00001

CENTERS FOR MEDICARE AND MEDICAID SERVICES
Medicare Evidence Development & Coverage
Advisory Committee

March 24, 2010

Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland

Reported by:
Paul Gasparotti

00002

Panelists

Chairperson
Clifford Goodman, Ph.D.

Vice-Chair
Saty Satya-Murti, M.D., F.A.A.N.

Voting Members
Phyllis Atkinson, R.N., M.S., GNP-BC
Virginia C. Calega, M.D., M.B.A.
Marion Danis, M.D.
Susan A. Levine, D.V.M., M.S., Ph.D.
Stephen Pauker, M.D., M.A.C.P., F.A.C.C.
Leonard M. Pogach, M.D., M.B.A., F.A.C.P.
James E. Puklin, M.D.
Robert L. Steinbrook, M.D.

Industry Representative
Eleanor M. Perfetto, Ph.D., M.S.

Guest Panel Members
Rajiv Agarwal, M.D., F.A.H.A, F.A.S.N.
Daniel W. Coyne, M.D.
Joseph M. Messana, M.D.

00003

Panelists (Continued)

Guest Speakers
Thomas MaCurdy, Ph.D.
Jerry A. Holmberg, Ph.D.
Ajay Singh, M.B.B.S., F.R.C.P., M.B.A.

CMS Liaison
Barry M. Straube, M.D.
Louis Jacques, M.D.

Executive Secretary
Maria A. Ellis

00004

TABLE OF CONTENTS

00005

00006

PANEL PROCEEDINGS

(The meeting was called to order at 8:15 a.m., Wednesday, March 24, 2010.)

MS. ELLIS: Good morning and welcome, committee chairperson, vice chairperson, members and guests. I am Maria Ellis, the executive secretary for the Medicare Evidence Development and Coverage Advisory Committee, MedCAC. The committee is here today to discuss the evidence, hear presentations and public comments, and make recommendations concerning the currently available evidence on the use of erythropoiesis stimulating agents, ESA, to manage anemia in patients who have chronic kidney disease.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record: The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. Each member will be asked to disclose any financial conflict of interest during their introductions. We ask in the interest of

00007

fairness that all persons making statements or presentations also disclose any current or previous financial involvement in a company that develops and/or makes ESAs. This includes

direct financial investment, consulting fees, and significant institutional support. If you haven't already received a disclosure statement, they are available on the table outside of this room.

We ask that all presenters please adhere to their time limits. We have numerous presenters to hear from today and a very tight agenda, and therefore, cannot allow extra time. There is a timer at the podium that you should follow. The light will begin flashing when there are two minutes remaining and then turn red when your time is up. Please note that there is a chair for the next speaker, and please proceed to that chair when it is your turn. We ask that speakers addressing the panel please speak directly into the mike and state your name.

For the record, the voting members present for today's meeting are: Saty Satya-Murti, Phyllis Atkinson, Virginia Calega,

00008

Marion Danis, Susan Levine, Stephen Pauker, Leonard Pogach, James Puklin, and Robert Steinbrook. A quorum is present and no one has been recused because of conflicts of interest. The entire panel, including nonvoting members, will participate in the voting. The voting scores will be available on our website following the meeting. Two averages will be calculated, one for the voting members and one for the entire panel.

I ask that all panel members please speak directly into the mike, and you may have to move the mike since we have to share. There is a TV network broadcasting and recording today's MedCAC meeting. This is in addition to the CMS Webinar and transcriptionist. By your attendance, you are giving consent to the use and distribution of your name, likeness and voice during the meeting. You are also giving consent to the use and distribution of any personally identifiable information that you or others may disclose about you during today's meeting. Please do not disclose personal health information.

If you require a taxicab, there is a

00009

signup sheet at the desk outside of the auditorium. Please submit your request during the lunch break. Please remember to discard your trash in the trash cans located outside of this room.

Also, there is a survey outside on the

table with the handouts. If you would be so kind to please pick one up, fill it out and return it before today is over, that would be greatly appreciated.

And lastly, all CMS guests attending today's MedCAC meeting are only permitted in the following areas of CMS's site: The main lobby, the auditorium, the lower level lobby, and the cafeteria. Any persons found in any area other than those mentioned will be asked to leave the conference and will not be allowed back on CMS property again.

And now I would like to turn the meeting over to Dr. Barry Straube.

DR. STRAUBE: Thank you, Maria. I'm Dr. Barry Straube, I'm chief medical officer for CMS and also the director of the Office of Clinical Standards and Quality here at CMS. The coverage and analysis group, which is one

00010

function in that office, is the lead for the MedCAC and for all coverage decision-making and evidence-gathering in the agency. So I want to personally welcome all of you.

For those of you, and I know many people, I see a lot of familiar faces in the audience, I am a nephrologist, that's my disclosure although I have no conflicts, and so this is of special interest to me personally.

We of course have a history of dealing with erythropoieses stimulating agents in a number of settings. We've been monitoring the use of ESAs in end stage renal disease for a number of years now, and it's linked to our payment and reimbursement oversight. With the advent of a bundled payment system for ESRD, and also the implementation of the first value-based purchasing program in the United States at the federal level, the ESRD quality incentive program, there will be some changes in terms of reimbursement for ESAs in the setting of ESRD.

But we all know that there are 25 million Americans with chronic kidney disease estimated, which is the same number or perhaps even more than patients with diabetes in this

00011

country. And those patients, as many of you know, develop anemia as their chronic kidney disease progresses. So in addition to the 400,000-plus patients on dialysis who are potentially candidates for the use of ESAs, we have a growing number of individuals not yet requiring renal replacement therapy. And so CMS recognizing this, we felt that we needed to

be proactive and start rolling down and analyzing what the current evidence is in order to decide whether or not we need to open up a national coverage decision in the future pertaining to this particular topic. Folks also in the room are probably very aware that we did perform a national coverage decision in the area of oncology, now two years ago, and this came about for reasons similar to this meeting. There were an increasing number of reports that suggested that there was some risk in morbidity and mortality in patients being treated with ESAs in the cancer arena. With continued reports coming out questioning what the ideal use of ESAs in chronic kidney disease, let alone ESRD, that's the reason for this panel.

00012

I want to end with a couple of big statements. One is that this panel is charged here today, and by the way, I'm very proud of the folks who have been picked and accepted to be on this panel and I want to thank them in advance for their service on this panel. We will be looking at the current evidence and the state of the evidence, and Dr. Goodman and Dr. Satya-Murti, who are the chair and co-chair of the MedCAC, will along with staff be talking a little more about process as we go along. This is not national coverage decision-making today. In fact, there is a lot of speculation as to whether we may immediately open up a national coverage decision following this meeting. We have made no decision regarding whether or not we need to open up a national coverage decision on this topic, but this panel is the first step to formally consider whether that needs to be done. So today's efforts are simply to look at existing evidence, for this panel of experts to give their best recommendations to CMS, for us to consider those recommendations in terms of the state of the evidence, and that with

00013

lots of other public input will determine what we do going forward in the future. I did want to mention, for the first time for our MedCACs, Bloomberg News Service has requested that they be able to televise this via Webinar, so we are, it is being recorded and being broadcast via Webinar also. And I believe we also have folks who are on the line listening, they are not able to participate. So we have had some increasing

efforts to try to increase the transparency of these meetings and make them available to the most people.

With that having been said, the last thing I will say is I want to thank Dr. Louis Jacques, to my left, who is the director of the coverage and analysis group, and to the entire team in the coverage and analysis group. This has been difficult in a number of ways to prepare for this and any other MedCAC, so Louis, I want to thank you. Louis is the CMS representative on the panel today, I'm just here as an observer.

With that, I will turn it over to Dr. Goodman. Thank you again.

00014

DR. GOODMAN: Thank you very much, Dr. Straube. Thank you and welcome. We have just this day until 4:30 p.m. for a pretty ambitious agenda, a topic that's complex and has considerable impact on the wellbeing of Medicare beneficiaries and on the Medicare program. With that in mind, we expect that all of our guest speakers, those providing scheduled public comments, any who provide open public comments at that point, and indeed our fellow MedCAC members will be on point and concise today.

As Ms. Ellis mentioned, please do speak into the mike, please be recognized first, and then come to the microphone. If you don't do that, then we won't hear you, and perhaps more important, our trusty court reporter won't hear you. And if he doesn't hear you, what important thing you have to say will not be captured for the record, and I'm sure that you'd like it to be captured in the record because if you're thinking it and want to say it, it must be important.

We have time today for scheduled public comments, and I want to take a moment

00015

just to say something about the scheduled public comments. I understand there are going to be at least a dozen such comments, each of which has been allocated a maximum of five minutes by CMS. And because of our tight agenda today, including the need to hear from all of our speakers and provide for full discussion and consideration, we will need to adhere to those five-minute limits.

And so I and my co-chair, Dr. Satya-Murti, will kindly though firmly suggest that each scheduled speaker think now about

focusing your comments on information that will assist this committee in answering today's voting questions. So if you have been planning to present some material that you soon find out might be repetitive of previous speakers or is merely background information about the organization that you represent, please consider dispensing with some or all of that material and focus instead on what you want this committee to know about the particular matters of the questions before us today. In any case, as Ms. Ellis said, please do heed the traffic light system up there, and

00016

do know that we will proceed to the next speaker once you have used your allotted five minutes.
With that, should we do our disclosures at this point?
MS. ELLIS: Yes, sir.
DR. GOODMAN: I probably have one of the longer ones. I'm Cliff Goodman, vice president of The Lewin Group, and I want to note that The Lewin Group is one of multiple subsidiaries of Ingenix, which is a health care information analysis firm. Ingenix in turn is one of multiple subsidiaries of United Health. I have no financial interests but I do want to disclose that as a salaried employee of The Lewin Group, I was on staff for a study conducted under contract to a company that markets ESA, and this study addressed the impact of bundling costs of end stage renal disease services into a single payment, as provided by MIPPA, which many of you may know as the Medicare Improvements for Patients and Providers Act, which did not address the matter at hand today. Dr. Satya-Murti.
DR. SATYA-MURTI: I'm Saty

00017

Satya-Murti. I am a clinical neurologist and I have been a contractor medical director for a number of years, hence my interest in MedCAC and inclusion. By way of conflicts of interest, one of my retirement plans has a defined portfolio, I don't have a choice where it invests. Two years ago, February-March 2008, I had a one-time consultation on the topic of anemia in ESRD but it did not involve ESA. I have no other conflicts of interest.
DR. GOODMAN: Thank you, Dr. Satya-Murti. Ms. Atkinson.
MS. ATKINSON: Phyllis Atkinson, I'm a gerontological nurse practitioner, private

house call practice. I have no conflicts of interest and nothing to disclose.
DR. GOODMAN: Thank you. Dr. Calega.
DR. CALEGA: My name is Virginia Calega. I am an internist and geriatrician and am employed by Highmark, which is a Blue Cross Blue Shield Association company. There are two conflicts of interest. One has to do with my financial portfolio, in that I do have a financial interest through mutual funds and other agents in these companies. And the other

00018

conflict is that I am in charge of medical policy for Highmark, and as such we have considered ESA agents in our medical policy.
DR. GOODMAN: Thank you. Dr. Danis.
DR. DANIS: I'm Marion Danis. I am a physician and I run the ethics consultation service at the clinical center at the National Institutes of Health, and head our section on ethics and health policy in the Department of Bioethics in the clinical center. I have no conflicts.
DR. GOODMAN: Thank you. Dr. Levine.
DR. LEVINE: My name is Susan Levine. I am the vice president of health technology research and consulting at Hayes, Incorporated. Hayes is a company whose core business is health technology assessment, and I have no conflicts of interest to report.
DR. GOODMAN: Thank you. Dr. Pauker.
DR. PAUKER: I'm Stephen Pauker, with Tufts University, am a professor of medicine there and a cardiologist there. I'm in a group called clinical decision-making, which seeks to make optimized choices, a program for patients and policies. I do have a conflict of interest

00019

here. I'm a taxpayer.
DR. GOODMAN: We share that conflict. Thank you. Dr. Pogach.
DR. POGACH: I'm Leonard Pogach, I'm a physician at the VA New Jersey Healthcare System. I'm attending this meeting today as a private citizen, my opinions are mine alone and do not represent the positions of the VA or any other government agency, and I have no other conflicts.
DR. GOODMAN: Thank you. Dr. Puklin.
DR. PUKLIN: I'm Jim Puklin. I am a professor of ophthalmology in the Department of Ophthalmology at the Kresge Eye Institute at Wayne State University, and I am chairman of the university-wide human investigation

committee and oversee all of their research projects at the university. I have no conflict of interest.
DR. GOODMAN: Thank you. Dr. Steinbrook.
DR. STEINBROOK: I'm Dr. Robert Steinbrook, I'm an internist and on adjunct faculty at Dartmouth Medical School. I have no conflict.

00020

DR. GOODMAN: Thank you. And our industry representative, Dr. Perfetto.
DR. PERFETTO: I'm Dr. Eleanor Perfetto, with Pfizer, I don't have any conflicts of interest, and I do represent the industry on the panel.
DR. GOODMAN: Thank you. And starting with our guest panel members, Dr. Agarwal.
DR. AGARWAL: My name is Rajiv Agarwal, I'm a practicing nephrologist at Indiana University, a professor of medicine, and a staff physician at the VA Medical Center in Indianapolis. I serve on the steering company for a clinical trial that's sponsored by Amgen, and I've consulted once for Hematide, which is an Affymax product. For these consultations I have been paid but I have not received any speaking fees or recent grants. I have received funding from NIH and VA Medical Review for related studies.
DR. GOODMAN: Thank you. Dr. Coyne.
DR. COYNE: I'm Dr. Daniel Coyne, I'm at Washington University, St. Louis, where I'm a professor of medicine in the renal division. I own approximately $2,000 worth of Merck

00021

stock, and in the past I've been a consultant for Amgen and for Roche, and I also received speaking fees from Amgen, Roche and Merck in the past, and have participated in research studies funded by Affymax, Ortho Biotech, Amgen, Merck and Roche.
DR. GOODMAN: Thank you. Dr. Messana.
DR. MESSANA: I'm Joe Messana, I'm an associate professor of nephrology at the University of Michigan, I'm a clinical nephrologist. And a potential conflict of interest for the purpose of this committee includes salary support through Kidney Epidemiology and Cost Center from CMS in support of development of the prospective payment system that's under rulemaking right now. I'm also on the board of directors and medical director of home dialysis for a limited

liability corporation, Michigan Dialysis Services, that provides dialysis care, and insofar as ESAs are a major contributor to the cost of providing dialysis, that's a potential conflict.

DR. GOODMAN: Thank you very much. Now we will proceed to the CMS presentation and

00022

voting questions.

MS. CICCANTI: My name is Maria Ciccanti, I would like to welcome everyone and thank you for attending. I will read the questions to the panel aloud for the record. Later today, as you know, the panel will render their votes on these questions. First let me start by reading the names of the CMS coverage and analysis group and the team members. First is Dr. Louis Jacques, sitting here at the front table, he is our group director. James Rollins, Dr. Rollins is sitting in the front row. Dr. Elizabeth Koller over here to my left, and Kimberly Long, my co-analyst, over there in the front. CMS has called this meeting of the panel to review the available evidence on the use of erythropoiesis stimulating agents, hereafter referred to as ESAs, to manage anemia in patients who have chronic kidney disease, hereafter referred to as CKD. Question number one: How confident are you that there is sufficient evidence to determine whether using a medical intervention, for example blood transfusion, iron therapy or

00023

ESAs, to maintain or raise the hemoglobin or hematocrit levels of anemic CKD patients affects each of the health outcomes below? Exercise or activity tolerance; Vascular events; Patient-perceived quality of life; and Survival. Question number two: For any health outcome listed in question one for which the panel indicates at least intermediate confidence in the sufficiency of evidence, how confident are you that maintaining or raising hemoglobin or hematocrit of anemic CKD patients improves each such health outcome? Intermediate confidence is defined as a mean score greater or equal to 2.5. For any health outcome addressed in question two for which the panel indicates at least intermediate confidence, how confident are you that there is sufficient evidence to

determine whether the use of ESAs to maintain or raise hemoglobin or hematocrit levels of CKD patients improves each such health outcome? Question 3b: For any health outcome addressed in question 3a for which the panel

00024

indicates at least an intermediate confidence, how confident are you that the use of ESAs to maintain or raise hemoglobin or hematocrit levels of CKD patients improved each such health outcome? 4a: How confident are you that there is sufficient evidence to determine whether the use of ESAs to maintain or raise hemoglobin or hematocrit levels of anemic CKD patients worsens any health outcomes listed in question one? 4b: For any health outcome addressed in question 4a for which the panel indicates at least intermediate confidence, how confident are you that the use of ESAs to maintain or raise hemoglobin or hematocrit levels of CKD patients worsens each such health outcome? Question number five: Please discuss any impact of the following factors on the conclusions reached above: a: Whether the CKD patient is undergoing chronic kidney dialysis or is predialysis status. b: Whether the CKD patient has pretreatment baseline hemoglobin levels as

00025

follows: Less than seven grams per deciliter; greater than seven grams per deciliter to less than nine grams per deciliter; greater than or equal to nine grams per deciliter to less than 12 grams per deciliter; or greater than or equal to 12 grams per deciliter. 5c: Whether an appropriate target hemoglobin or hematocrit level has been set for the CKD patient. 5d: Whether the ESA dosing strategy has been implemented to minimize the rapidity of hemoglobin or hematocrit rise and/or oscillations in their levels. 5e: Whether the CKD patient has demonstrated blunted or nonresponse to interventions to raise hemoglobin or hematocrit. 5f: Whether the CKD patient has been evaluated to determine the etiology or cause of the anemia. 5g: Whether the CKD patient demonstrates cardiac, cerebral or other

vascular comorbidities.
5h: Other.
Number six: What clinical trial
00026
designs would be most desirable to fill in any identified evidence gaps?
That's it on the questions, and now I turn this over to Dr. Koller.
DR. GOODMAN: Thank you. Dr. Koller.
DR. KOLLER: Hello, my name is Dr. Elizabeth Koller and I will be making the introductory presentation for CMS. Because time is limited I ask that you hold questions until later.
I will start with some historical background and then move on to an overview of today's data. The coverage of renal disease and erythropoietic stimulating agents, or ESAs, occupies a somewhat unique position in the Medicare program. Patients of all ages with chronic end stage renal disease requiring dialysis were added to the Medicare population by statute in 1972. Many services and supplies, including dialysis itself, blood transfusions and drugs associated with dialysis were covered. ESAs were covered as part B prescription drugs. Within one year of FDA approval of erythropoietin, EPO, the majority of Medicare patients on dialysis were using
00027
this replacement hormone.
Currently Medicare has a national coverage determination for the use of ESA in the setting of cancer but it does not have an NCD for ESA use by Medicare beneficiaries with renal disease in the predialysis stages or in more advanced dialysis requiring, or, you know, in the more advanced dialysis requiring stage.
CMS does have a claims processing mechanism for ESAs which applies to this class of drugs when provided under 1881(b) of the Social Security Act, but not to ESAs provided incident to physician service. This mechanism limits payment for billing claims to hemoglobin levels in excess of 13 grams per deciliter, and for billing claims with high doses of ESAs that are presumed to be erroneous.
With that brief historical introduction, we will now shift gears.
The presence of anemia in renal disease has long been recognized. Although the available data are not directly comparable, there does appear to be a temporal change in the severity of anemia. In the late 1980s,

approximately 75 percent of dialysis patients
00028
had hematocrit values less than 30 percent. Indeed, many had values less than 25 percent, as shown here. By contrast, currently approximately 50 percent of incidental dialysis patients have hemoglobin values less than ten grams per deciliter, or the approximate hematocrit equivalent of 30 percent. This may reflect changes in the patient population composition or management.

What then are the causes of anemia in renal disease? The list here is by no means exhaustive. The major cause is the toxins from uremia which suppress marrow production of red blood cells and attenuates the lifespan of any erythrocytes that are produced. There are blood losses that are associated with the hemodialysis procedure itself. Many patients are also malnourished and lack nutritional elements such as iron, which facilitate or are required for hematopoiesis. Medications such as phosphate binders can have toxic effects. There can also be decreases in the endogenous production of the hormone erythropoietin, or EPO, which is primarily being reduced. In addition, there may be resistance to EPO,
00029
whether it's produced endogenously by the body or exogenously from outside sources, in other words, there's poor dose response. Causes include infection and inflammation, which occur not infrequently in the dialysis and/or diabetes populations.

Of note, anemia of chronic disease is a comorbid condition that can occur in renal patients but it is not directly due to the renal condition. Like the phenomenon euthyroid sick syndrome, the resolution depends upon the recognition of its presence and correction of the underlying conditions. More rarely, anemia can result from poor marrow reserve or marrow fibrosis. These nonrenal causes are generally limited to geriatric patients but can be a diagnostic confounder.

Well, how does anemia, how does renal disease and its severity relate to anemia? The longitudinal data are limited and the cross-sectional data can be misleading. This longitudinal study demonstrates that anemia can potentially be attributed to renal dysfunction only when the creatinine clearance is less than 30, or past 40 milliliters per minute.
00030

Hematocrit levels decline precipitously just before incident dialysis, and rebound partially after the initiation of dialysis with its removal of uremic toxins. By contrast, EPO levels rise in response to the hematocrit nadir and initially decline as the hematocrit levels rebound with dialysis, so in other words, they work in concert. With continued destruction of renal tissue, the capacity for the diseased kidney to produce EPO subsequently declines after months of dialysis. In contrast to the predialysis patient in whom EPO levels respond positively to hematocrit declines from uremic toxins, the dialysis patient experiences loss of EPO production sites, resulting in permanent or near permanent loss of the hormone and its stimulatory effects, thus contributing to anemia.

Well, how is anemia due to renal disease itself treated? The classic treatment has been transfusions. There have been attempts to use androgens. Because of excess cell turnover and nutritional deficiencies, it is important to supply nutrients such as iron and folate. In patients who are EPO deficient,

00031

there is a role for physiologic replacement of the absent hormone.

A recombinant version of the EPO hormone molecule was approved in 1989 for the management of anemia and the reduction of transfusion in renal patients. We, however, have been unable to locate primary publications for several of those studies.

A modified erythropoietin, or with a longer half life, darbepoetin was labeled for the increase of hemoglobin levels. There have been other modifications in the erythropoietin molecule or its incipients, as well as the development of other molecules that stimulate the EPO receptor.

Perhaps, however, the criteria for anemia treatment should be examined. In other words, when should we treat and why?

It has been thought that mortality was greater in severely anemic patients. Data from the U.S. Renal Data System, USRDS would seem to support this. By corollary, it was believed that these outcomes could be reversed by the amelioration of the anemic state, but these data have limitations. They are not natural

00032

history data. Hematocrit entry to the USRDS database depends upon provider input, primarily

by an ESA billing claim. In addition, these observational data did not consider the impact of ESAs and other anemia management interventions.

Well, let us more carefully review the physiologic role of erythropoietin. Since glycoprotein is normally present in the blood at levels of approximately six to 32 units per liter. Anemia and/or hypoxia triggers a series of changes in EPO production. EPO itself activates a number of pathways, red blood cell production in the marrow, improvements in red blood cell survival, angiogenesis, and possibly proliferative effects on the marrow and tissues elsewhere in the body. EPO does this by binding with its classic receptor on precursor cells in the marrow, and possibly non-classic receptors.

Well, how does EPO, endogenous EPO differ from exogenous ESAs? In these graphs the red lines denote the upper boundaries for physiologic levels. Endogenous ESAs, even when given in low doses, result in supraphysiologic

00033

levels of the hormone for extended time periods. This supraphysiologic exposure is even greater at higher doses. This effect is present with subcutaneous administration but is even more prominent with intravenous administration.

How, has ESA use changed since its introduction? Use is greater in all patient populations. Use is greater in less anemic patients as demonstrated by the right axis. The doses are higher, as shown here. Initially it was hoped that ESAs would reverse or ameliorate many of the problems experienced by the predialysis and dialysis patient populations, problems that were attributed to anemia. There was a plethora of exploratory research and subsequent publications. Many of these studies, however, were not structured to definitively answer some of the fundamental questions about renal disease biology and patient management. The majority of the studies compared different ESAs, different routes of administration, and different dosing intervals. Many of the subsequent studies were not randomized, were

00034

too small or too short for hard endpoints. They did not exclude other causes of anemia, they lacked validated thresholds or algorithms for transfusion use. They included less anemic

patients. They did not stratify by drug naive levels, and there was no noted dose titration. For example, the pivotal studies for darbepoetin were active control equivalence studies. The U.S. study was relatively short, at 28 weeks. The use of non-naive patient populations limited the likelihood that a negative outcome could be detected. In addition, outcomes that depend on the duration of ESA exposure, whether they be positive or negative, would not be detected.

A few studies did try to examine the effect of ESAs on exercise and intermediate surrogates for cardiac function. We identified eight randomized cardiac studies. Many of these studies were open labeled and they permitted ESA dosing without limits. And as you can see here, the results here were quite variable.

We identified six randomized exercise studies. The results of these small studies

00035

were also mixed. Curiously, there was a non-ESA study assessing exercise training in renal patients that demonstrated positive benefits, but these did not seem to translate into an improvement in quality of life.

Currently, concurrently with these studies was the emergence of some negative safety signals from observational studies. In the first study by the CHOIR group, low initial hemoglobin values coupled with high EPO doses were correlated with higher mortality rates in dialysis patients 12 months later.

In another study also using the USRDS dialysis but employing different methodology, the authors identified a J-shaped curve outlined here in the yellow boxes. This curve showed increased mortality at both low and high hematocrit levels. They also noted that for a given hematocrit dose, mortality increased along with an increased EPO dose.

Concerns about these types of signals prompted additional studies and a reassessment of the relative benefits of anemia intervention and the types of intervention in various renal patient populations. I will briefly review

00036

four of the longer-term studies that were structured to assess survival in cardiovascular events, the Normalization of Hematocrit Trial, the CREATE study, the CHOIR study, and the TREAT study.

These studies are larger than prior

studies and have hard endpoints. Three of the four were open labeled. Three used erythropoietin. All applied a hemoglobin target. The ESA dose could be adjusted to reach the hemoglobin goal. Three of the studies were conducted in predialysis patients. Other causes of anemia were not rigorously excluded. Some patients with relatively mild anemia were enrolled and patients were not stratified by ESA-free hemoglobin levels. Analysis did not initially include a dose response as a variable, but there was a post hoc analysis of the NHCT that reported that mortality increased with decreased ESA responsiveness. The three studies which included withdrawal information had rates of withdrawal and/or an entity termed early treatment termination of 20 to 38 percent. Three of the studies were stopped early. This

00037

early stoppage had indications for the statistical significance of some findings; in other words, they did not reach statistical significance.

