number 5?

DR. MINTZ: 5.

MR. JORDAN: 5.

MS. GEYER: Number 5.

DR. MINTZ: And by that, I mean and/or be accredited by the AABB and/or FAHCT. And/or.

MR. JORDAN: Seconded by Jordan.

MS. GEYER: Would the committee like to discuss or vote at this time? Okay. We'll go around this way this time.

DR. LERNER: So, it's just vote, no discussion. I've never seen the accreditation.

DR. MINTZ: Okay.

DR. LERNER: May we discuss this?

MS. GEYER: Okay. If you'd like to discuss, go ahead.

DR. MINTZ: I have read -- I'm presuming this is open for discussion. I have read both. I am familiar with both. They are rigorous. They address the specifics of the entire process from the selection of individuals to the harvesting of the product to the processing of the product, the storage of the product, the preparation for infusion.

The FAHCT standards address clinical issues. The AABB issues are being brought to that level, and I feel they provide a level of assurance for quality care that merits this motion.

DR. LERNER: Let me just ask you one other thing. Do they include anything about collecting and preserving patient data, reporting it, anything like that?

DR. MINTZ: I should say that I really don't know that with respect to the FAHCT standards. The AABB standards require a lot of recordkeeping with respect to product. I don't believe that's what you're asking. You're asking outcome-type data and quality of life-type data, and they do not.

But I think that Dr. Holohan said this well. I'm not suggesting this is a sufficient condition. I'm suggesting it's a necessary condition, and it by no means is going to encompass everything that one would want, but it does encompass important aspects of this. So, I see it as necessary, if not sufficient.

DR. LERNER: I see. So, was that part of your motion then?

DR. MINTZ: No. My motion is strictly directed to this, what I see as a necessary component of this. There may be other aspects to this that we would wish to consider.

DR. HOLOHAN: To be precise, he may not say this, but it doesn't say what are all the qualifications that should apply. It says what qualifications. I presume that doesn't mean that others can't be added.

DR. MINTZ: Of course. Thank you.

DR. BAGLEY: I'll just point out a little caveat at this point, and that is that there are a couple of issues that we run up against with this.

Number 1 is that, you know, we are here getting advice on how we as an agency, who will make the final decision because we're charged by Congress to do that, and the Secretary is charged to do that, but she actually lets us make some of those decisions or recommendations, and we must do that.

We cannot defer that. As a legal standard, we cannot defer that to another body and say we will let someone else make the decisions about qualifications. So, we can't defer the entire process.

On the other hand, we have relied upon, you know, standards from other organizations, and we have incorporated those as components. We sometimes do that. I think the committee should be cautious about adopting those without having a full discussion of them and which we obviously can't do, but they aren't necessary, and the only -- it's not necessary that we do all of that, to at least reference them, and the final thing that -- in setting up standards, we often are fully aware that there are accrediting bodies, voluntary and very adequate accrediting bodies out there, which don't quite fill the bill for us.

You know, it would make sense, for example, to say that cataract surgery should only be done by ophthalmologists, but, you know, it's a little difficult to decide what that qualification really means. We can't really require membership in the American Academy of Ophthalmology or board certification oftentimes. That doesn't work because there may be fully-qualified ophthalmologists that choose not to be members.

So, in using outside standards, outside organizations and those, we have to be a little bit cautious about using them too broadly, and that doesn't mean that we can't look to outside standards, and the committee can obviously recommend that we look to standards which are set up or equivalent --

DR. MINTZ: Then I'd like to amend the motion, and I'd like to suggest rather than make it as declarative as I made it, that I'd like to say that Medicare -- just what it says here -- should consider.

So, let me make the motion that Medicare should consider accreditation by the AABB and FAHCT in its

coverage policy.

MR. JORDAN: That's acceptable to the seconder, Jordan.

MS. GEYER: Are you comfortable taking a vote note now, Dr. Mintz?

DR. MINTZ: I am now.

MS. GEYER: And?

DR. HOLOHAN: And your vote?

DR. MINTZ: Aye.

MR. JORDAN: Jordan, aye.

DR. JOHNSON: Johnson, aye.

DR. FRANCIS: Francis, aye.

DR. HELZLSOUER: Helzlsouer, aye.

DR. MINTZ: Mintz, aye.

DR. HOLOHAN: Okay.

MR. JORDAN: Can I ask? Before we leave that question, if we are going to leave that question, is the notion that Dr. Traynor raised of potentially also requiring registration of patients and the use of the registry in order to assure that appropriate flags are raised if we're headed in the wrong direction with this policy, a potential appropriate criteria to add at this point?