All of the studies show trends towards or frank statistical significance for increased cardiovascular events and/or decreased survival in favor of a lower hemoglobin target rate. In the TREAT study the cardiovascular findings were less prominent for strokes. Higher hemoglobin targets did not improve left ventricular mass in the CREATE study. Changes in the CREATE study were not actually sustained after the first year. And quality of life was not substantially improved in either the CHOIR or TREAT studies. Finally, there was a cancer signal in the TREAT study.

With that brief introduction, we will hear additional data on transfusion, ESA use, and the large clinical trials. These will be presented by Drs. Holmberg, MaCurdy and Singh. Thank you.

DR. GOODMAN: Thank you very much, Dr. Koller, and Ms. Ciccanti before that. Next we're going to hear from Thomas MaCurdy, the

00038

director of Acumen. Dr. MaCurdy, and Dr. MaCurdy, you've got a max of 20 or 25 minutes, I understand.

DR. MACURDY: Good morning. My name is Tom MaCurdy, and I'm a research associate at Acumen, which is one of the centers included in AHRQ's DEcIDE network. What I want to talk to you about today is to just give you a lay of

the land of how ESAs are used by various groups of the Medicare population, give you an idea of what the trends have been on a monthly basis essentially. I would note that this work is supported by AHRQ and in fact we are here representing AHRQ as part of the contract with the AHRQ DEcIDE network as a research facility. This simply lists individuals who worked on the project, and let me just note once again that none of these individuals have a conflict of interest. What I'm going to cover today is to give you a presentation, I will give you some profiles showing how the use of ESA in the Medicare population has changed over time, and essentially I'm going to look starting in the middle of 2006 to the current time, and I thought it would be good to give

00039

you some sense of an overview of what practice and policy events have come along that might, one might infer have a potential impact on ESA use. At the very end of the presentation what I'll do is take the timing of these events and map them to the various trends that we've seen so you can see how they might relate to one another.

The first one here in April '06, and luckily Dr. Koller just described the changes in payment policy and I'm just going to go through those fairly briefly. In April of '06 there was an implementation of policy in EMP, which is the ESA claims monitoring policy. In November 2006 there was the publication of two prominent studies, the CREATE and the CHOIR study. In January 2008 there was a modification of the EMT to further restrict payment or change in the payment rules, as was nicely described to you earlier.

One of the groups we're going to be talking about is those who have cancer. These are the three prominent, or four prominent events that we'll keep in mind when we do the mapping of the profiles of use. The first in

00040

September of 2005, is the BEST study. April 2007 is the cancer national coverage determination, which was a particular change in the payment policy by CMS for those individuals using ESA with cancer. The posting of that policy, the final policy was done in July of 2007, and the full implementation as far as the effect on claims was done in April 2008.

This is an outline slide that I'm going to come back to. You will see that each

time I change topics, you can keep track of where I am in the presentation, and I can as well. What I want to do here is first off cover utilization of ESA in Medicare's kidney disease population, then I want to talk about the use of ESA in Medicare's cancer population related to kidney disease, and then we'll talk about the role of intermittent kidney disease and the use of ESAs, and finally we'll come back, as I described earlier, relating the timing of the practice and policy events to potential impact on ESA use.
The first topic is utilization of ESAs. First of all, I will give you an overview of the size of the predialysis and

00041

dialysis patients in Medicare, and then we'll take a look at the trends of ESA use in those populations.
Just so that everybody is on the same page, this shows the size of the fee-for-service Medicare population. The top line is all Medicare beneficiaries, the second line down is fee-for-service beneficiaries, the line below that is the fee-for-service beneficiaries enrolled in parts A and B. The individuals that form the basic core are those who are enrolled in A and B in the current month, the previous month and the future month. So if you're in that, then you're in our sample and that's, everything I will be talking about through the rates will be based on that group.
Okay. I want to stop here and spend just a little time on how we define various kidney disease status. And so when I talk about individuals being classified by a kidney disease status, this is the slide I will be referring to. I want to start at the bottom rather than the top of this slide, because I think it's easier to start that way to give a fairly clean definition.

00042

What do we when somebody's on dialysis? What we mean by somebody being on dialysis in the current month, it means that we see procedure codes indicating that they did receive dialysis in the previous month, the current month and the future month, assuming they're alive and they didn't receive a transplant in the future month. So if we see that, they're on dialysis. If they're not on dialysis, if we see individuals with diagnosis codes 585.1 through 585.6 in two or three months, including the previous month, current

month and previous month, then we designate them as being on predialysis in the current month. Once again, two out of the three months.

If they're not on predialysis and we observe individuals to have a 585 diagnosis code or 285.21 diagnosis code, and the 285.21 diagnosis code is anemia with chronic kidney disease, you'll see it's a prominent code that shows up, then the individual is designated as having intermittent kidney disease.

So those are our definitions, if they don't meet any of those criteria, they are then

00043

classified as beneficiaries without kidney disease, and I will use that definition throughout.

This shows the size of the fee for service Medicare population by kidney disease status that I just described. This is done monthly. Let me note in the classifications I just described, those classifications are mutually exclusive and updated month by month, so an individual can switch from one month to another, that's important, but in a particular month they are in one of the classifications.

Just for reference, the very top line, the scale for it is on the far right-hand side, that's a very large group of Medicare beneficiaries without kidney disease. You will see that the predialysis group is the one far to this side and it is just below 300,000 per month to almost reaching 500,000 per month.

The dialysis group is relatively stable at about, approximately 250,000 per month, and then the intermittent kidney disease population starts at about 200,000 per month and grows almost to about 300,000 per month.

This is the number of beneficiaries by

00044

stage of kidney disease, the dialysis group to the far right. Anyone classified as Stage I, II, III or IV are the predialysis group typically. And that shows how it started at the beginning of our cycle period, and ends in 2008. One thing I should note on the predialysis definition is there may be many of you that wonder why our numbers look lower than you could get from the Renal Dialysis System.

If we expanded our window from a three-month window to a six-month window, we would increase the number of individuals classified as predialysis by a factor of three, so instead of having something like 600,000 in 2007 to 2008

we would have something on the order of just under two million, so that gives you an idea of how temporary the diagnosis may be. This shows the rate of ESA use by kidney disease status. You see for those individuals who are on dialysis in the top line, it's almost 90 percent receiving ESAs on a monthly basis, so it's very common for them. If you look at the predialysis group they start, about 25 percent are on, are receiving ESAs by month, and that drops down to about 20

00045

percent. If you look at those with the intermittent kidney disease classification it starts a little above ten percent and falls to just a little above five percent. And the blue, the blue row at the very bottom is less than one percent, but let me emphasize, it's not a very large base, so we're going to return to that group later on. This shows the rate of ESA use by chronic kidney disease stage. Let me just emphasize, by chronic kidney disease I mean dialysis and predialysis groups together, and we use that term fairly commonly. It means not intermittent or those who show no kidney disease. And that shows what the rate of ESA use is by these classifications and how it's changed from the very beginning of our period, mid 2006, to 2009. To give you an idea of number of individuals using ESA, this shows the size of the ESA user population by kidney disease status. The largest group, not surprisingly given their high rate of use, is the individuals on dialysis. They start just below, you know, in the order of about 225,000

00046

and rise slightly above that but not much. The next largest group in the middle of 2006 were those individuals who had no kidney, classified as having no kidney disease, but you will see that they fall fairly rapidly over this period, they start around 125,000 and fall to below 50,000 by the end of the period. The predialysis group slightly grows from about 75,000 up to about 80,000, a very slight growth. And you can see that the intermittent group, the group that we're classifying as intermittent kidney disease is low and is relatively stable. This figure essentially shows what the share of ESA users without chronic kidney disease or reporting intermittent kidney

disease, and let me just be very clear. If you take the ESA user population and we remove those individuals who are classified as either in the dialysis group or the predialysis group, then we ask what share of that remainder report intermittent kidney disease, that's what the share is that you see here, and it starts just below 20 percent and then it goes up to 30 percent. So of those individuals who are not

00047

classified with chronic kidney disease, you have a growing share that are reporting intermittent kidney disease.

The last, just for reference because we thought it was an important one to list, that orange line at the very bottom are individuals who are reporting anemia or receiving ESAs but have no 585 codes reported at all. This is the 285.21 code that comes in, and it's not uncommon for a Medicare beneficiary to be receiving ESAs with that code used for classification.

Okay, so what is our summary to this point? The rates of ESA use declined about seven percentage points for the predialysis and the intermediate kidney disease groups, but remained pretty stable in the dialysis group. There's a change in ESA composition of users over time. The dialysis group grew from about 51 percent of ESA users to 65 percent of the population by the middle of 2009, the predialysis group grew from 15 percent to 22 percent, and the intermittent kidney disease group fell from about six percent to four percent, so it remained fairly stable.

00048

Now I mentioned to you that that group that had the small rate of one percent was a large group, and in fact benes without kidney disease, there were about 145,000 ESA users in June of 2006, and it's about 50,000 ESA users in September 2009. So it's a large number of individuals, even though a small rate.

Three-quarters of these ESA users have cancer. So, we want to take a look and give you an idea of what ESA use has been in the Medicare cancer population related to kidney disease presentation I did before, size of the populations and look at trends in use. We use the same classification we had before, we divide the population into the four groups. All these individuals have cancer, so there's a cancer-only group who do not have any kind of evidence of kidney disease. There's the cancer

and intermittent kidney disease group, defined as we did before, cancer and predialysis, and cancer and dialysis, and once again, these groups are mutually exclusive given a particular month.

This shows the size of the cancer populations by kidney disease status. Once

00049

again, the top line is just given there for your reference, it's scaled to the right and there are a lot of individuals, of course, who have cancer but no evidence of chronic, of kidney disease. If you take a look at the red line, the red line shows how much the population of cancer, of those individuals who have cancer and predialysis over time, and it starts at about 30,000 and goes to about 60,000, measured on a monthly basis. Intermittent kidney disease starts just below 30,000 and rises to about 30,000. And those on dialysis are the smallest group here, so it's just above 10,000 and remains relatively stable.

This shows the rate of ESA use in those populations. Once again, not surprisingly, the individuals who have cancer and are on dialysis, it looks like those individuals that are on dialysis, so their rates of use are about 90 percent. The rates of use for individuals in this classification that have, that are in predialysis starts at just about 35 percent and falls to about 30 percent as a rate. And intermittent starts at

00050

about 30 percent and falls to just below 20 percent. And the cancer-only group has small use, it's below ten percent and remains below ten percent all the way through.

This shows the size of the ESA user population with cancer by the kidney disease status. You will see that the cancer-only group, once again, starts out very large in terms of use and falls pretty dramatically, from 100,000 down to in the range of about 30,000 over time. You can see that the groups that have some form of kidney disease are all in about the $10,000 -- 10,000 person range. I'm an economist, so sorry about that. And they rise slightly, with the predialysis almost hitting 20,000, and the intermittent is relatively stable.

To give you an idea of share of cancer patients on ESA by kidney disease status, it gives you an idea about how much the

composition of the population of ESA users changes. Not surprisingly, the cancer-only group falls pretty dramatically. It starts out at 80 percent and falls to about 50 percent. The predialysis kind of grows the most rapidly,

00051

from about ten percent up to 20 percent. Those on dialysis are the next, they start at about ten percent and rise to about 15 percent. Those on predialysis, or those with intermittent kidney disease are relatively stable.

Once again, just like we showed you before, this shows you what the share of ESA users are. Looking at the group that does not have chronic kidney disease but once again, take all individuals who have cancer, remove those individuals who are either on dialysis or predialysis, and then ask the question, what fraction of those individuals report intermittent kidney disease. You can see that this is relatively, it starts at about six percent and goes up to about 16 percent, so this is not really a predominant reason for why those individuals are on ESA. And once again, just for reference, that's the 285.21 code there, to show those are individuals who report no 585 code.

So just to summarize what we know from the cancer population, then, is changes in rates of ESA use for cancer patients with

00052

kidney disease mirrors the changes we saw for the kidney groups overall, so there's nothing special about the group. The kidney disease groups grew sharply as a share of the cancer population using ESAs, the dialysis group grew from nine percent to 20 percent, the predialysis group grew from nine percent to 27 percent, and the intermittent group grew from five percent to nine percent. So once again, even though those populations were falling, the group that was using ESAs and only had cancer was falling more rapidly.

Finally, we want to take a look at the role of intermittent kidney disease in the use of ESAs, because that seems to be a prominent group. This is the size of the ESA user population without cancer, or without chronic kidney disease or cancer. What's in the top two lines are really there for reference, the first one is the beneficiaries without chronic kidney disease and their scale is off to the right as a reference, or excuse me, as total

ESA users and their scale is off to the right as reference, and then the red line is the benes without chronic kidney disease. And the last one is the one I want you to focus on, the lower one, which is, these are beneficiaries that are not classified as having either chronic disease or cancer and are on ESAs.

DR. GOODMAN: Dr. MaCurdy, you have about five minutes.

DR. MACURDY: That's fine, I'm almost done.

If I now look at that group that I just classified, individuals who do not report as having cancer or chronic kidney disease and asks the question, what fraction of those individuals who are using ESA report intermittent kidney disease, you can see that this share grows, 50 percent up to almost 80 percent, so most of those individuals were reporting intermittent status. And just once again for reference, the anemia chronic kidney disease code is, starts at about ten percent and rises to about 20 percent for this group.

Okay. So all I want to do at this point, then, is just take the time profiles for the practice and policy events that we started with, and just map them to the figures you've already seen, just to give you an idea of how the timing kind of goes together. This is putting the, looking at the practice and policy events associated with chronic kidney disease, and maps it against the rates of ESA use for those individuals on dialysis, predialysis and the ones with intermittent, classified as intermittent kidney disease.

One of the main payment policies took place where it was the modification of the EMP in January 2008, which is in the middle. Most of that had to do with not, one would not expect that to have an impact on incident of use but kind of intensity of use. So the fact that one doesn't see much shift in the profile, but the claims changed a fair amount in terms of how many claims were being issued. But in terms of incidence of use, there's not that much difference.

This puts the time line of the practice and policy events mapped against the share of cancer patients on ESA by kidney disease status. You'll see first the posting of the cancer NCD, the national claims coverage determination, and then you can see the final

implementation when the claims took place. You
00055
will see that in fact there was, it started an increase in the trend at the time of the posting of the NCD with regard to the fraction of cancer patients who were on ESAs reporting both dialysis and predialysis. Finally, this takes a look at the individuals who were not classified as having chronic kidney disease, reporting intermittent kidney disease, and that does the same sort of mapping, puts all these together. You'll see that in fact at the time of the initial posting of the proposed cancer NCD, the share of -- I should just note, these two curves basically show the reporting of intermittent kidney disease among ESA users for those individuals that have cancer, report cancer, and those who do not have cancer. And you will see that there is a steady upper trend for the individuals who report intermittent kidney disease without chronic kidney disease or cancer, but it arises for -- and the purple line is the individuals reporting intermittent kidney disease among ESA users for individuals who either have chronic kidney disease or cancer, and you can see that in fact that trend
00056
starts up with the initial posting and then somewhat stabilizes after the final implementation of the payment rules. Thank you.

DR. GOODMAN: Thank you, Dr. MaCurdy. Before you leave the podium, Dr. MaCurdy, just some summary figures, if you would. As of today, or if it must be as of September 2009, how many Medicare beneficiaries are on dialysis? I think your last figure was about 264,000, which was on slide ten, but I just want to make sure we have those rough numbers in mind. So as of today, how many Medicare beneficiaries are on dialysis, is that the 264,000 number there?

DR. MACURDY: Yes.

DR. GOODMAN: Okay.

DR. MACURDY: And that's with our definition, it's really important to emphasize that, because it's not using the 585 code which is often done, say in the renal dialysis data system. It's defined to be an individual who has procedure codes indicating they did receive dialysis for the prior month, the current month and the future month.
00057

DR. GOODMAN: Okay, thank you. So that figure as you have defined is about 264,000.
DR. MACURDY: Right.
DR. GOODMAN: And the percentage of those 264,000 who were on ESAs, was that 89 percent?
DR. MACURDY: That's correct.
DR. GOODMAN: So 89 percent of the 264,000 are on ESAs.
DR. MACURDY: Yes.
DR. GOODMAN: Now, for Stages I through IV, the total number there is something bigger, and I suppose we can do the math, but what is that, about?
DR. MACURDY: Well, one has to be careful with these, because these are not mutually exclusive.
DR. GOODMAN: Well, here's what I want. How many people today in your estimation who are in any of the Stages I through IV are there, roughly?
DR. MACURDY: It would be the red line against the population, so it starts at about, just about 50,000 and grows to about 75,000.

00058

DR. GOODMAN: And those are the number of people in Stages I through IV who are on ESAs.
DR. MACURDY: That's correct.
DR. GOODMAN: So that number, what is it today?
DR. MACURDY: Oh, today, it's about 80,000.
DR. GOODMAN: About 80,000. So 80,000 people Stages I through IV are on ESAs, Medicare beneficiaries, and then those who are on dialysis that number 264,000, 89 percent of those are on ESAs?
DR. MACURDY: Yes, this would give the count here.
DR. GOODMAN: Thank you for that, and thank you for very helpful comments and analysis. Thank you, sir.
Next up is Dr. Jerry Holmberg, senior advisor for Blood Safety, executive secretary of the Advisory Committee for Blood Safety and Availability, from the Department of Health and Human Services. Welcome, Dr. Holmberg.
DR. HOLMBERG: Thank you, and thank the panel and organizers for inviting me to

00059

present today. I will be looking at the supply status, risk, and guidelines for blood

transfusion, and my outline of my presentation is primarily the status of the blood supply, the current risk of blood, activities to monitor adverse events, and transfusion practice patterns and guidelines.

As you can see, on March 5th when I prepared these slides for CMS, and by the way, panel, I don't know if I have enough time, so I will be going through these slides very rapidly, and you I believe have had a pre-meeting copy of that, so there will be some slides that I will omit.

DR. GOODMAN: Rather than going through them rapidly, yes, do hit the high points, thank you.

DR. HOLMBERG: We do have a system within the HHS called our blood availability and safety information system, and based on this in collaboration with the blood centers across the United States, we are able to determine the days of supply and an estimate of how much blood is available of each blood type within the United States. You can see on the,

00060

in the yellow block there, those are blood centers in which there are days of supply, and as far as the estimated hospital, we estimate that there is approximately six days of supply within the hospitals. As a total of blood available, it would be 661,000 units of blood available on March 5th. As you can see in our system, this is the hospital reporting where we have some sentinel hospitals and the average is about five days of supply or a little bit better than five-day supply, pushing six days on some days of the week.

We also collect a lot of data, the blood collection and utilization survey data, and this is available on the HHS website with the link down below.

I do want to point out that the NBCUS does also capture the cost of blood throughout the United States, and the average cost of red cells is about $214, this is the cost to the hospital. Of course in patients, this would be grouped together with the DRG under the HOPPS reimbursement. In 2006, this was $163.

There are over 30 million units of blood products that are transfused, about 14.6

00061

million red cells transfused during 2006. We're about ready to release our 2008 data very soon, by this summer we will have that information out.

I just want to show you also the differences between the collection and the utilization. You can see that the amount of blood that was collected was approximately 1.6 units -- I'm sorry, 14.6 million units of blood, and you can see the amount transfused there, and there is a gap of about 1.3 surplus of blood throughout the year. We only lost 150,000 units of blood to testing. This would be infectious disease testing and also donor screening testing.

This is a very important slide to look at. The top line is actually the collections based on an age population of 18 to 64, which we have about 84 per thousand. And then in the transfusion, 2006 is 48.9, and this is 48.9 per thousand recipients. What I've done is actually compared this across the world really, and I just want to show five countries that I do have significant data and references for. And you can see that in 2001 the U.S. was 48,

00062

and 48.9 in 2006. England, which has a lot of very strict guidelines, is about 45. And Australia, that has very elaborate guidelines, is down to 28. But Denmark, that also has guidelines, but may be a little more liberal in their transfusing of blood products, has a transfusion per thousand population of 58.6, and Sweden has 45. You can see that the majority of the recipients in the developing world is primarily those individuals in the elderly bracket.

The blood is tested for quite a few parameters and as you can see here, the list of the various testing that takes place. HIV-1 and 2, HTLV I and II, map testing for hepatitis C, and for HIV, West Nile, and hepatitis B testing. The risk is approximately, for HIV, one in two million. Also for hepatitis C it's one in two million, and hepatitis B is about one in 205,000 to 488,000. This is primarily because we have not migrated to nucleic acid testing in the United States.

Other risk factors to consider in transfusion is transfusion related to acute

00063

lung injury. This can be due either to human leukocyte antibodies or human neutrophil antibodies. Also, there have been deaths reported due to hemolytic transfusion reactions, both ABO and non-ABO, microbial infections, transfusion-associated circulatory

overload, graft versus host disease, anaphylaxis. And although we don't have any deaths reported as a result of antibodies, which you all might be familiar with, because the panel reactive antibodies, that's very variable so it is a risk factor. Here we have the FDA fatality reports up through 2008. This will be put on the web soon, and you can see that the majority of cases in 2008 of deaths related to transfusion, the majority were related to TRALI, and you can see that anaphylaxis is down to three, TACO three, and hemolytic transfusion reaction, ABO and non-ABO are seven and ten respectively. The seven microbial infections are really primarily infection, microbes in the New England area. What we do as far as monitoring for adverse events, we have just rolled out the

00064

hemovigilance program through the CDC national health care safety network and we are looking at that, this is a passive surveillance system. We also have had through the AHRQ system the patient safety organization AABB, the professional organization does report through that, and we also have the ability through FDA and CMS looking at databases to look at the Sentinel Initiative. And finally, I just want to bring to your attention that we do have the Joint Commission on Blood Measurement Elements. The joint commission is just rolling out, they're doing pilot testing at the present time looking at both blood measurement elements. One of the things that was considered in those parameters was to actually look at the target or the trigger for transfusion and what the hemoglobin level should be, but in the pilot stage that was not included. So we're in hopes that later on that that will be included, and I serve as a panel member on the blood measurement element technical panel. I just want to highlight some transfusion practices, and this actually comes

00065

from not only the American Red Cross but also from Mollison's Blood Transfusion text. This has been edited by Dr. Klein, of the NIH, who runs the transfusion medicine department at the clinical center. And I just want to say that transfusion is rarely indicated when the hemoglobin level is above ten, and is always indicated in patients when the hemoglobin is

below six. The determination of transfusion whose hemoglobin level is between six to ten grams per deciliter should be based on any ongoing indication of organ ischemia.
The Australians as I mentioned, with their ratio being so low and their parameters that they look at, you can see here that the use is likely to be inappropriate when the hemoglobin is greater than ten, and really it may be appropriate when hemoglobin is in the range of seven to ten, but the use of red cells is likely appropriate when the hemoglobin is less than seven.
This is from the British Journal of Haematology in 2001, and I think this really is an important point. And that is that chronic anemia is better tolerated than acute anemia

00066

because of better oxygen delivery association, and an increase in 2,3 DPG, which is responsible for releasing the oxygen to the tissues. This release of the oxygen causes a shift in the oxygen association curve, so it's much better handled in chronic anemia.
The reserve of oxygen carrying capacity is such that cardiac output at rest does not usually increase until the hemoglobin concentration falls below seven grams.
DR. GOODMAN: About another minute, Doctor.
DR. HOLMBERG: Okay. I just want you to take a look at the guidelines established in the University of Iowa, and they very clearly lay out some guidelines there on renal disease and you can look at that for yourself.
What I would like to really, in closing, just for you to consider, I think that one of the panel members, Dr. Steinbrook, in his paper in 2007 related to unfinished business, including completing and reporting on better safety studies assessing the risk of ESA as compared to blood transfusions, understanding the relationship with

00067

erythropoietin dosage to hemoglobin and cardiovascular risks. And also in Unger's paper just this last January, Erythropoiesis Stimulating Agents, Time for a Reevaluation, the need to establish through randomized controlled studies the optimum hemoglobin target, dosing algorithm, and monitoring approach for patients with anemia with chronic kidney disease, and conservative hemoglobin values well below 12 should be evaluated.

Thank you.
DR. GOODMAN: Thank you very much, Dr. Holmberg, very helpful.
Next, we have and welcome Dr. Ajay Singh. He is a physician and renal chief at Brigham and Women's Health. He is also an associate professor of medicine at Harvard Medical School. Welcome, Dr. Singh.
DR. SINGH: Thank you. My goal this morning is to discuss the use of ESAs in treating anemia in non-dialysis and dialysis patients. I hope to convince you that the best body of evidence with respect to safety of these agents are in fact the four randomized controlled trials that we discussed.

00068

A number of you have looked at, and the summary documents with respect to safety from the FDA for both epoetin and darbepoetin, and I think you recognize that there is limited published evidence on safety in those documents, and I think the RCTs now represent the best evidence.
I will try and discuss with you the fact that hemoglobin in fact now, based on this evidence, is an unreliable surrogate for outcomes, making the argument that in fact a surrogate should not only correlate with the true clinical outcome, but also fully capture the net effect of the treatment on clinical outcome, and I submit to you that hemoglobin does not do that.
And third, I will discuss with you the importance of shifting our focus away from hemoglobin targets and more in the direction of the safety of ESAs in this population.
Now if you look at what's going on in the field, at least a bird's eye currently, we now have in fact over a 7,000-patient experience from randomized controlled trials in both dialysis and non-dialysis CKD patients.

00069

They demonstrate collectively that there is either no benefit, or an increased risk with targeting a higher hemoglobin, but that using ESAs to target a higher hemoglobin, raising that hemoglobin either results in no benefit or increased risk of mortality and cardiovascular complications.
Since the launch of ESAs in 1989 there have been a number of FDA actions, including warnings and a black box, and now we have an FDA review panel later this year, and there's also a REMS strategy, a risk evaluation

management strategy with respect to cancer-induced anemia, reflecting FDA's growing concern about the safety of ESAs.

We have pending before us potentially new guidelines from the international guideline group in kidney disease, and of course, as Dr. Straube mentioned, in January 2011 there will be changes in the reimbursement of dialysis that will potentially reflect on ESA utilization.

Now this slide, I think, captures my point about the fact that hemoglobin is not a reliable surrogate. If you look at the point

00070

estimate of risk in the direction of harm from the four randomized controlled studies, the Normal Hematocrit study showed a 30 percent increase in risk of mortality or nonfatal MIs, CREATE a 22 percent increased risk, CHOIR a 34 percent increased risk, and TREAT a five percent risk.

Remember, a surrogate to be reliable needs to have both a correlation with outcome, but also capture the effect of intervening on that outcome, and this evidence in fact suggests that it does not do that, and I think we have to conclude that hemoglobin is really not a good surrogate for outcome, and there are many examples in medicine that share that characteristic, HDL being one, blood pressure perhaps being another.

There have been, has been some data with respect to potential benefits of ESAs in treating anemia, and these have been discussed in more detail by the preceding speakers. One of the benefits that I think many of us have seen in some of the published literature and potentially in clinical practice, is the issue of reducing blood transfusions.

00071

And I think it's true that the four randomized controlled studies did demonstrate that there was a higher rate of blood transfusions in patients randomized to the lower hemoglobin arm than to the placebo arm of the various trials. But I think as you go through or navigate yourself through the data, you will see that in fact there was no protocol or algorithm for transfusion in these trials.

If you read the information and protocol from these trials, it was unclear when investigators at various sites transfused patients. There was no validated hemoglobin threshold for transfusion and it's unclear, and in fact the

preceding speaker discussed this. There's guidelines saying it could be seven, it could be eight, it could be nine, ten. There really isn't any good sense about it and it wasn't there in the trials either. And in fact, the quality of data collected on who received transfusions is limited, so I would argue that we need to be cautious in interpreting the transfusion data from these clinical trials. With respect to health-related quality of life or patient-reported outcomes, I think

00072

the general conclusion that I will share with you as we march through these trials in the next few slides, there was an inconsistent improvement in quality of life in all of these trials. In Normal Hematocrit, in fact, between group differences in quality of life were not reported, only improvement in quality of life in one instrument as an e-mail was corrected. In CREATE, as we'll discuss, it was inconsistent in terms of timing and the design. In CHOIR, there was no benefit from three different instruments. And in TREAT there was moderate benefit for one instrument and no benefit for the others. The data on quality of life from these trials is limited. There's been no consistent benefit across instruments. Mostly the data originates from open label studies. The data doesn't necessarily suggest sustainability over time; so for example, in CREATE improvement occurred in year one, but that attenuated in subsequent years. In some of these trials the design mitigates the significance of the health-related quality of life data. Many of the trials, and this was noted in the FDA

00073

review, there was selective reporting of domains, and many of the instruments were not in fact validated for use in patients with kidney disease.

So let's march ourselves through the evidence. This has already been discussed and alluded to by Dr. Koller, but I will make some preliminary comments on these studies. Four randomized controlled studies. 7,000-patient data experience covering the gamut of kidney disease. Normal Hematocrit, symptomatic dialysis patients, where the patient population reflected the analyzed mortality of the dialysis population. Three studies in non-dialysis chronic kidney disease patients, CREATE, CHOIR and TREAT.

What's remarkable about these studies, the first three studies, Normal Hematocrit, CREATE and CHOIR, were studies that tested drug versus drug in both arms. In TREAT, the remarkable thing about TREAT was 20 years after the launching of this drug, we have a placebo-controlled trial which tested drug versus no drug.

In the Normal Hematocrit study, the

00074

hemoglobin threshold for the low arm was nine grams. It's important to remember that. A lot of people have quoted ten grams but it was nine grams in the low arm. CREATE was 11.6 in the low arm, CHOIR, 11.3, and in TREAT, nine grams.

Let's look at the Normal Hematocrit study. This tested the hypothesis that patients with normal hemoglobin, 13 to 14, will have better outcomes than patients with a lower hemoglobin. 1,233 hemodialysis patients at high risk for coronary disease or heart failure, and the primary endpoint was death or myocardial infarction. This study was terminated early due to increased risk.

Another important point. Some of our data was, the relative risk of 1.3 with a nonsignificant p-value suggests that it would suggest a trend. But in fact the DSIB in this study, and this was noted in the New England Journal, stopped the study because they were concerned about safety.

There was also a higher rate of vascular thrombosis in patients in the Normal Hematocrit study and they noted a higher rate of thrombotic events in general.

00075

Now I want to bring out two important points. In Normal Hematocrit not only were we testing a higher hematocrit versus a lower hematocrit, but a higher exposure decremental point versus a lower exposure, 460 units per kilogram in the normal arm, 160 units per kilogram in the low hematocrit arm. Higher rate of deaths, higher rate of nonfatal MI in patients who were normalized.

Now the next block below that, I took out this data, unpublished data from the FDA document that reviewed these studies. They talk about the nonfatal MIs, 3.1 percent in the high arm, 2.2 percent in the low arm. Look at the next line. The incidence of CVA, strokes, 39 percent in the high arm, 29 percent in the low arm. It's important to remember that, because in TREAT you have higher rate of stroke

in patients in the active treatment arm, and it was also observed in the Normal Hematocrit for the dialysis population. In fact, it was also observed in the Canada-Europe Study, higher rate of stroke in patients randomized to the higher arm.
There was also a higher rate of
00076
thrombotic events, 22 percent in the high arm versus 18 percent in the low arm. Remember, one of the common features of many of the studies of using ESA is higher rate of thromboembolism.
Let's move to the next study, the CREATE study. 600 patients, 100 centers, mostly European, used an agent that is not used in the United States but is an analog of erythropoietin or epoetin-alfa, epoetin-beta, a study that was sponsored by Roche. Patients were randomized, and CREATE had an interesting study design and it's important to note this.
It was not only looking at high versus low target hemoglobin, but it was early treatment versus late treatment. The early treatment versus late treatment is important to recognize when we interpret the quality of life data for the study, and I will come to that in a minute.
So the early treatment high target arm was 13 to 15. 10.5 to 11.5 was the regular treatment arm. Good separation. 13.49 grams per deciliter of hemoglobin was achieved in the upper arm. 11.6 grams per deciliter was the achieved hemoglobin in the low hemoglobin arm.
00077
All that separation in hemoglobin, what effect did we see in outcome? There did not appear to be any benefit, and in fact a trend to increased risk. So survival in the high arm, which is in the pink curve, is worse, 22 percent worse with a hazard ratio in the direction of harm of .78 in those individuals targeted to high use of epoetin-beta dose and a higher target hemoglobin. The epoetin-beta dose in this study was approximately 4,000 in the high arm, 2000 in the low arm.
Another important observation from this study was the effect on renal outcomes and what CREATE documented and presented in the paper, there were more dialysis events in those patients randomized in the high hemoglobin arm, 127 events verus 111 events, a hazard ratio in the direction of harm of .76 with a p-value of .73, so again, increased risks with targeting a higher hemoglobin in patients with ESA.

Now what about quality of life? In CREATE in the first year, quality of life did improve. This is data from the use of the SF-36. You see six domains reported here and you can see in group one, in this green, that

00078

it was an improvement in quality of life across the board. And in group two, remarkably there was a reduction in quality of life across the board. However, it's important to note because of the design of CREATE, you have to be cautious in interpreting the data. Patients, A, knew which arm they were randomized to, so this is an open label study. Second, and this has been pointed out by Dr. Coyne in an editorial, in the first year 98 percent of patients in the high arm received injections, whereas only 32 percent of patients in the low arm received injections. And so if you're sitting there and you're not getting injections, perhaps you might think that your quality of life is not going to improve. Also, the low hemoglobin patients had to develop worsening anemia prior to therapy before they were started on therapy. Furthermore, these changes attenuated over time, they went away in the second year of the study, so it wasn't sustainable.

Let's move to the third study, this is the CHOIR study. 1,342 studies, randomized in 130 centers. It was a U.S.-only study and

00079

looked at the effect of epoetin-alfa in raising the hemoglobin in patients to a high target of 13.5 grams versus a low target of 11.3 grams. Median follow-up was for 16 months. In these two panels, what you see on the right are the epoetin doses, and on the left you see the mean achieved hemoglobin. On the right you see the mean weekly dose of epoetin in the high arm of 11,215 patients, and a mean weekly dose in the low arm of 6,276, and in fact this was a skewed distribution and the median doses were 11,215 and 6,270, so there was a difference in the median and the mean for the epoetin dose. Look at the separation. 12.6 achieved hemoglobin in the high arm, 11.3 in the low arm. And so the question was, in this intervention here, high dose of ESA, raising the hemoglobin to 13.5, the question was, was that associated with benefit? This is the composite endpoint of death, nonfatal MI, CHF hospitalization and/or stroke. And you see that there were 125

composite events for those patients randomized to the high arm, versus 97 events to the low arm, a hazard ratio of 1.337, so a 34 percent
00080
higher risk with a p-value of .03, statistically significant. So, no evidence for benefit; in fact, evidence for increased risk. What explains this? The two components of the primary endpoint appear to explain this composite endpoint, and those two were death and CHF or heart failure hospitalization. Looking at the data for death, you can see there were 65 deaths, and there was a higher rate of death in those patients randomized to the higher hemoglobin arm versus the lower hemoglobin arm with a hazard ratio not reaching statistical significance of 1.48. Similarly for CHF hospitalization, about a 40 percent increase. There was not a significant increase in the rate of stroke between the two arms, and not a significant increase in the rate of myocardial infarction in the two arms. What about quality of life? In CHOIR this assessment of quality of life was limited, as has been pointed out, by the fact that it was an open label study, and we all recognize the importance of blinding in reporting patient reported outcomes. Three instruments we used,
00081
LASA, KDQ and SF-36. LASA is a scale, a visual scale which is used mostly in cancer patients, not able to be validated in kidney patients. KDQ, SF-36, more validity in kidney patients, and the SF-36 probably has the best validity in patients with kidney disease. Quality of life increased in both groups, the high and the low arms, but there was no statistically significant difference between the two arms. And so if you look at improvement, in LASA it was about 11 points, in SF-36 it was between nine to ten points on average, with improvement in quality of life in both groups, but no significant difference between the two groups. Was this sustained or were there changes over time? These are longitudinal analyses of fatigue and the next slide is of vitality, and if you look at the longitudinal analysis between the high group and the low group, very little difference, p-value of .52. If you look at vitality, very little difference with a p-value of .7, really no difference over time between the two arms of the study. The

quality of life certainly improved in both
00082
arms, but it didn't matter whether you were in the high arm or the low arm.
The fourth study, the most recently reported study, a study reported in the New England Journal of Medicine, fall of 2009. Dr. Pfeffer is the PI of this study, and TREAT tested the hypothesis that in patients with type 2 diabetes, chronic kidney disease not requiring dialysis, and concomitant anemia, would raising of the hemoglobin with darbepoetin lower the rates of death and cardiovascular morbidity, and/or death and end stage renal disease. So this was, again, asking questions with respect to hard endpoints. Important, though, this was a placebo-controlled double blind study. Recognizing the limitations of some of the other studies with respect to being open labeled, this had the advantage of being a double blind study.
Now, it was an international study, multicenter, 620 centers. We've discussed the double blind and the placebo nature, randomization between the active arm and a control arm. The active arm aimed to achieve a
00083
hemoglobin of 13 grams. The placebo arm had a rescue element to it, so if you dropped below nine grams per deciliter you were rescued with a small dose of RMS, with a resumption of the placebo if the hemoglobin once again went above nine.
It was blinded, which was really important, and there were these two composite endpoints that we discussed, the cardiovascular and death endpoint and a renal composite endpoint.
If you look at the separation in terms of hemoglobin, you can see the study was successful. Within six months you have good separation between the two arms. The median hemoglobin in the higher arm achieved was 12.5 grams per deciliter and the median hemoglobin in the lower arm was 10.6 grams per deciliter.
Look at the doses of darbepoetin. In the upper arm it was, 176 micrograms was the median dose, with a mean dose of 225 micrograms. In the low arm a median dose of zero micrograms, mean dose of five micrograms. So less than half of the patients received, were exposed to darbepoetin, and if they were
00084

exposed they were exposed to very small doses, because the drugs were stopped.
I'm going to quickly march through, because this is in your packet, the endpoints analysis. These are the composite endpoints for both cardiovascular and renal, and the important point here is there is no difference, this trial was neutral for the primary composite endpoints that we looked at, cardiovascular composite or the renal composite, no benefit in a placebo controlled study of raising the hemoglobin with darbepoetin. All cause mortality, no difference.
So in a placebo controlled trial, there was no benefit in hard endpoints of treating patients with an ESA and raising their hemoglobin.
This is an important finding. Some people have argued, well, this is not something we need to worry about. I would submit to you that having a stroke, or having a twofold increased risk of stroke is important. 101 patients randomized to the darbepoetin active treatment arm had a stroke. 53 patients

00085

randomized to the placebo arm had a stroke. A twofold increase, hazard ratio of 1.92, which was highly statistically significant and you can see the data there.
There was a, seemed to be a malignancy or a cancer-related signal, although the numbers were small and we need to be cautious in interpreting this data. If you look overall between the darbepoetin group and the placebo group, cancer-related AEs and death attributed to cancer did not seem to be statistically significant, although the rate of death from attributed cancer was higher than that in the placebo arm but was not statistically significant.
However, in the subgroup where patients when they enrolled in the study checked off whether there was a baseline history of malignancy, there were 348 patients enrolled that that happened. Overall mortality was slightly higher but not significant, but look at deaths attributed to cancer. Small numbers of patients, but 7.4 percent versus .6 percent. This data is commensurate with the data that we've been seeing from the cancer

00086

field where the treatment with ESAs appears to be associated with the worse outcomes in

patients with cancer, mostly from summary meta-analysis data in cancer. What about quality of life? Now remember, TREAT was a double blind study. In TREAT, in patients randomized to the darbepoetin arm the FACT-Fatigue, which is a visual analog scale, there was 54 percent of the patients, about half the patients had an improvement in quality of life of greater than three on this FACT-Fatigue, and the three is a significant, viewed as a significant or meaningful increase. Approximately 50 percent, 49.5 percent of patients of those in the placebo arm had an improvement. There was an improvement but it was a modest improvement and a modest difference between these two arms. Now as I discussed with you, the SF-36 appears to be a more validated scale for measuring quality of life, health-related quality of life. In these two prespecified domains, energy and physical function, there was no difference. There was no difference in the double blind placebo-controlled trial of

00087

improvement in quality of life with respect to SF-36. Well, you can step back and say what explains these differences. If you look at these four trials there seems to be heterogeneity in the clinical signals. In Normal Hematocrit, more vascular access, MIs, death. In CHOIR, heart failure deaths. In TREAT a higher rate of stroke, perhaps a higher rate of cancer-related deaths. What explains this? And if you, again, look at this, you can speculate about what might be the reason for this. One might be that there's a class effect. These agents are different in terms of, if you take them and put them on a western body, you will see there are different smears, and we will discuss that in the next slide. They were exposed to different doses, or levels of doses of ESA. In CHOIR, very high doses of ESA were used. In TREAT, fairly high doses were used in the high arm, virtually none in the low arm. And in CREATE, medium levels of dose, a medium dose of about 5,000 units in the high arm, 2,000 in the low arm.

00088

They were all different populations. In TREAT they were all diabetics, mostly type 2 diabetics, in CHOIR, 50 percent of the patient population were diabetics, and in TREAT 25

percent of the patients were diabetic. Could the differences in the population, differences in the type of agent, differences in dose, have accounted for the heterogeneity of the signal? So should we condemn the data and say well, this is a fuzzy mix of different signals, or should we say that because these trials enrolled different populations, all the trials showed increased risk but there was some heterogeneity in the type of signal? This just shows you a molecular comparison between darbepoetin and recombinant erythropoietin alfa, darbepoetin is shown on the right, erythropoietin alfa on the left. You can see different molecular weight, 30,000 versus 37,000; different glycosylation, 40 percent carbohydrate versus 51 percent carbohydrate; different half life injecting into mice; different receptor binding and different effect in terms of their bioactivity, not huge differences, but some difference.

00089

What explains the higher rate of adverse outcomes in these randomized controlled studies potentially, again, speculation perhaps? Could this, as some people have argued, could this be iron exposure? In the Normal Hematocrit study much was made about the issue that patients in the higher arm were exposed to large amounts of iron. Well, go back and look at that literature, and I've done that. The ascertainment of iron exposure in the Normal Hematocrit study was done post hoc, and this has been discussed in the literature by Dr. Vesera, and he himself concedes in the literature that the evaluation of iron exposure was, at best, had limitations. In the other studies, no real evidence to suggest iron exposure was responsible. In TREAT in fact, more patients were exposed to iron in the placebo arm. Not much difference in CHOIR in iron exposure between the two arms. What about a rapid rise in hemoglobin, as Dr. Unger suggested from the FDA in a recent New England Journal perspective article? I discussed this in more detail in the C. Jason editorial which is on line which you can get

00090

access to. But really firstly, hemoglobin itself, I would argue, is an unreliable surrogate, and I would argue that rapid rise in hemoglobin is an unreliable surrogate. But when you look at the unpublished FDA analysis, there is a correlation with not only rapid rise

in hemoglobin, but in fact a much stronger correlation with a rapid decline in hemoglobin. So what do we make about that? We need more data.

What about blood pressure? No significant difference between the two arms. Slightly higher diastolic pressures in TREAT and perhaps in CHOIR, between the high versus low hemoglobin arms.

ESA versus hemoglobin as a reason for this. In one of these trials, and in practice I believe, we use non-physiologic doses of ESA. 300 times the levels are achieved when you treat patients with ESAs than the physiological level, so clearly the non-physiologic levels of ESA could not be a reason.

What about activation of EPO receptors in non-hematopoietic tissue beds? We know that there are normally high affinity receptors in

00091

the bone marrow but there are low affinity receptors in the endothelial cells, in the heart and other tissue beds. Perhaps activation of those with high doses of ESAs may account for some of the clinical signals.

An interesting signal from the -- if you look at the FDA summary document for approval of epoetin, in that document you will see that there is increased marrow fibrosis in patients exposed to ESA in animal studies. This is in the original document. Perhaps there are other signals even within the bone marrow that we have not adequately studied and need to be scrutinized in greater detail.

And then perhaps high hematocrit itself may be a problem with activating endothelial cells in platelets.

Now, I wanted to share with you a couple of post hoc and observational studies. In CHOIR we have published a study that looked, and tried to flesh out whether this was an effect of hemoglobin or an effect of ESA dose in accounting for this increased risk. This analysis, what you see is an analysis of what happened, or correlated achieved hemoglobin,

00092

not targeted hemoglobin, achieved hemoglobin and outcome. Similar analysis was presented for Normal Hematocrit and published.

In the high hemoglobin high EPO arm on the right of your screen, group A, you see that achieving a high hemoglobin was associated with a better outcome than in fact achieving a low hemoglobin, turning on the effect of

potentially hemoglobin. Similarly results for the low hemoglobin arm. So perhaps there is also a difference between achieving and targeting the hemoglobin, and what we have reported is that in patients who are not able to achieve a high hemoglobin, the hyporesponsive group exposed to high doses of ESAs, those are the ones who seem to do the worst in terms of outcome.

And if we try to plot that in this analysis here, which was published by Linda Szczech, you can see a relationship between ESA dose and outcome. So on the vertical axis there is a low hazard ratio for the composite endpoint of mortality and cardiovascular complications, and on the horizontal axis is the EPO dose exposure from zero to 25,000

00093

units, and you can see that there seems to be a relationship between exposure to ESA dose and outcome, the higher the ESA dose, the worse the outcome.

This data has been discussed by Dr. Koller. This was an observational analysis by Dr. Carter and his colleagues published in AJKD in 2004, suggesting again, that ESA dose appears to be an independent factor in influencing outcome at any strata of hematocrit in a dialysis population. Again, speaking to the possibility that there may be an independent relationship of ESA dose and outcome, that we have hitherto not paid sufficient attention to.

This is a paper by Alan Brookhart and colleagues published recently in JAMA, which was a center level analysis, a very clever analysis trying to do the natural experiment using observational data. Sample size was 269,717 patients, looked at anemia protocols in 4,500 dialysis units, and the bottom line conclusion was that in those patients with a higher hematocrit, exposure to hire ESA doses was associated with worse outcomes.

00094

So, I would submit to you we have four clinical trials to suggest increased risk, that suggest that hemoglobin is not a good surrogate outcome, and now emerging evidence to suggest that exposure to high doses of ESA independently predicts worse outcomes in our patient population.

So in conclusion, the randomized controlled studies, I believe, demonstrate increased risk with targeting a higher

hemoglobin, remembering that targeting a higher hemoglobin embodies both a higher hemoglobin, whether it's achieved or not, and exposure to high doses of ESA.

Secondly, observational analysis, the Brookhart study, the Zhang study, and there are other studies that have been published, and secondary analysis of the randomized controlled studies that I shared with you, the CHOIR secondary analysis, shows that the risk does not appear to be just associated with hemoglobin, but appears to be, that there is a difference between targeted hemoglobin and achieved hemoglobin. Patients with higher achieved hemoglobin seem to do better than

00095

patients with a lower achieved hemoglobin.

I think I've shared with you the fact that the quality of life data across these four randomized controlled studies is inconsistent, and I think you have to be careful with its interpretation, particularly with respect to the CREATE study because of its design.

I shared with you some data that dosage of ESA may be associated with outcomes, the higher the level of ESA dose the higher the risk.

I believe that there is evidence for a hemoglobin threshold of greater than nine. Nine was the level in TREAT, nine was the lower level in the Normal Hematocrit study. Nine in my opinion is where the evidence is. I'm not sure where ten has come from that a number of people have adopted.

And I believe that there may be some evidence to suggest that we should focus on reducing ESA dose.

Just a little in wrapping up. Why should the hemoglobin be greater than nine? Because Normal Hematocrit and TREAT used nine. Raising hemoglobin from nine to higher levels

00096

is not associated, I believe, with clinically meaningful improvements in quality of life.

Why have I not talked to you about a higher or upper hemoglobin target? Because I don't think that the randomized controlled studies have adequately confirmed that there is a band of safety above nine. All we know is that above nine is where you need to be in the randomized controlled studies, we don't know what the higher end is. And there is, as I said, some data that suggests that higher achieved hemoglobins may actually be

beneficial. Avoiding ESA or using lower ESA doses, why? Because I think the observational data and the prospective analysis in the RCTs suggests there are risks associated with ESAs. ESAs are pleiotropic cytokines, they are hormones. They activate the higher affinity receptors not only of the bone marrow, but lower affinity receptors elsewhere. We don't understand enough about what activation of these receptors involves. I think data from Cancer, a spine study by Stovall from the Mass General, and in

00097

critically ill patients that Cohen published in the New England Journal, all collectively suggest that the worries we have about ESA use in CKD patients are worries that patients in other populations also have, and have been reported. I would like to stop at this point, thank you.

DR. GOODMAN: Thank you very much, Dr. Singh. Dr. Singh, we expect that you will be here for the balance of the day; is that correct?

DR. SINGH: Yes.

DR. GOODMAN: Thank you. We're a little bit behind schedule, so what we will do now is take our 15-minute break, understanding that all of the speakers from whom we heard this morning will be available later today. Let's take our 15 minutes, see you then. Thank you.

(Recess.)

DR. GOODMAN: We're going to reconvene now. All right then. I want you to take note please, in our agenda, we will next go to our scheduled public comments. I do know that

00098

following our scheduled public comments, there is time for open public commence. However, no one has signed up for that open public comment period, and if no one has signed up for that, we will move on to the next item in the agenda. Okay? So if you think you missed signing up for public comments, I suggest you do that immediately; otherwise, we're going to be going past it, and I'll ask Ms. Ellis to check on that before we hit that point in the agenda. Our first scheduled speaker is Dr. Marc Pfeffer, and he like all others will have five minutes, which I'm told is 300 seconds. Dr. Pfeffer, welcome, and you're on,

sir.
DR. PFEFFER: Thank you. My name is Marc Pfeffer, and I'm a cardiologist from the Brigham and Women's Hospital and Harvard Medical School. I'm representing myself. I don't own any stock. I have received consulting fees from Amgen in 2008, Johnson & Johnson in 2009 on an unrelated product, and I received grants, I was the principal investigator for the TREAT study.
My history with ESAs goes back to the

00099

Normal Hematocrit study where I served on the data safety monitoring committee and the BEST study of breast cancer in women, where I chaired the data safety monitoring committee.
I'm here representing the TREAT data, where I felt that this group should hear something more than what we had the opportunity to publish in the literature. I apologize for not having slides, because I did want to update this and, in so doing, I realized that I missed your date, but I will give you the best I can on our latest data from TREAT.
Now, I will start with our conclusion.
Dr. Singh presented TREAT, he was a TREAT investigator himself, and presented it very well. But everything I'm going to say after that is data that's only been analyzed at the Brigham and Women's Hospital. We have an excellent relationship with the sponsor Amgen, everything published has been checked by an academic and the industry source, but what I'm going to tell you has not been verified.
But I would like to start with our conclusion, and it first starts with the importance of knowing the patient population,

00100

and what I am going to talk about only applies to people with diabetes, chronic kidney disease not on dialysis, and moderate anemia, hemoglobin less than 11. And we concluded in this placebo-controlled trial that had more patient years exposure than all the other trials combined, and the only placebo control, that the events were not reduced, hard events.
And I will take you back to 2004. The study was done to show that we would improve clinical outcomes, so that's where the world was in 2004. We got to the end and did not find an improvement in clinical outcomes. We did find that we reduced red cell transfusion, we had a modest improvement in the FACT-Fatigue, which was our primary quality of

life outcome, but not supported by other scales. I will say subsequently we looked at that and that's a durable finding over at least two years, that is a durable finding, so that's new information for you.
The higher rates of stroke that you heard about, we found in every analysis that we've done, twofold greater risk of stroke, and we did find supportive data very insecure

00101

because there's no real definitive data in this cancer field. Our data smelled like the cancer data. So we concluded that for many, these risks, for many, and we're talking now about people not on dialysis, will outweigh the rather modest benefit.
Now we've had a little chance to continue to work with this data. I've heard a lot about rates of rise, and there was a very interesting way that TREAT was done in this double blinded fashion. All patients were randomized to active treatment, the first two doses were weight-controlled, so everyone received the same first two doses. After those doses the computer then kicked in, asking what was the hemoglobin, and now I'm going to adjust the next syringe. The investigator was just told go to box number six, take out the syringe and that's the dose for the person. First two doses, everyone randomized to active therapy got the same dose. So now we're doing an exploratory analysis, what happened with those two doses?
And as you can imagine, some people had a very brisk response to the same dose,

00102

others had no response, zero. Two doses of darbepoetin, no response of hemoglobin. So we did an analysis of the hypo-responders versus the rest, and this is all preliminary, unpublished, but I was hoping to share with this group. We cannot really identify who these people are by looking at them, by asking how old they are, by asking their gender. It's an operational definition based on the response they're getting to ESA. Those hypo-responders did worse than the peers who received darbepoetin.
Conversely, I can tell you about the people who had a brisk response who did better, so this is all very complicated and not that easy to analyze.
DR. GOODMAN: One minute, Dr. Pfeffer.
DR. PFEFFER: Okay. Then why don't I

jump to some data here. I'm also told a hemoglobin target, there's a safe hemoglobin target. Well, this observation that I wanted to share with you belies that. The people who had the least response would have been in this, quote, safe hemoglobin target, and you would not know that. So they had more events,

00103

hemoglobin that was lower than the brisk responders who did much better. So my conclusion, and I'm representing myself and my colleagues at the Brigham and Women's, we have not shared this with the sponsor, is that a poor initial response to the first two dose identifies a higher risk person. Whether the person with the subsequent algorithms that they would receive higher doses, we cannot tease out at this time.