DR. BAGLEY: When we consider a Medicare coverage policy, and we weigh the evidence, and based on the evidence make a determination that there ought to be coverage, as I said, it's very difficult to put our toe in the water and then pull it back out.

There are certainly times when we have put policy together and said we want to see what happens. We've done that, for example, in cautiously advancing coverage for certain vascular studies with MRI. We've done that with some of the recent policies we've used to advance coverage for PET scans.

Based on evidence which showed, I think, that it is a useful adjunct to clinical care, but in some cases where the evidence was not as robust as we might want it to be, we have embarked on a pathway where

we collect a certain amount of information through the claims processing, so that we can then see how it's being utilized and see what happens.

So that is a limited possibility, but, on the other hand, some ways where it doesn't work is we recently introduced a policy for pancreas transplant, and that pancreas transplant, we worked with NIH, who have been trying to set up a registry to track the data and get some long-term results on pancreas transplant.

We were unsuccessful in being able to put together a policy which would require participation in that registry, and, so, we were faced with providing coverage, and at the same time essentially dooming the NIH registry to failure because given the voluntary nature of it, it probably wouldn't work.

So, although we do do it at times, policies which require tracking, following and accumulation of data are very difficult to implement. It's very hard, and in fact, we are authorized by law to collect the information that is necessary for claims processing only, and the accumulation of information which might be useful clinically or the requirement that people participate in the registry runs afoul of other issues out there, the Paperwork Reduction Act, and the fact that we're collecting information not necessarily for claims processing.

So, while we can do it in some circumstances, it's very limited ability, and it's not likely to be as useful as clinical researchers would like it to be.

DR. HOLOHAN: Let me take the prerogative as chair to encourage people to move this along, and no disrespect meant, Dr. Bagley, but I don't think this panel can be expected to parse through all of the complicated details of Medicare policy and what they can and can't do.

The questions as posed to the panel were fairly straightforward. If they make a recommendation that is not implementable by the Health Care Financing Administration, I don't know that they should be -- they should have been expected to have known that ahead of time.

Can we move on to Number 4? What evidence supports the efficacy of more than one autologous stem cell transplantation per patient?

DR. HELZLSOUER: This is Kathy Helzlsouer. I would make a motion that there's insufficient evidence to support the efficacy of more than one autologous stem cell transplantation per patient.

DR. MINTZ: Second.

DR. HOLOHAN: Any discussion believed necessary by panel members prior to voting?

(No response)

DR. HOLOHAN: I don't think your -- all right.

MS. GEYER: So very sorry, Dr. Adamson. Do you want to vote, starting with Dr. Mintz?

DR. MINTZ: Mintz, aye.

DR. HELZLSOUER: Helzlsouer, aye.

DR. FRANCIS: Francis, aye.

DR. JOHNSON: Johnson, aye.

MR. JORDAN: Jordan, aye.

DR. LERNER: Lerner, aye.

DR. HOLOHAN: Okay. That was easy. Now, Question 6 is simply stated. Should there be specific protocols for performing the procedure?

I don't read this as extending to a requirement for the panel to right now develop those specific protocols.

Does anybody want to discuss this question as written? Does anyone want to rephrase it or does someone want to make a motion?

DR. MINTZ: I don't think we do. That's my fault, but I don't think there should be. I think that's beyond the scope of --

DR. HOLOHAN: Okay. So, no one is suggesting that this question be rephrased into a statement, a different format? It's acceptable for voting and discussion by all as written?

DR. MINTZ: I was suggesting that we -- I'm not comfortable in my realm of expertise in answering this question, and that I would not make a motion to this question.

DR. HELZLSOUER: I mean it's unclear to me -- and this is Helzlsouer. It's unclear to me what is meant specifically by the question.

DR. HOLOHAN: That's why I gave you the opportunity to make it mean something to you.

DR. HELZLSOUER: Well, --

DR. MINTZ: Can the panel elect not to answer -- I mean just elect not to have a motion with respect to every question?

MS. GEYER: I'm receiving a head nod.

DR. MINTZ: What?

MS. GEYER: I'm receiving a nod that the panel may choose to --

DR. HOLOHAN: Yes. I mean that's only sensible. They shouldn't be held to answer Talmudic questions if they choose not to.

DR. BAGLEY: Yeah. Just to clarify, I think the reason that question was asked is in terms of putting a policy together. For example, as a threshold question, should the timing of a stem cell transplant be important? Should that be included in the policy? Should patients be required to go through certain amount of medical therapy first or can it be a threshold issue or can the timing be simply up to the treating institution?

DR. HOLOHAN: Would you care to make a motion, Dr. Mintz?