And this raises the concern about those base targets. It also indicates that lowering a hemoglobin may not necessarily mitigate the risks in the patient that I was referring to.

DR. GOODMAN: Dr. Pfeffer, thank you very much. We hope you'll stay for the balance of the day, we may have follow-up questions. We appreciate your comments.

Next is Dr. Wolfgang Winkelmayer, associate professor of medicine, acting, at Stanford University, representing the American Society of Nephrology. Dr. Winkelmayer.

DR. WINKELMAYER: Thank you, Mr. Chairman, ladies and gentlemen. I'm

00104

speaking today on behalf of the American Society of Nephrology, which is a large not-for-profit organization of 11,000 physicians and scientists dedicated to promoting excellence in the care of patients with kidney disease.

As we have seen, anemia is a common complication in patients with advanced chronic kidney disease, and occurs in most patients even before they require chronic dialysis treatment. Prior to the availability of erythropoietin treatments, patients with advanced CKD were often anemic, and blood transfusions were common. Epoetin alfa was approved by the USFDA based on studies demonstrating its efficacy in reducing the requirement for blood transfusions. The effectiveness and safety of epoetin in large patient populations with CKD, however, was not formally examined in large trials until many

years later, and we've heard already from Dr. Singh, Pfeffer and others about these four landmark trials.

In summary, can I proselytize benefits more aggressive hemoglobin targets when

00105

implicitly, higher ESA dosing did not materialize, but important safety signals from more aggressive approaches were discovered in three of those four trials of CKD patients.

Now where do we stand in March 2010 in our considerations of the appropriate place of ESAs in the treatment of anemia in patients with CKD?

Most scientists and clinicians familiar with the evidence would agree at least on two things. First, ESAs are doing exactly what they were originally approved for, they help avoid blood transfusions, as most recently reaffirmed in TREAT, twice as many patients required transfusions in the placebo arm compared to the darbepoetin arm. Secondly, more aggressive anemia treatment does not yield better outcomes at the very least, and may actually be harmful to some patients. Thus, the value proposition in favor of using ESAs to treat patients with CKD towards more normal hemoglobin concentrations, compared with strategies that maintain more moderate hemoglobin concentrations, is not supported by the evidence.

00106

The difficult question faced by clinicians and payers is what level of ESA treatment and what hemoglobin target may optimize the balance among benefits, risks and costs, the answer to this question is currently unknown. It remains an important treatment and policy goal to avoid transfusions in the CKD population. This is based on the very important consequence of immune sensitization in these patients.

Many CKD patients will eventually reach ESRD with kidney transplantation, given the preferred option from both the patient and payer perspective. Each transfusion that these patients received may reduce the likelihood of receiving a transplant, and those who do receive a transplant, it diminishes the chance of long-term function of the transplanted kidney. Thus, it is clinically of the utmost importance to avoid transfusions in order to not jeopardize these patients' prospects of receiving and maintaining a kidney transplant.

Of note, considerations of equity also come into play. Women and African-Americans are at increased risk of requiring

00107

transfusions, and these population subgroups would be particularly endangered by any unreasonable barriers to receiving ESAs. In addition, we still cannot rule out that an intermediate hemoglobin target does yield clinical benefits in terms of reduced morbidity, mortality, or increased quality of life. The major ESA trials in CKD patients do not inform these considerations, as patients in their respective less aggressive treatment arms uniformly had hemoglobin concentrations that were in the intermediate range average, between 10.5 to 11.5 grams per deciliter, which is perfectly compatible with transplant guideline recommendations. Therefore, the constant question of whether to give conservative ESA treatments with intermediate target hemoglobin concentrations as currently recommended may yield important clinical and patient-reported benefits over no treatment or a very aggressive treatment strategy remains unanswered.

DR. GOODMAN: One minute, Dr. Winkelmayer.

DR. WINKELMAYER: While observational in nature, a recent study in JAMA has hinted

00108

that such benefits may actually arise. Dialysis facilities treating patients with severe anemia aggressively, at lower mortality among their patients compared to those using less aggressive ESA treatment strategies. While this analysis cannot establish causality, it clearly indicates that ESAs used in moderation among severely anemic patients may be beneficial, and posits that it ought to be tested in future trials.

In summary, we derive from the available evidence that current ESAs may be dangerous if used for overly aggressive treatment targets compared with practices that are compatible to guidelines. Continued access to these medications is required, however, to give patients with CKD a fair chance at first receiving and then maintaining the function of kidney transplant. Swift action is needed to support comparative and effective research that closes the evidence gap on the optimal role of ESAs in the treatment of relatively severe anemia and to more modest treatment targets, while maintaining these patients

transfusion-free. Thank you.

00109

DR. GOODMAN: Thank you very much, Dr. Winkelmayer. Very helpful comments. Next is Dr. Kerry Willis, senior vice president for scientific activities at the National Kidney Foundation.

DR. WILLIS: Good morning. In terms of disclosure, I just want to say that the manufacturers of ESA and of iron products have provided support for NKF patients and professional educational activities over many years. However, no funds were solicited or received for the guideline I'm going to talk about today.

The National Kidney Foundation has been developing evidence-based clinical practice guidelines for the care of patients with kidney disease since 1995 through our kidney disease outcomes quality initiative. I'm going to review the recommendations from our latest anemia guideline regarding hemoglobin targets. These are from the 2007 update, which reviewed published studies including CHOIR and CREATE, through the end of 2006.

The first recommendation states, in

00110

the opinion of the work group, selection of the hemoglobin target and selection of the hemoglobin level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits including improvements in quality of life and avoidance of transfusion, and potential harms including the risk of life-threatening adverse events. The designation clinical practice recommendation means that this is based primarily upon expert opinion and reflects the lack of specific quantitative information from the trials that could be used to weigh the potential benefits and harms of a given hemoglobin level.

The second recommendation states, the selected hemoglobin target should generally be in the range of 11 to 12 grams per deciliter in dialysis and nondialysis patients receiving ESA therapy. This was based on evidence from 12 randomized trials in dialysis patients and 15 randomized trials in nondialysis patients. These are the randomized trials the work group looked at which compared lower with higher hemoglobin targets. The whiskers show

00111

the target ranges in each trial. The triangles at the lower left are the placebo or untreated groups. The closed circles are the lower target mean achieved hemoglobin and the open circles are the higher target achieved hemoglobins. I'll give you a second to see how those go from left to right, and please note that in several of the trials, especially the more recent ones, the achieved mean hemoglobin levels were outside the intended target range. It's important to distinguish target hemoglobin from achieved hemoglobin. The target is the aim of the ESA therapy and the achieved hemoglobin is the result of the ESA therapy, and the achieved hemoglobin results often vary considerably from the hemoglobin target.

So turning to potential benefits, we've heard about health-related quality of life. It is an outcome of direct importance to patients and we feel very strongly that it should be valued accordingly when considering ESA therapy. Quality of life is measured with instruments that have been validated in a range of target populations, including chronic kidney

00112

disease patients --

DR. GOODMAN: One minute, Dr. Willis.

DR. WILLIS: -- and have levels of reliability and precision to those of other commonly used tests.

So, I want to quickly show you what we mean by potential benefit of treating to a higher hemoglobin target. All of the randomized trials we looked at that were graded level A showed some benefit. The number and class of quality of life domains varied, but several studies reported robust benefits spanning multiple domains, and benefit is seen in both physical and mental health domains.

Finally, we are in the process of developing a new global guideline on anemia and chronic kidney disease. Its key question is whether the benefits and harms of ESA therapy might be different at different stages of CKD and when certain comorbidities are present. An initial draft should be ready by the end of the year, and we suggest that CMS delay action until this guideline is available for review.

Thank you.

DR. GOODMAN: Thank you very much, Dr.

00113

Willis, very helpful. Next is Dr. Scott McKenzie, senior director for health economics

and outcomes research, North American Pharmaceuticals, Centocor Ortho Biotech, which is a J&J company. Dr. McKenzie.

DR. MCKENZIE: Good morning, and on behalf of our Centocor Ortho Biotech, we appreciate the opportunity to present data to the committee in their consideration of ESAs.

Over the next few minutes we will see that in anemia patients with chronic kidney disease not on dialysis, that epoetin alfa improves and maintains hemoglobin levels, that recently published clinical trials have reported low rates of blood transfusions, and that investigational and clinical trials of the ESAs have reported adverse safety signals in those that are targeted to a hemoglobin greater than 12.

As background, there are two FDA-approved ESAs which are indicated to improve and maintain hemoglobin levels and to decrease the need for transfusions.

Transfusions can be problematic in this population either because of short-term

00114

complications such as fluid overload, or long-term complications such as infection, iron overload or alloy immunization, which could preclude kidney transplantation. The CKD patient population is really a continuum, ranking anywhere from mild renal insufficiency to patients requiring product dialysis, and the FDA-approved prescribing information recommends initiation at a hemoglobin less than ten grams per deciliter, a target hemoglobin of ten to 12 grams per deciliter, and a dose reduction in the ESA as hemoglobin approaches 12 grams per deciliter.

Recently there have been two clinical trials that have been published looking at interventions targeting the labeling information of ten to 12 grams per deciliter target range, so I'm going to present these in parallel. First was a clinical trial looking at EPO naive patients that were initiated and maintained with intervention, and secondly was a trial with epoetin alfa-exposed patients that were maintained with epoetin alfa treatment.

In this slide you can see that in the first several weeks that epoetin alfa

00115

effectively increased hemoglobin levels. However, during the maintenance, the hemoglobin was anywhere from 11 to 11.4 grams per deciliter, again, with a target in the label

information of ten to 12 grams per deciliter. Secondly, in a maintenance trial with patients that were EPO exposed patients showed that there was maintenance of hemoglobin levels of 11 grams per deciliter.

Now both of these studies reported low transfusion rates, and in fact a pooled analysis of all study arms, representing almost 800 patients, reported a transfusion rate of six percent across the studies. Furthermore, looking at key adverse rates, they were low likewise, showing cardiovascular event rates anywhere from two to six percent, and death rates were anywhere from three to five percent across the arms.

Now as mentioned, the ESAs are indicated to decrease the transfusion need. However, over the past few years there have been investigational clinical trials looking at novel endpoints specifically based on the hypothesis that if there were increased

00116

hemoglobin levels, shouldn't we see a reduction in cardiovascular complications and death. One of these was the CHOIR study, which was previously discussed, and this is actually the results which show an adverse signal in those patients treated with the higher hemoglobin.

Now this information has been conveyed to the FDA and has been incorporated into prescribing information.

But what's important here is the fact around the quality of life, the fact that these patients in both study arms started at a hemoglobin of 10.1 grams per deciliter, and in the low hemoglobin group were targeted to 11.3 grams per deciliter. And in fact in this group there was significant improvement in quality of life across multiple domains in the low hemoglobin group, in addition to the high hemoglobin group.

Additionally as previously discussed, the TREAT study again looked at higher target hemoglobins and were reported to have comparable cardiovascular endpoints. However, there was increased stroke in the group that was treated to a higher hemoglobin range.

00117

DR. GOODMAN: About one minute.

DR. MCKENZIE: So in summary, in patients with anemia and chronic kidney disease not on dialysis, epoetin alfa effectively improves and maintains hemoglobin levels. Newly published clinical trials have reported

low rates of blood transfusions. And while recently published investigational trials have shown an adverse signal when patients are targeted to a hemoglobin greater than 12 grams per deciliter, these studies did show improvements in quality of life which has been shown in other studies when the hemoglobin is maintained at greater than ten grams per deciliter. Thank you very much.

DR. GOODMAN: Thank you very much, Dr. McKenzie, very helpful comments. Next is Dr. Alan Kliger, clinical professor of medicine at Yale School of Medicine, also chairs the Department of Medicine, Hospital of St. Raphael, New Haven, Connecticut. Dr. Kliger.

DR. KLIGER: Good morning. I am Alan Kliger. My potential conflict of interest is that I have got some research grant support from Amgen. I'm here for the Renal Physicians

00118

Association, representing over 3,000 practicing nephrologists in the United States.

Since FDA approval in 1989, nephrologists have used ESAs to treat anemia in dialysis CKD patients. While appropriate use of ESAs and iron have reduced substantially the numbers of patients with profound anemia, recent studies we've heard described this morning have raised substantial concern about the safety of ESAs when they're used to raise hemoglobin to the normal or near normal range of hemoglobins more than 12.

We ask the committee of experts in the treatment of anemia with CKD and dialysis to review the literature and to help give our members guidance in the safe and effective use of these agents.

So first concerning survival and cardiovascular risk, we agree that the evidence is strong. At high levels of hemoglobin, targeting hemoglobins at 13 and achieving hemoglobin levels over 12 by use of ESAs for both dialysis and predialysis CKD patients increases the risk of death and cardiovascular complications like stroke. Furthermore,

00119

there's reasonably strong evidence that high ESA dose in patients with resistance to ESAs, there's a risk factor for these same complications.

The evidence is less clear at lower levels of hemoglobin. In a study published this month in JAMA by Brookhart and colleagues that several previous speakers have alluded to,

USRDS data were analyzed by examining ESA prescription patterns in dialysis facilities. Since patients don't select facilities according to their ESA prescribing patterns, the authors called this a natural experiment, subject to less confounding than other retrospective studies and more similar to most of the major trials of ESAs. They found that when patients had hematocrits of less than 30, or in other words hemoglobins of less than about ten, centers using higher doses of ESAs and those using more frequent doses of iron had lower mortality. Since a prospective trial of patients with significant anemia will probably never be done, this study gives us reasonably strong evidence that ESA use and iron use are

00120

associated with improved survival when the hemoglobin is less than ten. Concerning patient-perceived quality of life and exercise tolerance, two studies published this month in the American Journal of Kidney Disease deserve attention. Gandra and colleagues performed a systematic literature review of prospective studies examining the impact of ESAs on energy and physical function in nondialysis CKD patients. These two measures of quality of life rather than the less specific general quality of life tools may be of more focused importance for CKD patients. They found that in patients with hemoglobins of between 8.8 and 11.9, ESA use correlated with higher energy, less fatigue, and with better physical functioning. In the second study, Johansson and coauthors did a systematic review, a meta-analysis of exercise tolerance and physical functioning in dialysis patients treated with ESAs. They also found a correlation between ESA treatments, higher hemoglobin levels and exercise capacity and physical functioning.

00121

The evidence is excellent that ESA use in patients with hemoglobins less than ten reduces transfusion requirements. This may be particularly important for patients awaiting kidney transplantation. We believe the evidence is reasonably strong that treating anemia in CKD and hemodialysis patients when the hemoglobin is less than ten improves survival, patient-perceived quality of life and exercise

tolerance. It's important to remember that evidence-based medicine is designed for use at the individual patient level. As CMS examines the strength of the evidence and considers its coverage policies, we trust that the Agency will preserve the ability of doctors and patients working together, considering risks and benefits, the particulars of each patient's condition and each patient's preferences, to make decisions about ESAs or other therapies one at a time at the bedside.

On behalf of the Renal Physicians Association, I thank you for this opportunity to speak.

DR. GOODMAN: And thank you very much,

00122

Dr. Kliger, and we do appreciate your emphasis on addressing the needs of individual patients. Thank you very much, sir, and I apologize for mispronouncing your name, but I got it right the second time. Thank you.

Next is Dr. Reshma Kewalramani, nephrology therapeutic area head and executive director for global development of Amgen, Incorporated. Welcome, Doctor.

DR. KEWALRAMANI: Thank you. Good morning. The risks associated with ESA therapy with targeted hemoglobin levels of greater than or equal to 13 grams per deciliter has been discussed this morning.

Amgen considers patient safety our highest priority. The risks associated with targeted hemoglobin levels above the labeled range of ten to 12 grams per deciliter is recognized and has been incorporated into product labeling. Discussions with the FDA are ongoing regarding labeling changes as well as evidence generation. As with any therapeutic, appropriate utilization requires an assessment of both risk and benefit. To that end I will focus my comments today on the four key points

00123

on the following slide.

The key points are, one, as we've already heard, dialysis patients are different than not on dialysis patients. This is true in a variety of domains, including the comorbidities, frequency of hospitalization, and importantly, the prevalence and severity of anemia. Dialysis patients are almost universally anemic, and the severity is greater. As such, ESA therapy is different in dialysis patients and the benefit-risk profile of ESAs should be considered separately for

dialysis patients and not on dialysis patients. Two, that while transiently effective, transfusions have real risks associated with them. Three, hemoglobin levels of less than ten are associated with significant transfusion risks and is associated with impaired physical function and exercise tolerance. And lastly, that because of this concept of hemoglobin variability, a hemoglobin target range rather than a single value is what is necessary as a therapeutic goal of ESAs. The totality of the evidence supports the

00124

labeled hemoglobin range of ten to 12 grams per deciliter as appropriate. There are two factors that distinguish anemia in dialysis patients compared to not on dialysis patients, and very simply this is a very low erythropoietin level in dialysis patients and obligate blood loss. Obligate blood loss refers to the fact that dialysis patients go onto a machine three times a week, and have blood loss through the tubing and the machine process itself. This can lead to a fairly severe anemia that's chronic and in the absence of ESA therapy can lead to the need for ongoing transfusions. As we've already heard this morning, there have been improvements in blood banking technology. However, for our CKD patients, volume overload, potassium overload and sensitization are uniquely important risks that cannot be underestimated. When targeting hemoglobin levels of approximately ten to 12 grams per deciliter, there is an unambiguous decrease in the needs for transfusion with ESA therapy. Data like the one on the slide here are rarely seen, they're fairly dramatic.

00125

There is a significant and marked decrease in transfusions whether we look at the left panel, which is randomized control trial data, or the right panel, which is Medicare data. You have heard already that transplantation is the ultimate therapy for our patients with end stage renal disease. PRAs or panel reactive antibodies can be a real impediment to successful transplantation. PRAs are basically a measure of sensitization and they only come about in one of three ways, pregnancy, previous transplantation and transfusions. I think we can all say, though, that we have a tool to manage at least one of

those risks. ESAs were developed and approved for the purposes of reducing transfusions.
DR. GOODMAN: Doctor, just about one minute left.
DR. KEWALRAMANI: Sure. You've heard the variety of data that comes from a number of sources with regard to the improvement in quality of life when using ESAs. There's an error on this slide on the left panel, but let me just summarize the results by saying individuals in this study who received ESA

00126

therapy and achieved a target hemoglobin of ten to 12 were able to walk on average a half a football field further than those who received placebo.
This is my last slide, and it's a key slide of data from recent analyses. On the left panel is an analysis of existing clinical trial data, and on the right panel is Medicare data from about 160,000 dialysis patients. I think what you can clearly see from the left panel is that when hemoglobins fall to less than ten grams per deciliter, there is an increased risk in transfusions. This increased risk in transfusion linearly goes up as the time spent below ten increases.
Let me just summarize by saying the following: The totality of the evidence is sufficient to support a hemoglobin range of ten to 12 grams per deciliter. This is aligned with the registrational trials, acknowledges the risks seen when targeting levels of greater than or equal to 13 grams per deciliter, and is consistent with product labeling. Thank you.
DR. GOODMAN: Thank you very much, Dr. Kewalramani, thank you for your statement.

00127

Next is Kathe LeBeau, with weKAN. She's the program manager of the Renal Support Network.
Welcome, Ms. LeBeau.
MS. LEBEAU: Thank you. Good morning.
My name is Kathe LeBeau and I am a home dialysis patient and awaiting transplant candidate. I'm representing the Renal Support Network, which is a nonprofit patient-focused, patient-run organization that helps by educating and empowering patients to take control of the course and management of their disease. I would like to thank CMS for taking patient concerns into consideration in determining policy regarding treatment with ESAs.
RSN is deeply concerned about the

impact on patients' lives and well-being if the use of ESAs is limited beyond its current recommendations by the Food and Drug Administration's guidelines. We've heard a lot of clinical evidence this morning. I'm here to put a face on this and talk about it in more experiential terms.

As a person transitions through the various stages of CKD, the supportive treatment

00128

with ESAs in combination with iron therapy as needed to achieve the very delicate balance of keeping hemoglobin in range is the most effective way to combat one of the most debilitating effects of the loss of renal function, that is anemia. In my case I don't feel normal and cannot function as well if my hemoglobin level falls below ten, and I prefer to be closer to 12 simply because I feel better. Many studies have shown that treatment outcomes and quality of life suffer when hemoglobin levels fall below ten, and my own experience confirms this.

At a hemoglobin below ten I tire easily. I become short of breath walking up stairs. I have trouble sleeping, and daily activities become difficult or even impossible to perform. Frankly, I can always tell by the way I feel and how well I function that my hemoglobin has dropped before a lab test ever confirms it. And the effects of anemia in combination with the fluid filled fatigue of CKD that I experienced prior to the onset of dialysis treatments left me even more debilitated.

00129

So a hemoglobin of ten to 12 seems to be the right balance to allow physicians and patients to determine what is the best level for them to maintain their well-being. Many people who have CKD can relate experiences of how anemia has affected them personally. Symptoms may include chest pain, feeling cold, feeling tired, and I'm talking about a level of tired you don't even imagine exists. Low energy levels, so that doing even routine activities of daily living become impossible. Poor appetite. Shortness of breath. Depression. A poor sense of well-being. An inability to work, manage a home, volunteer. In short, the loss of a meaningful life.

I would like to share with you some representative samples of what fellow patients have told me regarding how anemia management

impacts their quality of life. From Heather in Little Rock. When I was first diagnosed, I had to have blood transfusions every month in order to fight anemia. ESAs did not exist at this time. The introduction of Epogen had a huge impact on my life. It improved my energy level, which

00130

allowed me to get back to living life instead of just surviving. I was healthier, more productive, and much happier. I was able to complete college and work full time and enjoy life. From Sherry, in Portland, Oregon. Why is quality of life important? Think of a time when you were sick, maybe with the flu. Your body was weak and you didn't have very much energy. Would you like to live your whole life feeling like that or even worse? That's what it feels like to have a low hemoglobin level. You're frustrated because you don't have the energy to do the things that you want to do. When quality of life decreases, physical and emotion health decrease as well. And from Mandy in Denver, Colorado. My quality of life was greatly impacted when I was anemic. I could barely walk from one side of the house to the other without sitting down because I was out of breath. I went to school during this time but my husband had to drop me off because I did not have the energy to walk from the parking lot to the classroom without the fear of passing out.

00131

RSN is concerned that any change in the use of ESAs in anemia management in accordance with the guidelines currently recommended by the FDA will result in a dramatic increase in the number of patients with low hemoglobin levels, and the consequential increase in the need for blood transfusions. Performing a blood transfusion is like playing Russian roulette with our health, and even increases our risk for mortality. In addition, as you've heard, blood transfusions can severely affect a patient's ability to receive a kidney transplant. The reactive antibodies received from blood transfusions result in fewer potential kidney matches from donors.

DR. GOODMAN: Less than a minute, Ms. LeBeau.

MS. LEBEAU: Thank you. RSN supports the 2006 CMS anemia management policy. This

policy allows the physician to order an ESA dose to achieve a target hemoglobin level between ten and 12. This policy acknowledges that there is considerable difference in a patient's response to anemia management and
00132
contains provisions for appropriate dose reductions when a patient's hemoglobin exceeds this level.
Many considerations come into play when managing anemia patients with CKD. For example, patients with CKD are much more prone to infection, inflammation, cardiovascular disease and hospitalization. No two patients are alike or respond the same way. Since kidney disease is a chronic condition, that means people will have to live with it for the rest of their lives. Dialysis and transplant are treatments but there is no cure.
DR. GOODMAN: Thank you very much, Ms. LeBeau. We hope that you'll stay for the balance of the day in case there are further questions. We also appreciate that CMS assures that we do hear directly from patients and patient advocates.
Next up is Dr. Douglas Silverstein, representing the American Society of Pediatric Nephrology. Welcome, Dr. Silverstein.
DR. SILVERSTEIN: Thank you as a representative of ASPN for inviting me.
ASPN was established in 1969, over
00133
four decades ago. We include 500 physicians around the country, the majority of pediatric nephrologists, and we represent over 2,000 patients on dialysis and many thousands more with CKD.
I think it's important to remember when you hear a lot of the talkers today and talking about adults, and we're talking about children, and it's very very different. The comorbidities associated with ESRD, CKD, with anemia, some of them overlap as you can see on this slide, but some of them are very different. I want to focus on a few of them.
Poor growth, a specific issue for pediatric patients that does not apply to adult patients, a very unique issue.
Also if you look at the health-related quality of life, we share some of the problems, our patients do with some of the problems that adults do, but this impacts them differently related to neurocognitive development and also school performance. So all of those don't

overlap, there's some differences between the two groups. And it's important to remember that some of those studies looking at the

00134

adverse effects and also the benefits of ESAs are done in adult patients where there are many comorbidities that don't exist in pediatric patients, so those studies have not been done and need to be done.
Children have specific needs related to dosing, that children are smaller, and therefore their smaller size requires higher dosing because the patients have a different metabolism of the medication, particularly true in young infants and children.
Also blood transfusions, similar to adults, affect their ability to receive transplants, so if they're going to have an ESRD life of 30, 40 or 50 years, they have many more years in which they can have high sensitization impacting their ability to get a renal transplant. And the current targets are based on adult studies, they are not based on pediatric studies, that's an important thing to remember. We need more studies in pediatric patients.
Right now we follow what you follow, the NKF clinical requirements or the FDA recommendations, and it's important to remember

00135

that in all of the studies, as Dr. Singh pointed out and many others have pointed out relating to adverse effects, have not been shown in children. The CHOIR, TREAT and CREATE studies do not include children. In contrast, we've been able to show by various studies that these medications are very safe in children reaching the proposed targets. And so there are no specific studies that have been conducted to look at specific targets in pediatric patiens.
When we look at the relationship between anemia and exercise tolerance we have been able to show by various studies, there are five listed here, I don't expect you to read all of them, but basically showing that pediatric CKD and ESRD patients have reduced ability to involve, be involved in exercise.
And if you look at study number three, the Baraldi study, that an increase in hemoglobin from a very low to a moderate target resulted in improved work load, improved peak oxygen uptake, and also increased VAT.
We also have results of evidence

relating anemia to cardiovascular disease.
00136
It's the number one killer of adult ESRD patients. You may be surprised, it's the number one killer of pediatric ESRD patients when they reach young adulthood. 40 percent of the deaths in pediatric patients who reach adult ESRD die of cardiovascular disease. We've been able to show that anemia correction is associated with an improvement in cardiovascular function, and been able to show in the Mitsnefes study in 2000, study number two, that chronic pediatric dialysis patients have LVH associated with lower hemoglobin levels, less than 11, compared to those who did not have LVH. Again, wide targets, we need many more studies to look at this. There's also a relationship, like adults, between anemia and health-related quality of life in pediatric patients. It's been shown in various studies, I'm showing three here, I want you to focus on study number two, basically looking at health-related quality of life when it comes to limitations in physical functioning, school performance, activities with friends, various things, that is you use a hematocrit target of 36,
00137
hemoglobin of about 11.5 to 12, those below that target had a worse functioning of health-related quality of life parameters.
DR. GOODMAN: Less than one minute, Dr. Silverstein.
DR. SILVERSTEIN: And we also know that like adults, it affects patient survival by studies number one and number three. Hemoglobins less than ten or less than 11 increase the risk for death and increase the risk for hospitalization. So we've shown in studly number one and number three different targets, but the increased risk once you go less than ten in one study and less than 11 in the other. And it's important to remember that the FDA by the 1997 Act commanded that more studies be done in pediatric patients who were receiving medications, off-label or on-label medications. So there is a need for more data in pediatric CKD and ESRD; they're going to become adult ESRD patients. The hemoglobin targets right now have been looked at in adult studies associated with many comorbidities that are not seen in pediatric patients, and they
00138

have unique needs that need to be mandating more studies, as required by Congress.

DR. GOODMAN: Dr. Silverstein, finish this sentence please, sir.

DR. SILVERSTEIN: Okay. We are poised to contribute and participate in studies as mandated by Congress. Thank you.

DR. GOODMAN: Thank you very much, Dr. Silverstein, and thank you for calling our attention to the particular needs of the pediatric population.

Next I believe is Denise Eilers, from Davenport, Iowa. Welcome.

MS. EILERS: Thank you. Thanks for the opportunity to address the committee. I am Denise Eilers, from Davenport, Iowa. Although I do volunteer for Renal Support Network, I am not employed by anyone even remotely connected with nephrology. Despite the fact that I'm a registered nurse and a licensed long-term care administrator with 40 years experience, mainly in geriatrics, I am here because my late husband Jerry was a home hemodialysis patient for 25 years, from 1980 to 2004. During that entire time he worked full time, played golf,

00139

and volunteered in our community. Together we raised our son and traveled.

That sounds like a very normal life, and pretty much it was. However, the early years before ESAs were difficult at best.

Before ESAs, my husband did all the things I just mentioned but he was forced to choose priorities. We spent an inordinate number of evenings at home relaxing - translated, that means my husband was tired and slept, while I took care of the household chores. With limited stamina, he did choose his priorities. He worked hard to support us, never missed our son's events, and gave back to the community.

That changed in 1989. After a few months on ESAs, Jerry was walking the golf course instead of riding, helping around the house, how wonderful, and taking 50 to 75-mile bike rides with us. He was the last to bed and the first up in the morning. Our family and friends were dumbstruck by the change in him.

I would also like to address rehab. The ability to work is intimately tied with a person's self-worth and self-esteem. Despite the original intent of the Medicare ESRD

00140

program to keep patients employed, renal rehabilitation has generally been a dismal

failure. Patients have been channeled into perceived disability and learned helplessness. ESA has helped my husband, who was a CPA and the CFO of a multistate corporation, to be a more productive employee and to continue to be a tax-paying citizen. The fatigue was gone. These personal observations add up to the fact that ESAs in our estimation equate to better quality of life. The KDQOL does not tell it all. It's highly individual. I define quality of life as being able to do all the things in life that are personally meaningful. Make no mistake, and ask any patient. Quality of life is not one thing they consider, it's the only thing.

To briefly address the science, current research has shown that in some situations ESAs increase risk for cardiovascular events. However, anemia and CKD patients is another dynamic, and severe anemia in those groups should be treated regardless. In the Ensor study, dialysis patients maintained in the 11 to 12 range showed

00141

decreased mortality. In addition, preventing hemoglobin variability by more frequent monitoring can prevent the drastic peaks and valleys and would seem to be cost effective. We've heard about CHOIR, TREAT and CREATE, that have made the kidney community reevaluate its approach to CKD. With that said, please remember, parents are not stupid. They just simply need to be fully informed of the risks and benefits of ESAs, and in partnership with an unbiased health care team, make an enlightened decision about their use. In addition, underlying causes of ESA resistance need to be corrected. Rather than targeting a specific hemoglobin, Jerry's nephrologist at the University of Iowa used the lowest dose ESAs that allowed him to live his life very well. Longer more frequent dialysis is, of course, in my estimation, the absolute gold standard. Here I'm going to make a public confession. For years unbeknownst to Medicare, instead of our ordered four-hour treatments, Jerry and I refused to throw away partially used dialysate fluids, and routinely dialyzed

00142

four-and-a-half, five, or even more hours. We would also sneak in extra treatments. That defiance of the prevailing rules combined with the wise use of ESAs surely accounted for my

husband's good life.
Before I conclude, I would also like to briefly mention another reason I'm here. In 2006 I got a little surprise. My own eGFR wasn't exactly what it should be, not awful but not great. I'm now adhering to a medication regimen, my creatinine is stable, I probably will not need dialysis. However, should that change, I want to know that some type of ESAs are there for me too.
Professionally I fully understand the need to continually reevaluate and reassess best practices. However, I strongly feel that optimum care can only be achieved by a blend of scientific and anecdotal evidence.
Lastly, from my husband's and my experience, I would argue that quality of life offered by ESAs is not perceived or inconclusive, it is very real and measurable. I was Jerry's care partner for 25 years, but I can still only guess what it was like for him.

00143

I do know that we lived with the effects of CKD every single day of our 35-year marriage. Unlike other conditions, CKD affects every facet of a patient's life, from the kitchen table to the bedroom and beyond. When it comes to quality of life, patients and their families deserve to be heard and heeded. Thank you.
DR. GOODMAN: Ms. Eilers, thank you very much for your comments. Very helpful.
Next is Dr. Michael Lazarus, who is senior executive vice president at Fresenius Medical Care. Dr. Lazarus.
DR. LAZARUS: I am a nephrologist representing Fresenius Medical Care.
I would like to point out that dialysis patients are distinctly different than cancer patients undergoing chemotherapy and, likewise, are different from stage one through four CKD. One cannot transpose results in CKD patients over to the ESRD patients. Dialysis patients are frequently exposed to Heparin. They have frequent exposure to bleeding by a cannulation of their fistulas and grafts. They have dialysis-related blood loss as we've seen here before. But most importantly is the

00144

extremely high level of cardiac disease, the leading cause of death in dialysis patients, which is related to LDH.
About 75 percent of dialysis patients have LDH. This is related to a high rate of hypertension, fluid overload, increased cardiac

output due to fistulas, and increased cardiac output due to anemia. Most importantly, when you dialyze a patient, you try to remove fluid, there's often cardiac ischemia called cardiac stunning. In years before the use of ESAs, it was very difficult to remove fluid from these patients because they had cardiac ischemia. That has gotten much better since ESAs and we're better able to remove fluid from these patients.

This is a chart that Dr. Hakim and I did several years ago with these studies that you've seen multiple times today, and I just want to point out that the achieved maintained main hemoglobin was, particularly in the Normal Hematocrit study, 14 grams of hemoglobin, 42 percent, not 12, so the 12 is well within the upper limit of the experimental group.

I would like to also point out that

00145

although the entry to the Normal Hematocrit study, of which I was the principal investigator, was nine, all the patients who came in drifted up to ten, so the actual acquired hemoglobin was about ten in that study.

The target hemoglobin and the achieved hemoglobin has been talked about today, and the marked variability in dialysis patients. You can talk about targets and studies all day long, that is not what happens to these patients, and this is best reflected in this distribution chart of hemoglobin values in dialysis patients. You can see the red curve here, which is the distribution of patients at Fresenius Medical Care in 2006, with a mean hemoglobin of about 12. With the onset of the EMT with change in payment there was a shift to the left, but no change, notice, no change in the shape of this curve. Try as hard as we might, we could not narrow this large biologic gaussian distribution. There are people that are going to be above 12, there are people that are going to be above ten, and it's not the same patients with each of those extremes,

00146

patients move all around underneath this distribution curve.

The curve has not changed substantially in 2009. We narrowed it maybe a tiny bit but not much, and the curve from Fresenius is not different, and this is data from the curve of the rest of the United States. So we have to deal with this

distribution curve. You can talk about a ten to 12 target, patients are going to be all over the place, and one has to understand that patient variability in the management of patients day by day.
Now we did this model, the blue curve is our distribution curve at the end of 2006, early 2007, and we made the supposition that if we say that nobody, we will not allow any patient to go above 12, what would happen to the distribution curve, and you can see what happens. If nobody can go to 12 the mean will result in eight, and 60 percent of the patients would be less than 11, ten, and about 50 percent would be less than that.
DR. GOODMAN: About one minute, Doctor.

00147

DR. LAZARUS: Thank you. This is a curve, EPO and hemoglobin, and it's inverse, so this is probably confounded by intent here, but at the lower levels of hemoglobin doctors use more ESA dosage. And in our population, we find that massive doses of ESA are given to patients at the lower levels where they have immunologic disease, chronic inflammation and other causes for the anemia, and not renal causes.
And finally, we talked about quality of life data. This is observational data, but here we see the physical component scores and mental component scores getting better, observational data for 44,000 patients in our company.
And in closing, I would like to say that I practiced for 20 years in the dialysis unit before ESAs, and I cannot fathom going back to those days again. Thank you.
DR. GOODMAN: Thank you very much, Dr. Lazarus, very helpful. Next is Shad Ireland, executive director of the Shad Ireland Foundation. Welcome, Mr. Ireland.
MR. IRELAND: Good morning, thank you

00148

for having me. In the state of full disclosure I need to tell everyone that my organization, the Shad Ireland Foundation, has received significant funding from Amgen and other major organizations that are patient-centric in the renal community. It's a pleasure to be able to speak with all of you today.
In 1983 I was diagnosed with kidney failure. I started dialysis at age ten. I received numerous blood transfusions weekly,

which resulted in an increased antibody level getting to the point of a hundred percent. I was untransplantable. I waited for my first transplant for seven years, got a second transplant in 2001, and currently have a high rate of antibodies and am untransplantable. I am a home hemodialysis patient and I can tell you that the quality of life was significantly and dramatically different in the early '80s before ESAs.

In 2001 after receiving my second transplant, and that transplant not working, myself and my medical team came to the realization that transplant was no longer an option, and so we decided and implemented a

00149

program that would optimize my treatment plan. And so what we did was look at first line medications such as ESAs, phosphorus binders and other things, and how we could utilize those. We looked at longer and more frequent dialysis therapy and how we could push the enveloped. We also looked at proper nutrition in a way that wasn't being currently implemented. And we structured a cardiovascular treatment plan, which is something that is currently not widespread in the renal community.

And the results were astounding. I'm standing here today in front of all of you as the first dialysis patient in the world to successfully complete an Ironman. I've run 20 triathlons and this year I will come back to Ironman, I've got four events planned. My ESA use has been dramatically reduced and I believe that directly correlates to the exercise regimen that we've implemented. I've also seen a reduction in hospitalizations. I have been hospitalized twice in nine years. These results represent a significant cost saving to the renal community.

00150

Access to first line medications and therapy such as ESAs combined with a structured cardiovascular exercise similar to a cardiac rehab model, if those things were widely implemented, I believe and my organization represents that the results that I've seen personally can be duplicated throughout the renal community. My organization has several programs that have seen significant success. Our fitness grant program has a 97 percent success rate. We've worked with individuals age ten to 80 years old and they've seen

success. I can tell you that the current model and the range of ten to 12 has helped me to achieve a quality of life that I only dreamed of.

Ladies and gentlemen, this is 27 years of -- excuse me. This is 27 years of dialysis, this is success. Excuse me, I'm sorry.

Looking at these results, if we look at implementing them across the renal community, this success can be duplicated. I want to thank all of you for your time.

DR. GOODMAN: Thank you very much, Mr. Ireland. You look pretty fit from here, sir.

Our next speaker is Daniel Cho, the vice president of ProMetrics, Inc. Welcome, sir.

MR. CHO: I'm here today to speak about a direction for new clinical trials using measurements of blood viscosity to enhance hemoglobin targeting and potentially modulate utilization of ESA. I should disclose that ProMetrics, my employer, is a provider of blood viscosity testing to the research community. My collaborator, who is an academic cardiologist and who is not here today, is not paid by ProMetrics.

Chronic kidney disease is well known to have a major impact on the risk of mortality, and anemia is well recognized in CKD patients as a risk factor for left ventricular hypertrophy, as well as for stroke and myocardial infarction. While the anemia community has long been treated with ESA, randomized controlled trials like Normal Hematocrit, CHOIR and CREATE have previously shown poor outcomes using composite endpoints that included mortality and CV events, cardiovascular events, by treating CKD patients to higher hemoglobin targets.

However, more recently in the TREAT trial, a randomized control trial in patients with CKD and type 2 diabetes, it showed that darbepoetin, a longer acting ESA, did not significantly increase composite cardiovascular or renal endpoints which included mortality, nor other components with the exception of stroke, which increased nearly twofold.

CKD patients have been shown to have higher blood viscosity levels than relatively healthy controls. A number of outcome studies have demonstrated that risk of major

cardiovascular events including death and MI increased with blood viscosity. Adjusted for age and sex, blood viscosity levels have been previously reported to be higher in subjects that experienced cardiovascular events than those who did not. And with further adjustment for conventional cardiovascular risk factors, the association with blood viscosity remained significant only for stroke. Additionally, stroke patients have been previously shown to have chronically elevated blood viscosity

00153

levels relative to healthy controls. Blood viscosity is very sensitive to hematocrit levels. A ten percent increase in hematocrit has been reported to increase blood viscosity by approximately 20 percent. The FDA's own scientists have published recently their longstanding concern over the rapidity of hemoglobin increased, hemoglobin oscillations and target overshoots that, quote, instability in hemoglobin concentrations could exacerbate the cardiovascular risks through hemodynamic or rheologic mechanisms. Biophysical markers that cause viscosity may have a distinct role to play in monitoring more directly these hemodynamic and rheologic effects of anemia correction in CKD.

The detection of high surges in blood viscosity which result in ESA use stands among the diagnostic candidates for predicting cardiovascular morbidity in anemia correction, and are best supported by the current literature. High blood viscosity surges as a result of ESA may in turn be used to titrate ESA dosing and enhance hemoglobin targeting on a more patient-specific basis. Such a

00154

personalized approach may be an improvement to using universal hemoglobin targets that differentiate mainly by gender. New research is needed to characterize the blood viscosity profiles of patients with CKD and tests that stratify these patients based on the effect of ESA on their blood viscosity levels. Thank you.

DR. GOODMAN: Thank you very much, Mr. Cho. That concludes our list of speakers who had signed up in advance, and we appreciate all of your comments, and especially appreciate your ability to convey your main points in the time allotted by CMS.

We now move to the point of our agenda where we have open public comments, and we have

three individuals who have signed up to do this, and we'll ask them in order to come to the microphone here, and we're able to give you two minutes each to address this.
And I apologize to the first person, whose initials appear to be W.S., if that person could come up. The name looks something like Wowie Scott, initials W.S.
And again, you have to keep it to two

00155

minutes. We appreciate you coming here, and could you please face the panel, they're very interested in hearing what you want to say, or face any direction you would like, but we especially want to hear exactly what you have to say, and if you could state your name and affiliation, please.
MS. SCOTT: Sure. My name is Nancy Scott. I am a dialysis patient for six years today, and I'm a volunteer board member and serve as vice president for Dialysis Patient Citizens. I do have some prepared notes but I really am going to give you my personal story as well.
DR. GOODMAN: If you could do that in two minutes.
MS. SCOTT: I certainly can.
DR. GOODMAN: That's great, thank you.
MS. SCOTT: For anyone not familiar with the effects of anemia on a kidney patient, I can assure you that they are significant and powerful. When my hemoglobin level is low, I become tired and experience shortness of breath, therefore impairing my ability to complete normal daily tasks. When establishing

00156

ESA guidelines, officials must recognize that not all patients benefit from the same course of care.
And I'm going to give you a scenario, and I probably should read a lot more of this, but because of the time limit, February 23rd, my hemoglobin was 12.1. My nurse practitioner came in and said I have to cut your EPO, Nancy. And she knows I get crazy when that happens, because not only am I a retired nurse, I'm an ordained minister, I'm currently working on a master's in health care administration, and I serve as vice president in a health care community center, so my plate is full and I want to feel good.
So when she came in, she said we have to lower your EPO. I was at 3,000 units at that time. My hemoglobin kept going down to

10.5, 10.3, 10.1. Now you know how I felt. I felt like a sack of dirt and I could do very little, but I continued to try to do what I could do, okay? Here it is. She raised my EPO level as it was going down, and I'm up to 4,600 units. Now remember, I was at 3,000 when it was 12.1, so now I'm up to 4,600 units now and

00157

my hemoglobin is 11.1 right now.

So all of these people -- I feel better when my hemoglobin is 12. So why can't this be between me, my nephrologist at raising my EPO? Everybody doesn't function at a 10.1. I don't function at an 11.1 as well as I did do at a 12. So my whole point is this: Let this be between the individual patient and the doctor, not a bunch of people sitting down who are not on dialysis saying it should be between ten and 12. Thank you very much.

DR. GOODMAN: Thank you, Ms. Scott, for your personal story. Next is Fred Finkelstein, from Yale University.

DR. FINKELSTEIN: Thank you very much. I've had a particular interest in health-related quality of life measures, and I do share the concerns that have been expressed about some of the limitations of the health-related quality of life measures that have been used in studying ESA patients, ESA and CKD patients.

However, despite that, when I look at the literature, I think it clearly supports the fact that health-related quality of life

00158

measures are impaired when hemoglobin levels drop below 11, and more dramatically as they drop below ten, and I base this statement on the following:

First, there's the cross-sectional study of a large number of 2,000 CKD patients from the CHOIR study last year that made this point.

There was a comprehensive review published in Kidney International in 2009 by Leaf and Goldberg that makes the exact same point, decline in quality of life measures as hemoglobins dropped below 11, and more dramatically when they dropped below ten.

Thirdly were the articles that Dr. Kliger mentioned that looked at physical functioning and energy levels in both CKD and dialysis patients. That was just published in the American Journal of Kidney Disease with accompanying editorials, and underscored the

importance of these findings.
And lastly, the findings in the CHOIR study that there was a dramatic increase in all varieties of health quality of life domains in the patients as their hemoglobin levels were

00159

increased from a baseline of 10.1 to over 11 in the low group and over 12 in the high group. I think we would do our patients a disservice if we let hemoglobin levels drift below ten, and I think it's important to maintain the current guidelines of ten to 12 for hemoglobin levels. Thank you.
DR. GOODMAN: Thank you, Mr. Finkelstein. Third up is Michael Germain, I believe, from Tufts and Bay State Medical Center. Welcome, sir.
DR. GERMAIN: Thank you. My financial disclosures, I've received support from the pharmaceutical companies who produce ESAs and irons, and I'm here as a consultant for Ortho Biotech. I'm a full-time clinician in practice in Springfield, Massachusetts, and my concern is that as a clinician, we also always have to weigh the risks and benefits for the individual patients in front of us. And to be limited in that decision-making between us and the patient I think would result in more harm than good, and I think myself and my colleagues have heard the safety concerns associated with targeting higher levels of ESA above the current

00160

guidelines and the potential risks of higher doses of ESAs.
My concern is when we look at the studies that were presented today, it's not a hemoglobin of below nine that the control groups have had, whether they be the lower targeted hemoglobin range or the so-called placebo group, which had hemoglobins in the 10.5 range, never in the nine range. Those hemoglobins continued to increase over a four-year period of time in that control group in the TREAT study. So I as a clinician cannot see how a hemoglobin of less than nine can be extrapolated from that data.
I'm very concerned about hemoglobin variability, and I think if we change the way we practice currently based on the practice guidelines and the FDA package inserts where we're trying to trend the hemoglobin and keep people stable within a target range, if instead we say you can't dose erythropoietin until it falls below a certain range, or transfuse a

person, what we're going to get is extreme hemoglobin variability, and that's going to result in not only symptomatic episodes with
00161
the patient but it's also going to result in potential mortality that has been seen with hemoglobin variability, albeit on an observational basis. Thank you.
DR. GOODMAN: Thank you very much, sir. I understand that concludes our nonscheduled speakers here. We appreciate very much your comments, all three of you, and hope you will remain available for the balance of the day.
Well, panel, it's time for us to have discussions or, excuse me, questions for our presenters, and we'll do that up until noon, so we can just get barely started on it, I understand. Might I ask that our presenters, I see Ms. Ciccanti, Dr. Koller, Dr. MaCurdy, if you could make sure that you're in this front row, and Dr. Singh as well, if you could come up so we can find you easier if need be. So that would be, yes, Ciccanti, Koller, MaCurdy, Holmberg, please, and Singh, at the very least. Thank you.
And I do want to remind the panel at this point that an NCD, a national coverage determination is not on the table. It is not
00162
our job to make a policy decision here today. We don't make up practice guidelines, but it is our job to take a very careful look at the evidence here and try to convey through the answers to our questions and our accompanying discussion, convey to the Agency what our assessment or take is on the available evidence pertaining to the questions.
And with that, if there are any questions of presenters, we will take them. And I will go to Dr. Pauker first, sir, and we all need to speak directly into the microphone, please, starting with Dr. Pauker.
DR. PAUKER: I have two questions, both for Dr. Singh along with Dr. MaCurdy. You have presented today and suggest that quality of life was not sufficiently affected, or it showed no difference. I almost have to ask about the power of the study. Can you comment on the power of those studies? It's particularly important when he hear testimony here that you can perceive the quality of life has changed. Could you comment on the power in your study?

And Dr. MaCurdy, we heard from Dr.
00163
Holmberg about the cost of transfusions. Can you share with us about the unique cost of ESAs?
DR. GOODMAN: Thank you. Dr. Singh, if you would come to the microphone, please.
DR. SINGH: So, Dr. Pauker, the question is whether these studies were specifically powered to see differences or test for differences in quality of life between the two arms. The answer is, to my knowledge, none of the studies was specifically powered for quality of life differences. However, having said that, it is true that although there was improvement in quality of life in the CHOIR study in both arms, there was no statistically significant difference between the arms. In TREAT there was in fact a difference that was statistically significant between the two arms of the study.
I think another question, or way to pose that same question, and I think the FDA has done this in their final ruling with respect to patient-reported outcomes, is to determine what is a clinically meaningful, or what's a minimally important difference in
00164
quality of life using these different instruments. And I think the answer to that is that in any of those analyses, there does not appear to be a clinically important difference with the exception, I think, of the TREAT study, where there was a clinically important difference seen in the active treatment arm, and just barely missed it for the placebo arm.
So I think the important answer is, there is an improvement in quality of life in both arms of the study, so treatment of anemia does result in some improvement in quality of life, but there doesn't appear to be clinically significant or statistically significant differences for three of the four studies. And for TREAT there was a statistically important difference between the two arms, but I don't believe a clinically important difference between the two arms.
DR. GOODMAN: Thank you, Dr. Singh.
Dr. MaCurdy, on the matter of costs.
DR. MACURDY: Unfortunately, it's not something that we looked at, so I can't give you any information.
DR. GOODMAN: Dr. MaCurdy, as long as
00165

you're standing there, let's get a little closer to costs even if you can't get particular, and it's a follow-up to my earlier question with regard to how many people -- I see you're going to reach for an answer, thank you. Currently, how many people of what type who are Medicare beneficiaries are on ESAs, can you give that back to us?
DR. MACURDY: Yes. For September 2009, for dialysis patients it's almost 235,000.
DR. GOODMAN: Who are?
DR. MACURDY: Who are dialysis patients receiving ESAs.
DR. GOODMAN: Thank you.
DR. MACURDY: And for the predialysis group, it's almost 81,000.
DR. GOODMAN: Who are on ESAs?
DR. MACURDY: On ESAs. Who are what we defined to be the intermittent kidney disease it's almost 16,000. And for the group that's not classified as having any sort of kidney disease, it's 33,000.
DR. GOODMAN: Thank you very much, Dr. MaCurdy. Dr. Pauker, sorry he didn't have

00166

an answer as to the cost, but hopefully that will be partially helpful. Dr. Satya-Murti is next.
DR. SATYA-MURTI: My question is for Dr. Singh again. Thanks for the lucid presentation. The two take-home lessons from you, for me would be hemoglobin is an imperfect surrogate, and if so, do you have a suggestion for an alternative? We heard about viscosity this morning and we heard about, experiential narratives about quality of life. So, do you have an alternative to hemoglobin as such? And second is, if ESA itself could perhaps be toxic or hazardous at certain doses, do we have any animal models, or any nonhuman primate models, are you aware of any studies where ESA has been given without anemia just to see if there's a dose response and toxicity?
DR. GOODMAN: Dr. Singh.
DR. SINGH: So, I don't have another biomarker, you know, that says we can replace hemoglobin. My approach was to say that we should have a minimum threshold above nine so you can set a performance measure, percentage of patients who don't reach nine. Looking at

00167

Dr. Lazarus's data, that would be very few patients actually. And not to set an upper

limit, because setting an upper limit forces patients in the other direction.
So, I think to set a minimum level above which patients should have the hemoglobins, and I think if you look at the Fresenius data and even Medicare data, we're not that far away from that, if that's the level that we set it at.
With respect to your second question about animal data regarding the use or treatment with ESAs, my understanding is this is very limited in the published literature.
In the original summary document that the FDA has, you know, available to them, and I think is in your packets, there's a discussion about the use of ESAs in animal models. And in those studies that are cited by the FDA but to my knowledge are not published, they document marrow fibrosis in animals treated with ESAs that is reversible. I'm not aware of any other studies that have looked at this in humans or subsequently followed up on this, and it would be interesting and I think important if we

00168

could have further elaboration of what happened to those studies, whether they were published and what they revealed, either in longer term or larger cohorts.
DR. GOODMAN: Thank you. Next, Dr. Agarwal, followed by Dr. Danis.
DR. AGARWAL: Dr. Singh, you discussed four trials that targeted hemoglobin well above the FDA recommended targets of more than 13. Are you aware of any studies that compare in a placebo control or randomized controlled design at least that compare a nontreatment to a treatment to target between ten and 12, that's your signal for harm?
DR. GOODMAN: Dr. Singh.
DR. SINGH: No, I'm not aware of that. That's why I think it's concerning if we create a band of safety between ten and 12, I don't know that it's safe to do that. I think all we know is that in the Normal Hematocrit study the lower arm seemed to do better than the upper arm. The lower arm, the target was nine to 11. In the TREAT study the lower arm, the placebo rescue arm was greater than 9.1 in that trial, and I think that's what the evidences shows,

00169

for both dialysis and nondialysis patients.
DR. GOODMAN: Thank you. Dr. Danis, followed by Dr. Pogach.
DR. DANIS: I would like to ask

Dr. Holmberg what fraction of the blood supply is used by chronic kidney disease patients, and I'd like to ask Dr. Winkelmayer if there are any strategies that nephrologists can pose that allow for dosing strategies that are not the on-off approach that leads to such vacillations, so that we could anticipate having dosing that might allow for the kind of symptoms that patients have when they go on and off.