DR. MINTZ: Well, that makes it easy then. We could move that the Medicare, you know, leave that up to the treating institution and provider, and I would so move. So that there should -- so that my motion would be that there not be a specific protocol that directs the coverage decision.

MS. GEYER: Okay. May I clarify, Dr. Mintz?

DR. MINTZ: Please.

MS. GEYER: At first, you had said you would like to disregard the question as you felt the panel had insufficient evidence to answer it. However, now I'm hearing you would like to redirect -- make a motion to say that Medicare should look into this themselves.

DR. MINTZ: No.

MS. GEYER: No?

DR. MINTZ: No, I didn't say that.

MS. GEYER: Okay. So, I --

DR. MINTZ: I'll stick with my first --

MS. GEYER: Okay.

DR. MINTZ: -- point. I was trying to say that I didn't think that there was sufficient information provided to the panel for us to be able to say that Medicare should participate -- should have as its coverage decision elements regarding the protocol of care, and that's what I'm saying.

DR. HOLOHAN: Could you state that as a motion?

DR. MINTZ: Okay. That's what I tried -- yes, I will. I move that Medicare not consider treatment protocols with respect to its coverage decisions.

DR. JOHNSON: Second the motion. Johnson.

DR. LERNER: Can we have discussion on that?

DR. HOLOHAN: Yes, briefly.

DR. LERNER: Okay. Does that in any way inhibit or have an impact on a prior motion that we did affirm on developing a policy that might exclude some patients?

DR. MINTZ: Well, I was thinking a protocol somewhat differently.

DR. LERNER: I know. There's a definitional issue here.

DR. MINTZ: I think the -- what we excluded was refractory relapse, which is a clinical condition. I don't think that's a protocol.

DR. HOLOHAN: All right. Am I correct in your sense that the word "protocol" as written here and as your motion addresses would reach to specific selection of drugs, drug dosages, the addition of TBI or non-addition of TBI?

DR. MINTZ: Timing, right.

DR. HOLOHAN: Timing, etc.

DR. MINTZ: That's right. Yes, sir.

DR. HOLOHAN: And in that case, you've made the motion. It's been seconded.

DR. MINTZ: Correct.

DR. HOLOHAN: And the vote is?

DR. MINTZ: Mintz, aye.

DR. HELZLSOUER: Helzlsouer, aye.

DR. FRANCIS: Francis, aye.

DR. JOHNSON: Johnson, aye.

MR. JORDAN: Jordan, aye.

DR. LERNER: Lerner, aye.

DR. HOLOHAN: We're getting there. Question Number 7. Does anyone feel compelled to discuss this or is someone ready to make a motion?

DR. MINTZ: Both. I think that this is a clinical issue, and I think that while we heard today that the standard of practice is -- for stem cell transplantation is clearly peripheral blood, that it'sa clinical decision, and that there may in fact be patients -- in response to my question, I think Dr. Barlogie said 85 percent can be managed through, you know, to the point where peripheral blood can provide sufficient cells. It did leave a residual group of patients for whom that may not be the case.

My sense is that it's a clinical decision whether or not to harvest these cells for peripheral blood or bone marrow, and that I don't see where coverage should turn on the source of the stem cells.

MS. GEYER: Would you like to turn that into a motion, Dr. Mintz?

DR. MINTZ: Sure. I move that coverage not be related to the source of the hematopoietic stem cells.

DR. HELZLSOUER: Helzlsouer, second the motion.

DR. HOLOHAN: Shall we vote? We can start here because it will be faster.

DR. MINTZ: Aye, Mintz.

DR. HELZLSOUER: Helzlsouer, aye.

DR. FRANCIS: Francis, aye.

DR. JOHNSON: Johnson, aye.

MR. JORDAN: Jordan, aye.

DR. LERNER: Lerner, aye.

DR. HOLOHAN: Which leaves us with only Number 8. Are there any other questions or concerns, aside from transportation, that the panel would like to address? Dr. Francis has a point.

DR. FRANCIS: I'd simply like to register the concern that as this is a disease that affects African Americans at disproportionate rates, that folks engaged in the treatment of this disease be especially sensitive about whether or not patients who are African American have adequate access to this modality, and to note that none of the patients who spoke yesterday were African American.

DR. HOLOHAN: Agreed. Well, the panel having addressed --

DR. LERNER: Are we allowed to propose anything else under Number 8?

DR. HOLOHAN: Sure.