And I wanted to ask either Kerry Willis from the National Kidney Foundation, or Kathe LeBeau from the Renal Support Network. We heard some very dramatic stories from patients and family members about the benefits of quality of life with ESAs. We haven't heard from any individuals who have experienced strokes following the use of ESAs, and we haven't heard from transplanted patients. If we're thinking about aiming for having the most affordable package for the universe of patients

00170

with kidney disease, I wonder about what they would say about the tradeoff of lowering coverage, or bringing down coverage for dose of ESA, versus prolonging coverage for immunosuppressive therapy so that patients who are transplanted did get more than three years survival of their kidney.

DR. GOODMAN: Thank you. Dr. Holmberg first.

DR. HOLMBERG: Thank you. I do not have that data parsed out that way, we don't collect data in that light, but I can tell you that if you just put the numbers together of the dialysis patients, if I had the numbers correctly, we're talking about 350,000, and in the United States we transfuse 14.6 million units, so you know, I can't parse it any more granular than that.

However, also what I presented to you was that most of our blood in our country and in most developing countries go to the elderly individuals.

DR. GOODMAN: Thank you, Dr. Holmberg. Dr. Winkelmayer.

DR. WINKELMAYER: Thank you for the

00171

question, Dr. Danis. You asked me about hemoglobin variability and any clinical strategies that might be available or proven that might reduce this variability. Taking a step back, hemoglobin variability has been shown to be associated with worse outcomes in

end stage renal disease patients. Patients with greater hemoglobin variability, however, are inherently different compared to those patients who do not vary the hemoglobin as much, indicating that this association might be loosely confounded.

In order to answer what strategies could be employed to reduce variability, one needs to go beyond the realm of ESAs and look at all inputs into the anemic care production function, if you will, and that specifically includes ESAs and their half life, and secondly, MI and substitution strategies. One might posit that longer-acting ESAs might be associated with a greater difficulty in steering hemoglobin targets or hemoglobins across time, although that has not been shown in studies that were relatively low in power.

Secondly, there is different ways of

00172

supplying these patients with sorely needed iron, which they have a hard time mobilizing from their iron stores. The two key ways to provide iron to these patients, one is a maintenance approach, where small doses of iron are given every treatment or once a week or something like that. And the other one is a bolus iron approach where you give large doses of iron in a relatively short period of time, such as one gram cumulatively over five to eight dialysis treatments.

One may posit, of course, that if you employed the bolus approach that you essentially create a swinging system and this might enforce it, in that patients get replenished with the iron, they respond better to ESAs, the hemoglobin goes up. You crank down the iron or stop the iron, you crank down the ESAs, you follow the hemoglobin downhill essentially, and at some point you kick in again. Whereas if you have a more continuous administration of iron, that might not be the case as much.

Those studies have not -- I guess there was a small study that has compared those

00173

two treatment strategies, it was inconclusive, but a large sufficiently powered trial has not been able to provide us any evidence on how we can better reduce hemoglobin variability.

DR. GOODMAN: Thank you, Dr. Winkelmayer. Dr. Willis, if you would, and Dr. Danis, would you repeat the question you had for Dr. Willis briefly?

DR. DANIS: Essentially I was commenting that we have heard only here from patients who have been benefitting from receiving ESAs in terms of their quality of life benefit. We haven't heard from individuals who suffered adverse consequences. So I'd like to hear whether you know about their perspectives, and also the perspective of transplant patients who are doing without things like immunosuppressive therapy and whether they would trade off.

DR. GOODMAN: Thank you, Dr. Danis. If you can address that, Dr. Willis, please do.

DR. WILLIS: I can tell you what I know. The first thing is that unfortunately among chronic kidney disease patients and dialysis patients in particular, strokes and

00174

heart attacks and things like that are such frequent events that even though we initially get hundreds of phone calls a day from kidney patients, and we have never heard from one who thought that they had had a stroke or a cardiovascular event attributable to an ESA. In other words, this is a statistical phenomenon, so --

DR. DANIS: But from their perspective, if they know that the ESAs put them at greater risk, how willing are they to live, looking back, you know --

DR. WILLIS: I can sort of answer it, and obviously this is purely anecdotal. But when the black box warning was first put into the ESA label by the FDA, we prepared a whole list of frequently asked questions for our -- we have like a hot line, an 800 number. And we thought people would be saying, oh, should I go to my doctor and get off this. But we got, the majority of calls were people saying are they going to take it away, like in other words, am I at such high risk they're going to take it away.

Regarding transplant patients going

00175

without immunosuppressive drugs, I think that, I doubt that they would attribute that to other kidney patients getting ESAs.

DR. GOODMAN: Good. Thank you, Dr. Willis. Cognizant as I am of traffic flow in this edifice, it would a real good idea for us to break for lunch now, as opposed to even five or ten minutes from now. So Dr. Pogach, if you would allow us, we will be pleased to lead off with you following lunch. Please look

at your watches now, add one hour, and we'll start then. Thank you very much. Very helpful this morning.
(Recess.)
DR. GOODMAN: Let's reconvene now, please. And those of you who are still talking are going to miss a very important question, I imagine, since it's coming from our Dr. Pogach. When last we spoke prior to lunch, Dr. Pogach was up with a question. We will go with that and then we'll proceed to a slightly revised program. Dr. Pogach.
DR. POGACH: I had two questions, the first for Dr. Pfeffer and Dr. Singh, which will be that they will be able to go back and

00176

reanalyze the CHOIR and TREAT data as to the specific reasons reached in the transfusions, and in their treatment arms.
My second question would be for Dr. Kewalramani. You cited the Canadian study as evidence to support the impact of EPO on exercise. If you look at the original study, it demonstrated in a prespecified secondary analysis a difference between the two defined EPO groups and the placebo group, and across the groups the main hypothesis did not reach significance, but there are baseline differences. The high EPO group compared to the low EPO group and placebo had a fewer number of subjects who were not transfusion-dependent, there were 11 in that group versus 19 in the other two groups. In addition, they had a higher baseline exercise capacity of 16.1 minutes on the exercise test versus about 11.2 and 11.4 in the other two groups. In addition, it was underlined as treaters and not intention to treat.
So my question was, given the imbalance among the treatment groups, does that impact, have any impact upon the internal

00177

validity of the results, and do you still feel this can be generalized to all patients with dialysis?
DR. GOODMAN: Did you get all that? Let's start, Dr. Singh I think would be first. And would the speakers, once again, please come to the front of the room where it will be easier to find you, anyone who spoke this morning, our invited speakers. Dr. Singh, please.
DR. SINGH: I would just discuss the CHOIR data because Dr. Pfeffer is going to

follow me with respect to the TREAT data. But in the CHOIR data there was a small difference between the two groups in terms of transfusion rate and we do plan to try to look at this or analyze this, but we don't have any information as yet. I think the problem with the transfusion data is that the protocol or the ability of the trial investigators to actually protocolize the transfusions was very limited. We don't have a good understanding of why individual sites actually transfuse patients and that limits, I think, the quality of that data, or that exercise.

00178

DR. GOODMAN: Thank you. Dr. Pfeffer.
DR. PFEFFER: Similarly for TREAT, it wasn't a major outcome that we put a lot of effort into. We'll go back and look at what was associated with the hospitalizations, what adverse events were occurring around that time, but it wasn't something that we really highlighted prior to the study.
DR. GOODMAN: Thank you, Dr. Pfeffer. Yes, Dr. Kewalramani.
DR. KEWALRAMANI: I will point you to the briefing documents that Amgen submitted for a more thorough review of the vast quality of life data. But to address the specific question as it pertains to the commonly known SCESG study, you're absolutely right. In the primary publication the difference between the placebo group and the treatment group did not reach statistical significance. However, when we were looking at the evidence around about the 2007 time frame when we were preparing for the review with the FDA, we realized that the original amounts did not account for multiplicity adjustment, and so we went back and redid the analysis taking into account the

00179

statistical analysis and this multiplicity. When we did that, there was a statistically significant difference between the group that received ESA therapy and the group that did not receive ESA therapy, i.e., the placebo group. That slide set is available on line, and we've actually just completed a publication and I'm happy to submit that to you. It hasn't been accepted yet, but the analysis has been completed now.
DR. GOODMAN: Thank you, and that was Dr. Kewalramani.
Well, when CMS asks MedCAC to answer questions, we do our very best. They don't

always tell us in what order we might answer those questions, and in conferring with our fellow panelists and with CMS staff, in light of the very good information and insights that we've seen this morning, what we've decided to do is change the order of the questions just a bit, and what we're going to do now is to start with what was originally question five. These are, were originally designed to be some discussion questions that might help provide some backdrop for further detail to the

00180

earlier questions one through 4.A. but what we decided was that we wanted to get those insights now about the discussion questions, and that will help us determine how we answer the previous four questions. So we will start with those and I will do my best to kind of moderate a discussion about them. And for those of you that have the questions, number five says, please discuss any impact of the following factors on the conclusions reached above. Well, we want to discuss that impact now before we reach those conclusions if that's okay with the panel, and I believe it is. And so the first one, I want to make sure everyone has it in front of them, concerns the matter of whether the CKD patient is undergoing chronic dialysis or is in predialysis status. So when we're considering the results of these trials, the impact of these interventions in particular on health care outcomes, does it matter whether the group of patients considered is undergoing chronic dialysis or is in predialysis status. So I'm going to pick on Dr. Singh

00181

since he's looking very intently at me and I'm thinking this is computing with him. Dr. Singh, in some of the literature that we've seen, including a recent New England Journal article, there was mention made that whether a trial addressed one group of patients or another might have an impact. And then when we looked at a breakdown of available trials, some of them did address the chronic dialysis patients and some did not. Would you care to comment at this point and get us started on the extent to which that distinction matters, especially with regard to the outcomes of interest?

DR. SINGH: So, I have published two editorials in JASN, the Journal of the American

Society of Nephrology, one that addressed nondialysis patients and the other dialysis patients, and I can send these two you.
DR. GOODMAN: You can't do that now.
DR. SINGH: Not now, but I will send it to you, and I will just briefly highlight the points. I think that the dialysis and nondialysis patient populations are different, they're different for a number of reasons. I

00182

think that the dialysis population has a larger number of comorbidities, they have probably a greater degree of erythropoietin deficiency because their kidney disease is more advanced, and they also have an iltumor that is much more intense than that in the nondialysis population. I also think that the sources of blood loss in dialysis patients is greater. So I think how you treat these patients is going to differ based on whether they're dialysis or nondialysis patients.
In the nondialysis population the closest studies we have are the three studies that I alluded to, of which I think the TREAT study, which is a placebo-controlled study, demonstrates that in the placebo arm, you are able with treatment of patients' iron deficiency and, you know, certainly about 20 percent of patients receiving blood transfusions, you can manage these patients with very low or no doses of ESA. And then hemoglobin levels targeted at staying above nine end up averaging ten to ten and a half. Some would argue that that population that was looked at in TREAT is a CKD with type 2

00183

diabetes only. But I think in my judgment, one should be able to generalize that population to other nondialysis patients, even nondiabetics.
In the dialysis population, I think it's more challenging. In those patients, just treating them with iron therapy and blood transfusions, risks in a significant portion of patients with relatively low hemoglobin levels, quite low, much lower than eight, seven. And there is lots of reports of pre-ESA, in the pre-ESA era, withholding ESAs completely in this population is, would be a real problem, and I think that Dr. Lazarus's comment about not fathoming what life would be like is a pretty accurate description. So I think you need to be able to nuance dialysis from nondialysis.
I think some dialysis patients could

have substantial reduction in ESA and I believe they should have substantial reduction, because I think beyond a certain level of treatment or ESA dose, you're really not getting any further additional benefit in hemoglobin.
DR. GOODMAN: Dr. Singh, let me cut more to our ultimate chase, and that is, we

00184

care about, the Agency for its Medicare beneficiaries cares about how these interventions affect outcomes. So the outcomes that we care about are exercise tolerance, vascular events, patient-perceived quality of life and survival. So for those outcomes, what do you think about the sufficiency of the evidence for those two groups, and maybe perhaps what the evidence says?
DR. SINGH: I think the evidence says that in both patient populations, target a higher hemoglobin target, whether a hemoglobin is greater than 13 grams per deciliter is associated with harm. The signals may vary but there is no benefit, and in fact there's an increased risk of death and cardiovascular complications in both patient populations.
DR. GOODMAN: In both patient populations?
DR. SINGH: In both patient populations.
DR. GOODMAN: And you're saying that there is what, adequate or sufficient evidence to make that conclusion for all four of those outcomes, is that what you're saying?

00185

DR. SINGH: I think the Normal Hematocrit study indicates that in targeting patients for a higher hemoglobin, you know, greater than 13, is associated with harm. I think the three studies, CHOIR, CREATE and TREAT in nondialysis patients, suggest individually, different signals, that there is either no benefit or harm in patients targeting a higher hemoglobin, I think in both populations there's evidence to that point.
DR. GOODMAN: Let's stay on this point with regard to dialysis and non. Dr. Agarwal first.
DR. AGARWAL: When we are treating patients with chronic kidney disease we have two things in mind, how can we make them live longer and how can we make them live better. I don't think we have figured out how to make them live longer, but we do everything we can try to do to make them live better.

One of the things that we have never captured in these trials, or very few trials have captured, is recognizing the heterogeneity of the CKD population. CKD is like saying puff, you have a disease, but it's a very

00186

heterogeneous disease. You can have varying levels of GFR, you can have varying levels of proteinuria, and one thing we have learned over time is that proteinuria is where the risk travels from, and many of these trials never adjust for baseline levels of proteinuria, not all the trials, but many of the trials ignore this stuff.

When we are looking at risks over time in these individuals, I think we have to recognize that the baseline level of cardiovascular disease and the levels of proteinuria, how it is impacted by treatment can be very heterogeneous.

DR. GOODMAN: What would you say, though, about differentiating between those on dialysis and those not?

DR. AGARWAL: Clearly the dialysis patients reach dialysis because they survived cardiovascular disease. The statistics show that 25 people die before one reaches dialysis. Most patients with chronic kidney disease die of cardiovascular disease, very few reach dialysis. So once you have reached dialysis, you have a selection bias, you have survived

00187

cardiovascular disease. Once you have reached that, unfortunately, you also have a lot of cardiovascular morbidity, arteriosclerosis and atherosclerosis, probably more arteriosclerotic than atherosclerotic. But if you compare the quality of life of a dialysis patient with that of CKD, the patient who has nephrotic-range proteinuria suffers as much as a patient on dialysis, it's got very little to do with estimated GFR. So there are some similarities but there are stark differences in the two groups of people that we are talking about.

DR. GOODMAN: And when we talk about differences and similarities, we care about the evidence for those.

DR. AGARWAL: Yes, and there is evidence.

DR. GOODMAN: Dr. Puklin.

DR. PUKLIN: I'm going to turn this argument upside down for a moment if I could, and I would like to have the comments of Dr. Singh and others on this. There's no question,

and I'm not a nephrologist, but there's a difference between patients who are not on dialysis and patients who are on dialysis, and

00188

Dr. Singh just responded to that question by citing the research studies from the randomized controlled trials that separate those groups. I've been impressed by the speakers here who've talked about how the quality of their life is affected and have described what we could call personalized medicine, the patients themselves who have titrated their own drugs in response to the type of disease that they had, and modified their various activities to allow themselves to run triathlons, to overcome all sorts of other disabilities. So couldn't your answer be to this question, yes, this is a difference between these two groups, but when you're faced with a patient who's in kidney failure, you personalize the drugs of choice and the dose level, and the target levels, to produce maximum functionality, maximum well-being. And in that way you don't regress the concept of being on chronic dialysis or being predialysis, you're facing the concept of a human being who has a malady and who wants to retain as much functionality as possible.

DR. GOODMAN: Thank you, Dr. Puklin.

00189

I would just remind us, though, that the ability for, as I understand it, the ability for a physician and a patient to make that individualized choice, it couldn't hurt being informed by a good appraisal of the available evidence along those lines. Dr. Messana.

DR. MESSANA: Returning to the question of whether CKD patients are the same as dialysis patients for the purpose of answering this question, I would remind those of Dr. Lazarus's comments. ESRD patients hopefully have vascular access. Once they have a permanent vascular access that's at risk for thrombosis, and that is a question on the table. That is less likely in this country at least, to be a risk for CKD patients. And I think there are other differences, maybe related to intermittent changes in volume status that are more acute, more immediate, who are undergoing intermittent dialysis, as compared to CKD patients who have a more stable, albeit abnormal volume status. And lastly, I'd ask Dr. Singh to comment on the typical dose range required in

the CHOIR and CREATE trials to achieve the high
00190
hemoglobin, as opposed to the typical dose of ESA required in dialysis patients in this country to achieve those kinds of targets, and does that provide evidence for a difference between these two populations.
DR. GOODMAN: Dr. Singh, want to try that one?
DR. SINGH: Clearly the dosing patients in dialysis and nondialysis populations is very different. In CHOIR we used, just to give an example, we used somewhere in the range of 9,500 units per week for the higher arm and around five to 6,000 when we look at the median for the lower arm. Just to compare that with the dialysis population, in the United States there is order of magnitude higher levels of epoetin being used in the dialysis population. The average dose from what I remember from a paper by Dr. Carter's group that was published in Kidney International, the average dose is about 7,000 units per dialysis treatment, or per administration.
There are marked differences between also Europe and the United States. In a recent
00191
paper, in Europe, zero to five percent of patients on dialysis are treated with greater than 18,000 units of erythropoietin per month, whereas in -- or per week, I'm sorry, I misspoke, per week -- whereas in the United States, that number is over 30 percent. And so there is clearly differences. Now there may be differences in comorbid conditions and so on that might explain it, but there are a number of differences that are attendant in ESA dosing between dialysis and nondialysis between different countries that I think we don't have a really good explanation for as yet.
DR. GOODMAN: Dr. Messana, what do you take Dr. Singh's answer to mean to you now with regard to your question?
DR, MESSANA: I'm not sure. I think he admitted that there are differences between CKD and ESRD, but I'm not sure how, whether he believes that they're important enough in terms of addressing these questions, but I don't want to put words in his mouth.
So do you still believe that given the different patterns of volume status and the clearcut clinical differences between CKD and
00192

ESRD, the different dosing requirement in U.S. CKD compared to U.S. dialysis patients, that they're comparable for the purposes of answering these questions?
DR. GOODMAN: Is that a thumbs up or thumbs down, Dr. Singh?
DR. SINGH: Well, I think that in our nondialysis patient population, I think you should be, generally be able to use very little, you should be able to use very little or no ESAs, as shown by the placebo arm of the TREAT study. I believe in the dialysis population, it's going to be difficult to sustain that. I don't believe that you can get away with using no ESAs in dialysis patients, I think one would need to use ESAs, because otherwise you would have a precipitous drop in hemoglobins, very substantial decrement in quality of life and need for transfusions if you completely withdraw ESAs in that population.
So I do not believe that you can withdraw ESAs. I believe you can reduce dose in that population. There may be a very small subset of patients in whom you may be able to

00193

withdraw ESAs, but I think in the vast majority of patients that ESA therapy for better or for worse is necessary in the treatment of anemia of the ESRD group.
DR. MESSANA: Thank you.
DR. GOODMAN: Thank you. Dr. Singh, we're going to come back to that. Dr. Pauker is next.
DR. PAUKER: The discussions here, it's not clear to me within the two categories, dialysis or not dialysis, for four out of the six categories they don't fit. These are large categories and notwithstanding like the (inaudible) there's a huge gap and we're not going to be able to say A or B or C. That suggests to me some kind of scale that includes dialysis, crit, you know, all kinds of things together in that scale, and in that continuum we have to guard against complications and say what should happen in that individual patient. I think we can't just lump everyone together in a predictive scale that may be done, or maybe we need further research. But I think that has to get done before we wind up chucking the things either way.

00194

DR. GOODMAN: Thank you, Dr. Pauker. Just for the limits of my cognition, it does

help at least to try to see for some of these dimensions if they matter overall, yes or no, but of course you're right, this is a multivariant issue, very difficult to deal with.

Any other great insights with regard to the matter of dialysis or not? I understand it's kind of a basic break, but any other insights that any of our speakers could offer about that? Yes, Dr. Winkelmayer.

DR. WINKELMAYER: Just a two-sentence comment from another drug class that we've very familiar with, dose of statins, which have been very much tested and evaluated, and found to be efficacious in patients without kidney disease. In a subgroup of meta-analyses for the pravastatin pooling project, it was also found to be efficacious in patients with chronic kidney disease. In patients with ESRD statins, in two randomized controlled trials that were sufficiently powered, both published in the New England Journal of Medicine, statins were not efficacious with regard to the same endpoints.

00195

An indirect illustration of why dialysis and nondialysis patients may behave quite differently.

DR. GOODMAN: Thank you for that.

DR. KEWALRAMANI: May I just add a comment?

DR. GOODMAN: Yes, you may. This is Dr. Kewalramani.

DR. KEWALRAMANI: With regard to this question about whether dialysis patients are different than CKD patients not on dialysis, I think we covered a lot of the points today. But just to add one more point to the consideration, dialysis patients, as you know, in the United States are almost all under complete surveillance by way of the USRDS system. We have data in fundamentally an entire registry of patients who have dialysis, anemia, and have ESA therapy, so there is a wealth of evidence in dialysis patients that doesn't exist in CKD patients, and I think if you think about the difference, it's an important difference to consider.

DR. GOODMAN: Thank you. So this is the issue of looking for the key under the lamp

00196

post, the lamp post light's just part of this population. Dr. Agarwal.

DR. AGARWAL: Just one more comment. There's a fundamental difference between

peritoneal dialysis patients and hemodialysis patients. PD patients actually require much less EPO doses.
DR. GOODMAN: Thank you for that.
Dr. Steinbrook, if I might pick on you here for a second. What is your current take with regard to this distinction about dialysis and nondialysis insofar as the evidence tells us about impact on the health outcomes we care about? Are you starting to see some light on this issue? We're looking, again, for ultimate impact on those four main types of outcomes. Dialysis or not, does it ultimately make a difference, do you suppose, based on what you've heard and the evidence at present?
DR. STEINBROOK: If we're just looking at this in terms of the sufficiency of the evidence, I think that in speaking generally and regarding some of the studies regarded one of the populations, not the other, that the evidence base is in the same ballpark. I think

00197

a lot of what we've heard deals with the fact that people who have some kidney function as compared to some who have no kidney function end up being managed differently and have different baseline requirements for ESAs, if at all, so I think it depends on what you're looking at.
In terms of the evidence base, I think we're there, but there may be differences in terms of recommendations going further and anticipating some of these other questions for discussion, where the difference could be important.
DR. GOODMAN: But you do, it sounds like you're acknowledging that the available evidence is sufficient to draw some findings with regard to the impact on these outcomes.
DR. STEINBROOK: Yes.
DR. GOODMAN: And what those impacts are may differ?
DR. STEINBROOK: Yes.
DR. GOODMAN: They will, okay. Other comments on this aspect? Dr. Danis.
DR. DANIS: I want to ask the other panelists who are nephrologists, I got the

00198

sense from Dr. Singh that while dialysis patients will undoubtedly need some level of ESA supplementation, there's some question that in predialysis there may not be a need at all, and I want to hear from the panelists.
DR. GOODMAN: It looks like Dr. Coyne.

DR. COYNE: I don't think we can say never in CKD patients, but I think the best evidence is from the TREAT trial. So what we had lacked was the natural history of what happened to hemoglobins in people who were largely untreated. In TREAT, the salvage arm got ESA therapy whenever their hemoglobin was below nine and then it was stopped once the hemoglobin was above nine. The average dose in that group was zero, and the mean dose, or the median dose was zero and the mean was five. So we can use it as salvage therapy in those patients and at lower levels.

I think the big difference in my mind between CKD and dialysis patients is that dialysis patients require this therapy almost universally, almost continually, whereas in CKD patients the vast majority do not require it. They may need it when the eGFR is less than 30

00199

to 40, and I would favor 30. And if they require it, they are a distinct minority of the CKD population. Once eFGRs are less than 15, if you have a nondialysis patient less than 15, the incidents of needing these ESAs go up, and that's using hemoglobins basically nine or ten, to decide that you're probably going to put them on it to avoid transfusional risks.

DR. GOODMAN: Thank you, Dr. Coyne. Dr. Agarwal.

DR. AGARWAL: This issue of anemia has been looked at pretty carefully in chronic kidney disease, and there was an enhanced analysis a few years ago, and what they did was looked at it cross-sectionally, when does anemia occur in association with estimated GFR? That was done by G. Seward, published in JASN, and what they found was when your creatinine becomes abnormal, that's when you statistically have lower hemoglobin compared to the control. In other words, in a woman about 1.3, in a man about 1.4 or 1.5 range, that's the creatinine, and that would correlate with an estimated GFR of less than 60, that's when you see the onset of anemia.

00200

That's a mean, though. You won't see many patients who are that level of anemia even when they have florid proteinuria. There are studies in diabetic patients, for example, with a lot of proteinuria, and they will get anemia or chronic kidney disease, and they will require the support.

When you're talking about the

populations, it's one thing, but when you're treating individuals in the clinic and say that you have a hemoglobin of ten and you have an eFGR of 65 and therefore you don't have anemia of chronic kidney disease, I think is just plain wrong.

DR. GOODMAN: Thank you, Dr. Agarwal. And I will just remind us again, we are very interested in clinical expertise here today, but whenever possible if we can refer to the body of evidence, that will be of greatest help to the Agency. Any last comments on the dialysis-nondialysis issue? Not that we've totally resolved it, but want to hit some high points? All right.

Let's move to this matter of pretreatment baseline hemoglobin levels. CMS

00201

laid out four intervals here, and what we want to explore at this point is to what extent does the baseline, the pretreatment baseline hemoglobin level bear upon ultimately the health care outcomes when physicians are managing patients with ESAs or otherwise. So what matters here, the four intervals are under seven, seven to just under nine, and nine to just under 12, and then 12 and greater. And again, these are the pretreatment baseline hemoglobins. How important are they with regard to predicting the impact in health outcomes of having been managed this way.

Dr. Satya-Murti.

DR. SATYA-MURTI: I would like to actually combine B with C, they seem to have similar ranges and numbers. But even if you don't, a little point of despair for me is that FDA labeling says it's for treatment of anemia, and yet we haven't even agreed on how to define anemia in this population. Is hemoglobin or hematocrit a valid marker, or patient symptoms or experiences as we heard this morning? Without any firm belief in being able to identify what anemia is, I think some of these

00202

terms seem to be legacy terms as to what determines anemia and whom should we treat. So this is a very crucial question, ten, nine, so I would like to hear not only from the panelists but our experts as to should we abandon hemoglobin as a target unless it's less than seven and the patient has syncope, or should we strive for something else, or simply shelve these decisions until we agree on what a valid surrogate or index of symptoms in anemia

would be?
DR. GOODMAN: Dr. Satya-Murti, is it not important to consider both the baseline level and the target? They're not the same things obviously.
DR. SATYA-MURTI: Right, so that's why I think we should combine B and C. The same doubts, hand wringing doubts about what is a valid identifier applies to both B and C.
DR. GOODMAN: Thank you. Dr. Pogach first, and then Dr. Levine.
DR. POGACH: I would like to actually begin with the one about chronic conditions. If you have individuals who cannot exercise for other reasons, there are a lot of comorbidities

00203

in these studies, and perhaps Dr. Singh or someone else would comment, who have heart failure, who have peripheral vascular disease. They are not likely to be able to increase their exercise capacity, not because of anemia but because of other conditions. So one of the questions should be, can one evaluate baseline hemoglobin independently of somebody's ability to respond because of other organ issues. I think, again, the issue is probably going to be a heterogeneous answer, that those people who otherwise could achieve a higher capacity might respond, and those who can't won't, irrespective of the hyporesponse definition.
DR. GOODMAN: Dr. Levine. Thank you, Dr. Pogach.
DR. LEVINE: Well, it seems to me as I've been listening that one of the key benefits of ESA that's being promoted is reduction in transfusions. So it seems to me that an important issue is what is the threshold for transfusion.
DR. GOODMAN: Okay, that's certainly part of it. Ms. Atkinson.
MS. ATKINSON: The question is

00204

pretreatment, and when we look at question one, which I know we're not looking at, but it talks about treatment being blood transfusion, iron therapy or ESA. So when we think pretreatment, is treatment including all of those things or strictly ESA?
DR. GOODMAN: To answer the earlier questions, it can be any of those, but if you'd like to concentrate on any one of those, that's all right as well. If there's a difference, then do raise it. Did you want to comment about that at this point? Okay. Dr. Pauker

and then Dr. Coyne.
DR. PAUKER: One of the technical points. In 5-B the fourth category is greater than 12, and Dr. Singh keeps referring to greater than 13. We have some confusion about what categories we're talking about. I understand that he's talking ten to 12 in some cases, but Ajay said 13. Could we hear from Ajay why he's saying 13?
DR. GOODMAN: As a target?
DR. PAUKER: And he mentioned the number 12.
DR. GOODMAN: Dr. Singh.

00205

DR. SINGH: The reason I set the target at 13, that is the target that has been used in the randomized control studies in the four trials that were discussed this morning. In Normal Hematocrit the target was 13 to 15. In the TREAT study the target was, I don't have my notes in front of me, but 13 and higher. In CHOIR it was 13.5, and in TREAT it was 13. So the reason -- that's the target hemoglobin. It's important to distinguish between achieved hemoglobin and target hemoglobin. In CHOIR, for example, achieved hemoglobin average was 12.6 and then, you know, the other trials range from that.
So I think the reason, where does 13 come from, that comes from the evidence of what the target was in each of these trials. In each of these trials when you targeted 13 or higher, it was associated with either no benefit or, in certain parameters, or increased risk of death or cardiovascular complications.
DR. PAUKER: That's what I mean, maybe we should have 13 too.
DR. GOODMAN: Dr. Coyne is next.
DR. COYNE: So, related to the issue

00206

of mortality, prior to the introduction of EPO the mortality rate in dialysis patients was significantly higher than after its introduction, and within a few years the mortality rate fell by about 10 percent or so, that's in the USRDS data. So by the time we brought the hemoglobin in the dialysis population up to about ten, we saw a marked reduction in mortality, and I think most of us in the renal community are not interested in testing that hypothesis with randomized trials. But we have to remember that if the mean hemoglobin in the population is ten, about half the patients were below that level at any given

time.
Transfusional risk has been tracked by the government for many years and is available from the USRDS database also. And when the mean hemoglobin in the dialysis population reached about 11, since then the quarterly transfusional rate in dialysis patients has remained flat. As we saw, the mean hemoglobin has increased in 2006 to about 12 or even higher, and that did not lead to any further reduction in transfusional rate in dialysis

00207

patients.
DR. GOODMAN: So what do we conclude based on the things you just said?
DR. COYNE: That maintaining a hemoglobin between ten and 11 probably increases survival in dialysis patients, and dramatically reduces transfusional rate.
And lastly, from the U.S. transplant data, we have evidence on panel reactive antibodies. And again, in about 1998 the incidence of very high PRAs, greater than 80 percent, which is difficult to transplant in such patients, that incidence on the active waiting list is, if anything, higher now. So when the mean hemoglobin in the dialysis population was about 10.8, the rate of high PRAs, whether you want to look at 79 percent or 80 percent plus, has remained flat to even increasing. The major driver is actually probably more prior transplants, sensitizing patients, and not transfusional rate.
So again, I would conclude that a mean hemoglobin in or around 11 in the dialysis population minimizes as best we can transfusional risks and incidence of high PRAs.

00208

DR. GOODMAN: Dr. Jacques has a comment.
DR. JACQUES: Just because people seem to be wondering about the context of this particular question, what we were trying to get at is simply is your hemoglobin in and of itself the ultimate predictor of your outcome. So that, for example, if you, simply to use the old medical term, have good protoplasm and your hemoglobin natively simply stays above 12, does that simply indicate that you have low inflammation, low whatever, and are simply likely to survive no matter what happens to you in terms of medical intervention? And at the same time, if you have the exact opposite, are you likely to have a bad outcome despite any

medical efforts, even if they might be heroic. So that was the context in which we posed that question.

DR. GOODMAN: And that's why it's with regard to the pretreatment baseline. Dr. Steinbrook, and then I'm going to ask Dr. Pfeffer to come up. Dr. Steinbrook.

DR. STEINBROOK: I think one of the things about this question is it can be looked

00209

at in different contexts, and certainly so much is focused here in terms of the public discussion and the medical discussion about numbers and ranges of numbers. And I can just say, I'm an internist, not a nephrologist, but based on what I've heard today and what I've read previously, it seems to me that the action is somewhere between nine and 12. I don't think anybody -- I mean, if somebody is healthy and is able to maintain a hemoglobin above 12 and is able to remain healthy and they don't need intervention, that's great. If somebody is considerably lower, less than seven, or seven to nine, I think in general terms one would suggest that one intervenes. But then you have this range of nine to 12. I don't know whether the evidence is robust enough to parse it down to ten or 11, or 9.5 to 10.5, recognizing that there's variability between individuals and standard deviations, and individuals and reactions, you know, all that sort of stuff. But it seems to me that the action is between nine and 12, and the goal would be to try to narrow that as much as possible.

00210

A final comment. We also have to factor in the ways in which erythrocyte stimulating agents are delivered, if it's determined to treat in that direction. I've heard nothing to suggest that you can get to some particular point, it's better to use a bigger dose than a smaller dose, so that also has to be factored in.

DR. GOODMAN: Point well made. Dr. Pfeffer, on this or the earlier point briefly.

DR. PFEFFER: On Dr. Jacques' point.

DR. GOODMAN: Go ahead, sir.

DR. PFEFFER: I just have to say something about dialysis-nondialysis. In TREAT we had the opportunity to watch people go across that threshold, 600 people went from nondialysis to dialysis, and their mortality subsequently was very very high, so there is a

difference, and that just has to be on the table.
DR. GOODMAN: There's a difference in the people who crossed over.
DR. PFEFFER: And once you cross over, your hazard of death is much different than your peers who haven't crossed that line.

00211

That's my point.
DR. GOODMAN: And those aren't the same people.
DR. PFEFFER: Of course they're not.
DR. GOODMAN: All right.
DR. PFEFFER: And then to the question of protoplasm, I think that's the fundamental question. I think that's the fallacy of picking a number. That, in CHOIR -- let's talk about hemoglobin achieved, because that's what you see. These trials all have a strategy to go to a target, but the fact that we didn't get to that target tells you something. None of the trials got to that target. So their strategy was to increase, increase. Our strategy was to increase until we hit that. Well, as Dr. Lazarus said, this isn't engineering, you don't hit a number and it's not perfect, and just measuring hemoglobin it bounces around. And I think we're fooling ourselves to think that I can look at somebody and dial a number, and have that number live with that person for the next few years, so there's something about picking that range. And then your question about

00212

protoplasm. I don't know what it is, and that's what I was trying to say in my five allotted minutes. I do not know what it is, but there are some people with the same dose who have a very brisk response. Now, a lot of people are saying brisk response, rate of rise is high, that's not a problem as we see it. What we see, these are the people, whether it's the way they react to the compound, their protoplasm that we can't detect that's different, they do very well.
So we overshot. Our target was 13. And if you hear the target is such a terrible thing, 25 of our patients overshot, walked around with a hemoglobin of 13.9, and those people had the lowest risk. So I think we have to be a little careful about our belief system, and believing that we know more than we know.
DR. GOODMAN: Thank you. No one would promise that, I assure you, at this point.

DR. PFEFFER: Well, that is the problem that we had, people's perceptions were so great that research was stopped.
DR. GOODMAN: Thank you. We would point out that FDA labeling and available

00213

existing guidelines, evidence-based more or less, do continue to refer to various intervals, so much of the evidence is defined in terms of these for better or for worse, perhaps it's for worse. What we're trying to do here today is see whether that evidence can stand up. I think Dr. Messana was next.
DR. MESSANA: My point was actually covered, thank you.
DR. GOODMAN: Great. Dr. Puklin was next. Dr. Puklin, we got it covered?
DR. PUKLIN: I think you covered it, yes.
DR. GOODMAN: Dr. Pauker, and then back to Dr. Agarwal.
DR. PAUKER: One question about that comment that patients are quite different, even in gender. Is that relevant in patients, talking about subgroups, is talking about it important or not?
DR. GOODMAN: Dr. Singh, looking across the various RCTs, was there any viable subgroup analysis of males versus females?
DR. SINGH: No, there doesn't seem to be any difference. And I just want to point

00214

out one other subgroup which was important, and that was in the TREAT study, and I was hoping that Dr. Pfeffer might address this as well, because he had the subgroup analysis for TREAT on his fingertips, and it was a fairly extensive subgroup, and Marc, do you want to talk about it or should I?
DR. PFEFFER: What's the question?
DR. SINGH: Well, the question is for proteinuria in particular. There seemed to be no difference in outcome in patients with proteinuria.
DR. GOODMAN: If you could just hold on, Dr. Pfeffer, we'll get to proteinuria in a minute. But the answer to Dr. Pauker's question is no?
DR. SINGH: The answer is no.
DR. GOODMAN: Dr. Pfeffer, on the matter of proteinuria, briefly and to the point.
DR. PFEFFER: Dr. Agarwal brought that up, and obviously we even stratified for

proteinuria. In diabetics, patients had over a gram, but everybody had some proteinuria. Proteinuria was a predictor of bad news

00215

outcomes, it was a particularly strong predictor for bad news renal outcomes, but it wasn't a predictor for response to the drug.

DR. GOODMAN: Thank you for that. I don't want to leave this point about these intervals. Dr. Singh, would you come back please to the microphone. In answer to Dr. Jacques' question, does it or does it not matter what your baseline hemoglobin is with regard to how these interventions will affect the four health outcomes that matter to us?

DR. SINGH: I believe that the hemoglobin is a very unreliable surrogate for outcome.

DR. GOODMAN: No sir. Starting with the baseline level, not the target, does your baseline level predict outcomes after having been treated?

DR. SINGH: In the randomized controlled trials I have not seen any data that suggests that the baseline hemoglobin at which you're enrolled in predicts how you do. What I have seen is that in the post hoc analyses presenting this data, achieved hemoglobin in those trials predicts outcomes. The higher the

00216

achieved hemoglobin is, the better the outcome; the lower the achieved hemoglobin is, the worse the outcome. And at least in CHOIR, the independent predictor of outcome in these studies was the dose of ESA these patients were exposed to, not the hemoglobin. So it didn't matter what hemoglobin you were at, it seemed to be whether you were hyporesponsive or not, and what dose of ESA you were exposed to.

DR. GOODMAN: So the target hemoglobin did or did not matter either?

DR. SINGH: It did not matter, so in both arms, although in the higher arm it was statistically significant, but even in the low arm there was a trend towards ESA dose, a strong trend towards ESA dose being a predictor of outcome in patients even in the low target arm. So it seemed to me the analysis was that the target didn't matter, and in that regard Dr. Pfeffer presented data from TREAT, where the target didn't matter as much as whether you responded to the drug. And he didn't present dose data, and I don't want to speak to him, but at least in CHOIR the dose predicted

outcome, the higher the dose, the worse the
00217
outcome.
DR. GOODMAN: What you're saying, then, neither the baseline treatment nor the target hemoglobin affected outcomes, you're saying the dose and the response to the dose mattered.
DR. SINGH: That the responsiveness to the dose mattered.
Now, one other caveat to that is that there is a lot of observational data that demonstrates that the hemoglobin level, the lower the hemoglobin level, the worse outcome there is in terms of the dialysis population. There's many studies that show that the lower the hemoglobin, the worse the outcome, and the higher the hemoglobin, the better the outcome. And the analysis of the randomized controlled studies mirror that in terms of achieving a higher hemoglobin was associated with improved outcome. In the randomized studies, at least in the CHOIR study, higher dose made a difference. The higher the dose you were exposed to, the worse the outcome, and it was an independent predictor.
DR. GOODMAN: Thank you for that.
00218
We'll do Dr. Agarwal, Dr. Messana, and then we'll go back to Dr. Kewalramani.
DR. AGARWAL: I think it's important for the panel to know about the analysis of FDA in this matter, and since you wanted a reference, it's Unger, et al. in the New England Journal of Medicine, Volume 362, page 185, 2010.
So what they have is a very insightful analysis analyzing the four recent ESA trials and addressing directly Dr. Jacques' question on whether the hemoglobin itself is bad. And basically they came up with three potential reasons why the adverse events could occur. First they stated the adverse cardiovascular events could be due to raising hemoglobin itself. However, this appears unlikely, because within randomized groups of trials as well as in nearly all observational studies, higher hemoglobin is associated with fewer cardiovascular events. There is this hemoglobin paradox here. If you target to a higher level, then you have increased events; if you achieve a higher level, you have a lower event. And I think this is why we are getting
00219

into this hyporesponsive stuff, because if you don't achieve that, that means you were resistant. And therefore, whether it's the drug or the condition that led to the hyporesponsiveness, led to the increased event, that's not clear from any trial. So with hyporesponsiveness, condition is important.
DR. GOODMAN: Let's not lose this point, Dr. Agarwal. Tell us, if you would, in a sentence, capture in a sentence, if you would, the point you just made. Just restate it, please. I don't want to lose it.
DR. AGARWAL: One sentence. There is a hemoglobin paradox. High hemoglobin targets increase adverse outcomes, high achieved hemoglobins lower cardiovascular outcomes. That's it.
DR. GOODMAN: Thank you very much. Next is Dr. Messana.
DR. MESSANA: Just addressing the point made by Dr. Singh in relation to the observational trials on hemoglobin, and achieved hemoglobin. I think through general consensus that those are quite confounded observations. In our own trial using Medicare

00220

data, low hemoglobin was associated with much higher, low achieved hemoglobin was associated with much higher mortality after adjustment for ESA dose. However, when you adjusted for comorbidities, you markedly reduced the observed hazard ratio for mortality in patients with low hemoglobin.
Others have used laboratory markers of inflammation as an adjustment rather than claimed comorbidities and come up with similar results, the registrar study. And the question of unobserved comorbidities in the confounding of this hemoglobin-mortality association in observational studies is very real. And so I think we can only draw limited conclusions from the observational literature with regard to achieved hemoglobin.
DR. GOODMAN: So, I want to catch it one more time, because you talked about the kinds of studies. What can we conclude based on the available evidence about that impact?
DR. MESSANA: From the available literature, the observed association between achieved hemoglobin and mortality is likely heavily confounded in this population.

00221

DR. GOODMAN: Heavily confounded in which population?

DR. MESSANA: The ESRD -- well, the dialysis population, which is where most of the observational data is from.
DR. GOODMAN: Good, thank you.
Dr. Kewalramani.
DR. KEWALRAMANI: Because these areas are complex and there are a few different concepts that folks are referring to, these concepts can often unfortunately be combined, and inaccurate conclusions can be reached, so let me just try to separate these.
There is a difference between targeting a hemoglobin, that's the number you're trying for; achieving the hemoglobin, that's where you actually get to. And there is a very important difference that has been confused I think here today as well with regard to the entry criteria for studies and what the lower arm of these studies are.
So let me just summarize this by saying in the Normal Hematocrit study, the goal of the lower arm was 30 percent for a hematocrit or ten for a hemoglobin. There's a

00222

range around that, but the goal of the therapy if you read the protocol, it says the goal of therapy is 30 percent, i.e., hemoglobin of ten, and then there is a range around that.
The second point to be made is as the sponsor of the TREAT trial, I know a little something about this data. The TREAT study does not have, it does not have a target for the lower arm. The entry criteria for TREAT was hemoglobins of less than 11. And we rescued individuals, it's not a target. If you happened to drift down to less than nine, you received rescue therapy to get you above nine. But I cannot overemphasize that there's no target for the lower arm of TREAT.
And I just want to end with a comment that Dr. Messana made. There is a lot of data now out there through observational research about this. When the appropriate statistical analyses are done, as Dr. Messana has pointed out, these analyses are quite confounded. There are five studies that have been published and they do not, I repeat, they do not show a dose relationship with adverse outcomes. Thank you.

00223

DR. GOODMAN: Thank you. And Dr. Kewalramani's point is well taken, that there's a difference between baseline and target and achieved, and sometimes rescued, so the panel

well recognizes that, thank you. Dr. Puklin is next, and then Dr. Koller I believe had a comment.

DR. PUKLIN: Let me ask the question as a follow-up to the previous comment. Is there a difference in these studies between the target hemoglobin level and what is actually achieved? So therefore, it may be that the patients who have the best outcomes, are achieving a hemoglobin of 13, may be doing well, but it may be that the patients who can't get their hemoglobin up who are getting a lot of erythropoietin, who have the complications, and that hemoglobin never goes into the 13 range. So it may not be that putting the hemoglobin in the 13 range level is a problem, it's the patients to whom you give a lot of medication to get their level up, and they don't make it; is that right?

DR. GOODMAN: I see Dr. Singh first.

DR. SINGH: That's right, and I think

00224

that was why it's very problematic to set an upper limit, because we don't know what the zone of safety is. What we do know, I believe, and I would like to disagree with my friend Reshma. I think she's parsing this to the Normal Hematocrit study, what the lower target is. When somebody tells you that the protocol, and this is in the New England Journal, is nine plus or minus -- I mean -- well, it's 27 percent hematocrit to 33 percent hematocrit in the low arm, and the target is 13, it tells me really what the target is, greater than 27 and less than 33 percent. That's the target. Because, you know, targeting one number of ten is really a hypothetical issue.

DR. GOODMAN: Thank you, Dr. Singh. Dr. Koller, is your comment appropriate for this point? Thank you. Dr. Koller, please.

DR. KOLLER: There is actually another analogous situation with regard to this. It comes from the study by Leland Jones, and they looked at the use of ESAs in the treatment of breast cancer.

DR. GOODMAN: What kind of study was it, by the way?

00225

DR. KOLLER: It was a randomized clinical trial and it was a large study. And they used it in patients who were receiving ESAs for anemia of cancer, not anemia associated with chemotherapy. And most people read the first draft of the study, and the

study was actually discontinued because of untoward effects, and they note that the mortality rate is higher in the ESA treatment group. But if you go to the next page, there are some interesting graphs, and the graphs basely look at the mortality rates, look at who died and who lived, and they divide them up into were you exposed to ESAs or were you not exposed to ESAs, did you live or did you die, and if you died, you actually had a lower level of hematocrit.

DR. GOODMAN: Achieved or targeted?

DR. KOLLER: Achieved. So that was regardless of the treatment arm, so if you did not receive any ESAs, you were more likely to die if you had a low hemoglobin level. And if you received ESAs, you were more likely to die also if you had a low hemoglobin level, but you seemed to have a compounded risk if you were

00226

exposed to ESAs, so there were four different levels of mortality.

DR. GOODMAN: And so our take-home point in a sentence is what, Dr. Koller?

DR. KOLLER: I think it was getting to the point that Dr. Jacques was trying to raise earlier, that there is something about some people who may carry some risks, there may be people who have issues with, they have poor responsiveness, that's probably an indicator of an underlying problem. And in addition, people, you may compound that risk by giving ESAs, and particularly if the ESA dose is increased sequentially.

DR. GOODMAN: Thank you. Just in order, Dr. Pfeffer, then Dr. Danis, then Dr. Satya-Murti. Briefly, Dr. Pfeffer.

DR. PFEFFER: No, just a factual comment. You were asking about baseline hemoglobin and risks. In a multivariant analysis of baseline hemoglobin, even in TREAT where you could only have a very narrow range because you had to have a hemoglobin less than 11, was an independent predictor of cardiovascular and renal events. Every gram of

00227

hemoglobin lower, eight percent increased chance that, accounting for age, proteinuria, smoking, blood pressure, LDL, so hemoglobin is a risk factor.

DR. GOODMAN: Baseline hemoglobin.

DR. PFEFFER: Baseline hemoglobin. You asked that question.

DR. GOODMAN: I did indeed, and the

result that you just mentioned is or is not published?
DR. PFEFFER: I think that was not included in our primary publication because of space, but if we just talk about a multivariant analysis, so I don't know how detailed that was.
DR. GOODMAN: Thank you very much, Dr. Pfeffer. Dr. Danis and then Dr. Satya-Murti.
DR. DANIS: Dr. Goodman, I don't know if it's okay to mention this at this point. I just want to not leave unquestioned the statement that Dr. Kewalramani said, that she did not think there was a correlation between the amount of ESA used and adverse outcomes, and that does not comport with what I've heard. And I, I would like to either have people say

00228

something about it or not, because to me that was one of the things that I have been thinking about as some kind of metric that we could begin to use or recommend for coverage decisions.
DR. GOODMAN: Who among the panel first has a succinct answer to Dr. Danis? Is that Dr. Agarwal first? You'll start, and then Dr. Messana.
DR. AGARWAL: What we know is that lack of response to erythropoietin is associated with poor outcomes, poor hard outcomes. That's all we know. That is because of the factors that lead to hyporesponsiveness, or is it because of increased dose that we use, has not been teased out. So when somebody says there's no signal, I disagree. I say the answer is we don't know.
DR. GOODMAN: There is a difference. Dr. Messana, on this point, and then Dr. Coyne on this point.
DR. MESSANA: Depending upon which statistical technique you use, you get different answers, and I think the good doctor is referring to a recent analysis that used

00229

marginal structure modeling as opposed to more traditional survival analyses, and came up with different results, suggesting this confounding business.
DR. GOODMAN: Thank you. On this point, Dr. Coyne.
DR. COYNE: Yes. I would also point to the CHOIR reanalysis, which found that there was increased mortality with dose. And lastly I point to all four of the trials that were

covered, that the high arm did worse, and we therefore are left with that using these drugs at higher doses leads to worse outcomes. And it defies logic to say that that is not due to the higher hemoglobin, that it's not due to the higher drug that you're giving the patient, but it's due to I don't know what. It should have happened, if it's idiosyncratic, it should have happened just as often in the low arm, which in most of these trials was also receiving active treatment.

DR. GOODMAN: So we should conclude what, then, Dr. Coyne, from that?

DR. COYNE: That ESAs carry increased risk and the possibilities for that increased

00230

risk are with the higher hemoglobin alone, which is difficult to rationalize; the rate of change, which is falling out of favor; the dose of the drug having non-hemoglobin effects; or some combination of the three.

DR. GOODMAN: Thank you. Dr. Singh, was it on this point, sir?

DR. SINGH: Yes.

DR. GOODMAN: On this point.

DR. SINGH: In the CHOIR analysis I disagree with Dr. Agarwal. The CHOIR secondary analysis, dose of ESA independently predicted bad outcome. And remember, in these randomized controlled studies if the randomization worked, which we believe they did, there would be roughly equal numbers of hyporesponsive patients in both arms. The patients in CHOIR had an excessive rate of death in the high arm where high doses of ESA were used. Similarly in TREAT, if the randomization works, hyporesponsive patients should be roughly similar in both arms, but one group in TREAT had more strokes than the other group?

DR. AGARWAL: I don't want you to get away with this. When you're using two

00231

different targets, you are targeting a hemoglobin to 11.3 versus 13.5, it's obvious that you're going to use a twofold higher EPO dose in the upper arm. That's what you found. When you say that it's associated with a higher dose, I disagree with you. That's an observational look at your randomized control data which does not make a randomized controlled trial, we are only looking at randomized control data. My answer is we do not know whether it's the dose or the disease that is leading to the worse outcomes, it's a

hypothesis.
DR. GOODMAN: I think both points are fairly made. Thank you, Dr. Agarwal, very much.
DR. PFEFFER: I have to respond.
DR. GOODMAN: Not yet, Dr. Pfeffer.
Dr. Satya-Murti.
DR. SATYA-MURTI: So this morning, I think it was Dr. Pfeffer mentioned, and then Dr. Agarwal mentioned that response to ESA is important. So I thought I heard it said that the response to the first two doses of ESA would be determinative of risk. So, has a

00232

subset analysis been done with the available data and compared just at the stage when the first two doses have been given, and the response taken into account, and the two different groups been analyzed regardless of what happens subsequently, to find out what the ultimate risk is, say at the end of a year or so forth, starting with the baseline data of poor response, however you start to define it, so this would probably be a subset analysis.
DR. GOODMAN: So, is that a question, Dr. Satya-Murti?
DR. SATYA-MURTI: So has there been data and analysis of poor responders versus good responders, say longitudinally, with the first two doses?
DR. GOODMAN: Are you directing that to Dr. Pfeffer?
DR. SATYA-MURTI: In particular, and any of the other panelists.
DR. GOODMAN: Dr. Pfeffer, in response to Dr. Satya-Murti's question.
DR. PFEFFER: Can I just comment on the risk, because I think that's fundamental to --

00233

DR. GOODMAN: Please respond to his question first.
DR. PFEFFER: Yes, we have done that analysis. It's a very confounded analysis, as everybody is saying. We are using events post randomization to identify human beings based on their hemoglobin response. And when we do that, that takes out only half of the patients who received darbepoetin. So we look at those half. The 25 percent who after two doses, the same fixed dose that the rest of the cohort got, had no change in their hemoglobin. And we tracked them from those five weeks there out, and they do worse than their peers. But it's

very difficult to match them. To match them to placebo we tried to do propensity and it was very difficult. So yes, we can find 25 percent of the people who do worse than their peers, the hemoglobin achieved is lower, but I can't tell you what it is about them except this operational definition, they received two doses and didn't have a brisk response.
Now, I must talk about risk, because I think this panel has to put everything in perspective.