DR. LERNER: Okay. This is Lerner. In appreciation of the testimony of Dr. Kyle and Dr. Traynor's statements about patient education, I'd like to see if it's appropriate to propose a motion that detailed patient information be developed that at a minimum described the procedure in lay but very detailed terms, then that discussed the risks and benefits and that discussed questions that a patient might ask so that he or she could make an informed decision in collaboration with their physician.

DR. HOLOHAN: That's fine. I think we could probably -- if you want to so move, we might vote on that as a sense of the panel, but I'm not sure that it directly ties necessarily with the coverage issue per se. It certainly would be unusual to have that as a condition of coverage.

Does anyone want to second that motion as a sense of the panel? That is, providing clear, comprehensive information to patients who are being approached with the possibility of being treated with high-dose chemotherapy and stem cell rescue for myeloma.

MR. JORDAN: I'll second.

DR. MINTZ: I have a question. I mean what

-- is this within the purview of HCFA?

DR. HOLOHAN: No, it is not. I thought that I --

DR. MINTZ: You did say that. I just -- I wanted to affirm that I heard that correctly. So, is the motion -- it's more a sense of the panel than a directive?

DR. HOLOHAN: That's the phrase I used, I believe.

DR. MINTZ: Right, right. Okay.

DR. HOLOHAN: Vote?

DR. MINTZ: Mintz, aye.

DR. HELZLSOUER: Helzlsouer, aye.

DR. FRANCIS: Francis, aye.

DR. JOHNSON: Johnson, aye.

MR. JORDAN: Jordan, aye.

DR. LERNER: Lerner, aye.

DR. HOLOHAN: Ladies and gentlemen, thank you very much. I have been asked if we could permit Kathy Hill, I believe, to speak briefly to the panel. Is she present? Since she's not a clinician or a physician, I will permit that.

MS. HILL: Thank you for this time. It's a little bit after the fact. I did want to make a clarification earlier that the Torino study, the median age was 64 with more than half of the people being over 60, and I just wanted a clarification of that before.

Also, what I had wanted to say prior to the discussion was that the medical evidence that has been supplied by these physicians over the last two days has been evidence from 1996 to 1999, from the TAC that was expanded to the new MCAC.

So, I'm appreciative that we've moved on from that place to where we are today, and I think that it was also important to note that not everyone who has myeloma is a candidate for a transplant, and there are protocols in place by the physicians, and the patients have to meet a stringent protocol before they're even considered, and the teaching hospitals and academic centers in the Medicaid hospitals that I presented to all of you have a specific protocol that's already in place for that, which may help to make some of the decisions, but in view of all the testimony and the voting, I just want to say thank you for the opportunity to be able to present this and bring this before you on this important issue for all the patients who are suffering and depending on you to prolong their lives.

Thank you.

DR. HOLOHAN: I'm now going to be told whether we can close or not.

DR. BAGLEY: Before I turn it over to Ms. Geyer to close, I would just like to say that I would like to thank you all for being here to participate in this non-randomized, non-controlled observational clinical trial. It's the first time through it.

Just as a matter of process, it was interesting to watch, you know, clinicians and policy-oriented folks around the table in a public forum being so timid because I can tell you if we'd been in -- if we'd been locked in a room, we would still be arguing about Question 1. So, perhaps the public process does have some efficiency to it after all, and again as a matter of process, this being the first time, but our intention and the way we've defined things is we take the recommendations of the panel.

We at HCFA as a staff will take those recommendations. We will do everything we can with them. We will work on policy, and as a matter of feedback, this will then eventually go back to the Executive Committee which this is just one panel of the entire advisory committee.

The Executive Committee, being the chairmen of all the panels, will have a chance to both get feedback on how we have implemented any policy recommendations, to discuss the committee process about what worked and didn't work, what we can improve on, how we can improve the functioning of the committee, and it is going to be a continuing process as we move along.

So, again I'd like to thank you all for being there, and I'll turn it over to Ms. Geyer.

MS. GEYER: Again, I would like to thank all the presenters and the participants for being so timely and well organized, and it's a tribute to all of you that you made it here in the bad weather.

I'd like to personally thank my group. It's the first time we've done a team approach to work at HCFA, and I think each and every one of them is a result of this being a success as well. So, I'd like to thank them, and I would like to conclude with saying when the tentative dates are for the next Drugs, Biologics and Therapeutics Panel Meeting.

We are hoping to meet again in February, perhaps on February 28th and 29th of the year 2000, and then again perhaps in September of the year 2000. For updates as to when we will be meeting, you can monitor our web site, and information about our web site is available on the front desk as you leave.

Thank you.

DR. HOLOHAN: Let me make one last final statement to the panel. I admire your perseverance.

(Whereupon, the meeting was adjourned.)