00234

DR. GOODMAN: We're trying our best, Dr. Pfeffer.
DR. PFEFFER: I know you are, and I'm trying to help.
DR. GOODMAN: We appreciate your help. What is your answer to that earlier question?
DR. PFEFFER: What is the risk? I think if you look at the studies, here we're talking about a placebo-controlled study with 4,000 people. 1,203 had something terrible happen on the cardiovascular, 1,260 had something terrible happen on the renal. The dose difference was night and day. One group received 225 micrograms on average, mean, the other group received five. Huge difference in dose. The difference in mortality was none. The difference in the prespecified composite endpoint was nil. We did detect a safety signal in stroke.
So if you look at CHOIR, there were 50, maybe 80 deaths. I'm talking about 600 people died. And with this huge dose difference, there was no statistical difference. So the risk that I think we should be talking about is the risk of stroke, not --

00235

there is no risk for death in this huge range of doses, from zero to 200.
DR. GOODMAN: Okay. Now, based on the evidence that you just cited, one of the outcomes about which we care is vascular events, stroke, MI, CHF. What then would we conclude from the evidence that you just cited, Dr. Pfeffer?
DR. PFEFFER: Well, our major conclusion was that we were neutral on our primary endpoint, which was a composite of death and the cardiovascular. We used safety at a different threshold for efficacy. I would not be standing here saying we reduced stroke if the numbers were reversed, because it was a component of one of the endpoints. But since

it's safety, we're making a big point about that. But it isn't -- for efficacy it was neutral. We are pointing to a safety signal for stroke.
DR. GOODMAN: Thank you very much. I wanted to do the following, if you don't mind. I'm going to ask in the following order, Dr. Pogach, Dr. Calega and Dr. Steinbrook to tell us what the panel might want to conclude or

00236

find based on this immediately preceding discussion about the relationship between the treatment, hemoglobin and outcomes. What can you take from this most recent discussion that we just heard? We started off talking about baseline, we talked about targets and achieving those targets. What can we conclude about these levels of hemoglobin at this point? And we'll start with Dr. Pogach; do you want to take a try at that, Dr. Pogach?
DR. POGACH: So you're talking now about the baseline hemoglobin values?
DR. GOODMAN: Yes. We started with that, and we got into a discussion about these relationships with regard to targets, baseline, achieving target. What can we conclude here?
DR. POGACH: Well, I haven't seen the multivariant analysis just referred to. I don't think that there is necessarily evidence, at least from what I've read, that would say that the baseline hemoglobin would necessarily predict the survival benefit, independent of comorbid status.
DR. GOODMAN: You would not?
DR. POGACH: I would not.

00237

DR. GOODMAN: Thank you.
DR. POGACH: I think that it's obviously highly confounded as to why people have a low hemoglobin in the first place, that if there's serious other conditions, if there's hyporesponsiveness, it's whatever the protoplasm is which is the issue, not necessarily the hemoglobin value itself.
DR. GOODMAN: Thank you. Dr. Calega, do you care to comment at this point?
DR. CALEGA: For me the discussion is very interesting because we have two groups of individuals, or two groups talking about a threshold, treating to a threshold above nine, and we have other groups that are talking about treating to a range of ten to 12, each with their own set of issues in terms of how to titrate the patients. But I find it

interesting, if you are going to treat to a threshold of greater than nine with no target, and we're hearing that as you push the dose there are worse outcomes. We're also hearing that there are hyporesponsive patients who, when you push the dose on them, have worse outcomes.

00238

What is our target to treat? Are we treating to a dose of EPO in these patients if we're not treating to a hemoglobin or hematocrit level?

DR. GOODMAN: Is that a question to be answered by one of our speakers?

DR. CALEGA: Speakers or the panel.

DR. GOODMAN: Dr. Puklin, on that?

DR. PUKLIN: Yes. You see, that's where science may fall apart. We've heard a number of people tell us that they can tell by how well they feel as a human being, so that's not a target number. But it may be in this disease that that's the best one can do, is to keep treating them and if they respond and feel good, that's the endpoint. I think it's inappropriate to apply a standard across the board to a whole group of people who have different etiologies and they start out with different hemoglobin levels. And if you target the threshold at 13, you may end up with complications that you don't want to have, and if the patient is happy with a hemoglobin of ten or 9.5 and they're feeling well, that could be the endpoint.

00239

DR. GOODMAN: Thank you.

Dr. Steinbrook.

DR. STEINBROOK: Number one, it stands to reason that, all things being equal, having a lower hemoglobin to begin with for whatever reason is not good, as compared to having a higher hemoglobin.

Number two, it seems to me that we're still somewhere between nine and 12, I'm talking about achieved, targeted, how you get there, something like that, and I'm not sure that good quality data allows us to narrow it that much. Similarly, with the ESA --

DR. GOODMAN: When you say nine to 12, you mean targeted, or achieved?

DR. STEINBROOK: Either of the above, because I just think it would be nice to have a tighter range, even given the uncertainties and people going up and down, but I think we're somewhere in nine to 12.

The problem with ESA dosing is that it's never, unless I'm wrong about something, it's never been sort of an independently defined variable going forward prospectively in a randomized controlled trial. I think we need

00240

that and we can come back to that later. But having said that, I've heard nothing that would lead me to want to use more EPO than the minimum that I needed to to achieve a result. Maybe it's not bad with all this confounding where you can't independently tease it out, but I've heard nothing that says that it's good to use more rather than less.

DR. GOODMAN: When you say you've heard nothing, that includes having heard the evidence that's been presented today?

DR. STEINBROOK: That's what I mean by the evidence. I mean, I understand all this business about confounding and observational studies, and that's why we need it to be an independent variable going forward and we expect it to decline. But having said that, to turn it around, maybe it's confounding, but I haven't heard anything that says higher dosing, all things being equal, is good.

DR. GOODMAN: Thank you, Dr. Steinbrook. Dr. Pauker was next.

DR. PAUKER: A real quick question. As a non-nephrologist I get more and more confused. As I get more confused, I don't

00241

belief the evidence, so let me ask. Dr. Pfeffer says in his study, they had a control group, and I understand that they defined hyporesponsive as response to that initial standard dose or two. I hear Dr. Singh talking about hyporesponsiveness, but I haven't seen that same test, so I don't know how the trial, how hyporesponsive is defined in the trials. Is that a lack of response to any dose or standard dose or random dose, or what? Can you fill us in here, Ajay?

DR. GOODMAN: On the matter of responsiveness, Dr. Singh.

DR. SINGH: You've been confused? I've been confused with all your patient decision analysis since I was a fellow.

DR. GOODMAN: We only have until 4:30.

DR. SINGH: Okay. But I think with respect to your question, it's very difficult when you see a patient coming into your office or in dialysis to know who is going to be hyporesponsive, who is not. Some of the

patients, you can potentially predict, you can say well, the more inflamed patient, or the patient who has a lot of comorbidities is
00242
likely to be hyporesponsive.
But as Dr. Pfeffer pointed to in the analysis that they have, it was very difficult to say this group of patients is hyporesponsive and this one is not. I think the real issue is, you know, is there a threshold above which you should be treating patients hyporesponsive or not, and then using judgment to try to minimize the amount of ESA dose you can to achieve, you know, some quality of life reduction, if you can.
I think you can put this argument on its head and say if you have a patient with a hemoglobin of ten, you've been giving them higher and higher doses of ESA and they're not responding, they're hyporesponsive, should you keep increasing the dose of ESA when you're getting no further improvement in their hemoglobin level, and potentially no further improvement in any other symptoms, is that a sensible approach to take in that situation.
DR. PAUKER: So you believe any dose?
DR. SINGH: I believe that the way to deal with this is to try and use the lowest possible dose you can, and define whatever goal
00243
you want of your therapy, as Dr. Steinbrook just alluded to most lucidly.
DR. GOODMAN: Thank you.
Dr. Perfetto.
DR. PERFETTO: Thank you. Dr. Singh and anyone else who might know the answer to this, I'm trying to reconcile in my mind this issue that I've heard about, the confounding by indication and the hyporesponsiveness, so I think I have two questions. One is, in the trials, if someone was identified as hyporesponsive because their dose was being increased and their hemoglobin was not increasing, was the dosing stopped or were they continued to be treated? That's the first question.
And then the second is, what I seem to be hearing, and you can correct me if I have a misinterpretation, is that it may be those people who are nonresponsive who would be the most confounded in figuring out their negative outcomes.
DR. SINGH: I will just speak for the CHOIR data and let Dr. Pfeffer speak for the

TREAT data. In the CHOIR data there was a
00244
protocol for dosing to a maximum dose of 20,000 units per week. So you kept increasing the dose until you got to a maximum dose and then stopped after that.
DR. PERFETTO: So, was it more likely that someone who was hyporesponsive would be hitting that maximum?
DR. SINGH: Correct, yes, and that's what the data showed. So if you were, hyporesponsive patients in both arms, the low arm and the high arm were treated with higher doses, and independently had a worse outcome. I accept Dr. Agarwal's point that you have to be very careful about it with the post hoc data, but that's what the post hoc analysis showed.
DR. PERFETTO: So, would you suggest that if we had had some either biologic or dosing protocol way of identifying someone who was hyporesponsive, that we could just stop them at some point rather than having them max out and rather than having them reach that level of risk that we don't understand?
DR. SINGH: Correct. We could have a threshold of hemoglobin and have a maximum dose
00245
of EPO for most patients with some exceptions as a second dose, just so you limit the dose that the patient is exposed to.
DR. PERFETTO: Thank you.
DR. GOODMAN: Dr. Perfetto, he answered your question then?
DR. PERFETTO: No, I think there was more to it than just that, and I would prefer to have the dosing in the other studies.
DR. GOODMAN: On that particular question, Dr. Pfeffer.
DR. PFEFFER: This gets back to the issue of what we were doing in 2004. We were so fixed on hemoglobin, raising hemoglobin would improve patients, that the computer algorithm was such that we were raising the dose, raising the dose to try to get to that. Dr. Agarwal was telling you that we didn't have a target for the low arm, it was placebo, it was just rescue because the world said they must be treated. But what we were explaining is the first two doses were fixed, and then the computer kicked in and said you're not where we want you to be, you get more, or you are where we want you to be, you get less. So I can't
00246

tell you anything after that. Were we smart enough to do it again, we would now identify this group, we would fill this in to say well, it's not so much the hemoglobin, but don't keep giving those people higher and higher doses.

DR. PERFETTO: But in that dosing process, if someone's hemoglobin wasn't going up, would the computer have continued to give higher doses?

DR. PFEFFER: Yes, and it was built into the rate of rise, it was built into the hemoglobin level. Therefore at the end of the study I can step back, not being smart enough to have done this in 2004, and tell you what we observed. But this is post hoc and it is biased, but we had a group of about 25 percent that didn't get the increase in the first two doses, then the computer kicked in. They ended up getting 180 micrograms per month, compared to another group that got 60 micrograms per month, so it got a little confusing.

DR. PERFETTO: So what would your response be to this dilemma that I'm trying to work through, the hyporesponsiveness versus the

00247

confounding indication, or the mesh of those two?

DR. PFEFFER: First of all, I'm against speaking of their cardiovascular outcomes, we saw no difference in death. This doesn't work for stroke, by the way, I didn't say that, but the hyporesponsive story doesn't work for stroke, so if stroke is the thing we're concerned about then we're off on a tangent and that's the facts, it's just not an easy answer.

DR. GOODMAN: That's about as far as I think it's going to go, Dr. Perfetto. Dr. Pogach.

DR. POGACH: I haven't heard anything about whites and blacks. My understanding is that blacks have a well-known survival benefit in dialysis. Does anyone know of any literature either from the randomized clinical trials, post hoc analysis or observational studies that could link that in some way to responsiveness to EPO or hemoglobin?

DR. GOODMAN: Did any of the trials break that out? Dr. Singh, are you aware of any?

00248

DR. SINGH: No, I'm not aware of that from our trial, subgroup for race. I don't

remember the data from TREAT but Dr. Pfeffer can get you that.
DR. PFEFFER: I need a minute to get that.
DR. GOODMAN: We'll get to that. Dr. Kewalramani, on this point?
DR. KEWALRAMANI: Yes.
DR. GOODMAN: Okay, briefly.
DR. KEWALRAMANI: I just wanted to address Dr. Perfetto's point about hyporesponse, confounding and randomized clinical trials. I just want to point out again, because this field does get complicated and it sort of forces us to mix concepts, but just to be sure, there have been no randomized clinical trials assessing hyporesponse. The concept of hyporesponse has come about by way of analyzing either existing databases or randomized clinical trials, so that's one point.
The idea of confounding, that is what is the bugaboo in trying to understand these patients who don't respond to ESAs, is it

00249

because they have bad protoplasm or is it because of trying to get them to a high hemoglobin level. That concept is confounding as we try to figure it out. And just to make sure that we're all grounded, the risks that we saw in CHOIR and such are RCTs in terms of level of evidence. Those RCTs were done at higher hemoglobin targets, that's what the RCT was, it was not about dose, it was not about analyzing other things.
DR. GOODMAN: Okay, thank you. We actually have talked about this matter of blunted or nonresponse, so we've touched upon that a little bit. I wanted to move to this matter of rapidity of rise, some mention was made of it earlier, and one of our questions, it happens to be 5.D, was addressing whether the ESA dosing strategy has been implemented to minimize the rapidity of hemoglobin or hematocrit rise and/or oscillation in their levels. There was some mention made of that this morning. Dr. Agarwal, did you have a comment on that?
DR. AGARWAL: The rapidity of response has been a concern, and Unger and associates in

00250

the New England Journal article mentioned that it could be one cause of the increase in adverse vascular events that we saw in the four randomized trials. Outside the FDA, the

practicing nephrologist does not measure hemoglobin as is recommended in the PI. Nobody can practically have a patient come in twice a week to have his hemoglobin measured, especially when you're treating patients with nondialysis CKD. You can measure as frequently as you want in dialysis, but you can't in the chronic CKD. What these trials have missed is the concomitant change in blood pressure, and they have never monitored it during the time that the hemoglobin has been going up.
In the TREAT trial there was a difference between the two groups. In diastolic blood pressure the p-value was less than .001. The diastolic blood pressure difference was two millimeters of mercury. Now you might think that's nothing. But a million-people meta-analysis from Lewington from Oxford, it shows that if you reduce the blood pressure ten over five, you reduce the stroke risk by half, or if you increase by five

00251

millimeters diastolic, you double the stroke risk. So that two millimeters which may be fairly trivial is not so trivial after all.
In the CHOIR trial, again, the blood pressure was high statistically between the two groups.
What I am trying to get to is that rapidity of rise in hemoglobin should perhaps be replaced by blood pressure monitoring at home by these patients, so they can tell you when they're getting into trouble.
DR. GOODMAN: Okay. But as a measure itself, the rapidity of hemoglobin or hematocrit change is or is not relevant, or it's just an indirect way of getting something.
DR. AGARWAL: It's only in the FDA analysis, it's never been actually analyzed while in the publicly available literature.
DR. GOODMAN: Thank you, Dr. Agarwal. Dr. Coyne, and then Dr. Singh.
DR. COYNE: I think it's worth mentioning that the FDA work group, the TREAT group, to try to minimize the rapidity of increase, so if there's a value in doing that, it should be reflected in the TREAT results.

00252

In earlier trials such as the Normal Hematocrit trial, one of the criticisms of that trial was the attempt to rapidly increase the hemoglobin from a mean of about ten on entry to 14, although the achieved was actually lower.
I'm not certain if the question refers

to randomized trials. If that's the case, then I think those are the answers.
DR. GOODMAN: If it does refer to that, what do the RCTs say?
DR. COYNE: The RCTs say that both TREAT and the Normal Hematocrit trial still found harm even though they had fundamentally different rates at which they were trying to raise the high arm.
DR. GOODMAN: Both found harm.
DR. COYNE: Both found harm although there was, you know, there was net increase risk of death and MIs in the dialysis study, the Normal Hematocrit. In TREAT the cardiovascular risk was limited to increased risk of strokes.
DR. GOODMAN: Thank you, Dr. Coyne. Dr. Singh and then Dr. Puklin.
DR. SINGH: The rapidity of rise issue

00253

has never been published. The FDA report was never peer reviewed and published. Its origin is from the safety review of 1,598 patients. In that safety review they found there was an association between worse outcomes and rise of hemoglobin. If you go to that FDA document, there was also a correlation of, a similar but strong association to decline in hemoglobin. This was a mixed bag of 1,598 patients. Subsequently in 2006 the FDA conducted a review, and this is again in the document that they presented at their meeting in September 2006, of both the Normal Hematocrit and the CHOIR data, looking at rapidity of rise. They reported that there was an association between rapidity of rise in both CHOIR and in Normal Hematocrit, and outcome. The problem was that they recoded all the events in CHOIR and Normal Hematocrit, including the adverse event data. So they took even non-adjudicated adverse event data and included that as outcome in the analysis. At the time when we published the New England paper on CHOIR, there was some preliminary analyses that we did looking at

00254

adjudicating outcome data and rapidity of rise, and there was no association. And I know that Dr. Pfeffer mentioned that it did not appear to be an association with this rapidity of rise, and in fact the patients who had the brisk increase in hemoglobin did better. So I'm not sure. I mean, I don't believe that there is any evidence, strong

evidence or otherwise, that suggests that there is association between rapidity of rise and outcome, certainly not in the published literature.

DR. GOODMAN: Thank you. Anything else, Dr. Puklin?

DR. PUKLIN: Yes. I just wanted to, it occurred to me, for the nonresponders who are getting erythropoietic stimulation, has anybody looked at bone marrows on these patients as a reason why they don't have a response, as opposed to things like blood pressure? That might be something that ought to be included in further investigations.

DR. GOODMAN: Any point on that, Dr. Singh?

DR. SINGH: No. It's an interesting

00255

hypothesis because in the animal studies treatment, at least this was in the original safety review of Epogen. Treatment with Epogen in animal studies was associated with mild fibrosis, so it would be interesting to see what happens in the hyporesponsive patients who were given higher and higher doses. One of the important points would be that if the patients responded to low doses of ESA and had a brisk response of hemoglobin, fine. If they didn't respond, the question is what do you do with these patients, do you keep increasing the ESA dose or do you stop. And if you stop, then the utilization of ESA will go down substantially. My question is, A, even though these patients do worse, and B, we know they don't even respond in the hemoglobin, so what are we doing with increasing ESA doses in patients progressively if they're hyporesponsive.

DR. GOODMAN: Thank you, Dr. Singh. In order, Dr. Messana, Dr. Danis and Ms. Atkinson.

DR. MESSANA: The notion of hyporesponsive patients, that being something that they carry like a chronic diagnosis, is

00256

not well founded in the observational literature. The USRDS has done analyses and published some beautiful figures that show that someone who's hyporesponsive now may not be so three months or six months down the road. Our own observational studies suggest that there are a bunch of intercurrent events that are associated with transient hyporesponsiveness, hospitalization, infections, a number of things, but these are all observational. And

so I think one must distinguish between transient hyporesponsiveness and those people who have chronic conditions that may make them hyporesponsive, and bone marrow disease may well be a candidate for a small fraction of the hyporesponsive patients.
DR. GOODMAN: Thank you, Dr. Messana. Dr. Danis.
DR. DANIS: This is about the responsiveness issue. I understand that there has not been done any trial testing responsiveness, but do people feel that we can look at the body of evidence and say whether there are certain doses at which we ought not to bother ramping up any further, or is there

00257

so much variability that there's nothing to be said here about how far to, in general guidelines, recommend what's a test of responsiveness?
DR. GOODMAN: So that's apart from the rapidity of rise?
DR. DANIS: Yes.
DR. GOODMAN: And I know we talked about this. Dr. Steinbrook in particular said maybe it's about what we do between nine and 12.
DR. DANIS: I'm not talking about -- well, the issue of what level, yes.
DR. GOODMAN: Yes, what to do, yes. Dr. Agarwal, on that point.
DR. AGARWAL: There is some guidance on this in the package insert because the FDA had revised the package insert, and I read the package insert yesterday. Basically what they have is they allow the physicians to increase the EPO dose in increments up to 12 weeks, and if they don't have a response then they stop increasing the dose. And I think that's been the FDA's answer to this responsiveness question.

00258

They are not saying to keep on increasing, increasing until you reach the sky. They're saying three months is all you have, you titrate the dose at periodic intervals, and you stop. And the starting dose of EPO is between 50 and 100 units per dose, if I remember correctly, and you get three increases of 25 percent increments in about two to four-week intervals, and that's it. So I think it's putting the brakes on how high you can go from their perspective.
DR. GOODMAN: Okay. On that point,

Dr. Coyne?
DR. COYNE: On this point. It really gets at the question of what's a maximal dose that's appropriate for the population, and between the United States and the rest of the world there's a great difference. And if you go to the European dialysis population, very little, zero to five percent of those patients receive more than 18,000 units per week, and their main hemoglobins are in the middle levels in general. In the United States the mean dose used to be about 18 to 20,000 and the median dose about 14,000, so we continue to use quite

00259

a bit, and we have about 30 percent of our patients, although it's probably coming down a bit, but about 30 percent were over 30,000 units per week.
And CMS defines a medically unbelievable amount as 400,000 units per month or the equivalent of about 90,000 units per week of epoetin in dialysis patients. So we really lack any strong foundation, in my opinion, to support these doses that exceed 30 or 40,000 units per week in dialysis patients.
DR. GOODMAN: When you say we lack foundation, you mean there's not enough evidence upon which to draw such a conclusion?
DR. COYNE: Yes. We have only achieved those generally outside of trials because of repeated increases because patients didn't achieve some arbitrary target.
DR. GOODMAN: So the evidence is not overwhelming, is it?
DR. COYNE: Yeah, I'd say it is not.
DR. GOODMAN: Thank you, Dr. Coyne.
Ms. Atkinson.
MS. ATKINSON: On that issue of unresponsiveness, during any of the clinical

00260

trials when someone was unresponsive, was the agent ever changed? Because Dr. Singh, you clearly pointed out earlier this morning that we can't compare apples to apples, that these agents are definitively chemically different. So I'm curious as to when there's unresponsiveness, and you're saying no.
DR. SINGH: No, not in the context of trials.
DR. GOODMAN: I want to make sure. State the question again, Ms. Atkinson, and I want to hear the response from Dr. Singh. Ask it one more time.
MS. ATKINSON: When there's a patient

that's unresponsive, does the agent, the ESA itself change, are we changing different agents?
DR. GOODMAN: Dr. Singh?
DR. SINGH: The answer in the trials is no, the protocol did not permit changes to other ESAs. In clinical practice, I don't know what other doctors do, but generally the consensus has not been to change from one agent to another if the patient is not responsive to one of them.

00261

DR. GOODMAN: Thank you.
Dr. Steinbrook, was your hand up?
DR. STEINBROOK: Not specifically.
DR. GOODMAN: Do you need to amplify it now?
DR. STEINBROOK: No.
DR. GOODMAN: Okay. Dr. Kewalramani.
DR. KEWALRAMANI: I just wanted to add three points to this discussion. The first is that the Phase One/Phase Two results with Epogen demonstrates that there's a very broad variability in the doses needed to get a response in terms of hemoglobin, it's a 40-fold variability. The second point is to amplify what Dr. Agarwal said, since 2007 there has been language in the U.S. label in both Epogen and Aranesp that guides physicians around this concept of hyporesponsiveness, although there's no clear definition, no widely accepted definition, there's a functional definition in the labeling that does guide you in this direction, as Dr. Agarwal said.
And the third point is that this discussion around hyporesponse is a really important one, and comes from analysis of these

00262

data from clinical trials that we're all trying to understand better about what it says. There has not been a randomized clinical trial, as we've discussed, about this. Amgen and the FDA are in conversation with each other about the appropriate studies that need to be done in a randomized clinical trial fashion that would address the hyporesponse of patients.
DR. GOODMAN: Thank you. Did I see Dr. Silverstein's hand up? Yes, sir, please come to the microphone.
DR. SILVERSTEIN: Just a very quick comment which is sort of a clinical observation but also a question for various people. When I have a patient who's unresponsive, and these are pediatric patients, the first thing I do is

I check their iron level, I check their PTH level, I check their nutritional status, I check a lot of things before I up the dose. And so my first thing is that statement that I think that has to be done, and I'm assuming most of us are doing that. But the second question really to various people is that, in all these trials which have shown quote-unquote

00263

hyporesponsiveness or requirement for higher dosing, were all these other factors placed into the analysis? Were PTH levels checked? I mean, three-quarters of adult patients and about two-thirds of my pediatric patients have high PTH levels consistently. And so the question would be, is, were these goals, were these factors all factored in when you looked at hyporesponsiveness. Because if a patient has a PTH level of 1,500, they're not going to respond to an ESA like a patient who has a level of 250.

DR. GOODMAN: Dr. Silverstein, actually we ask the questions, we hope you have the answers. Are you trying to make a point, sir?

DR. SILVERSTEIN: Well, my point is when you look at hyporesponsiveness or dose requirements, are all those other factors considered in order to ascertain whether that was the cause of hyporesponsiveness, as opposed to the patient requiring a higher ESA dose?

DR. GOODMAN: Do you have an answer to that question? Are you asserting something, sir?

00264

DR. SILVERSTEIN: My answer would be that I think it has a large impact on it and therefore, unless these things are looked into in all these studies that have been published, I don't know how you can say a patient is either unresponsive or is responsive to ESA.

DR. GOODMAN: Okay. Thank you for that. Back to Dr. Steinbrook.

DR. STEINBROOK: To follow up on the points which were made about ESA dosing, listening to them, there seems to be a disconnect between the way in which the label is written and perhaps what the usual and customary practice is. And while we haven't specifically heard any information today about dosing patterns or data in patients, I mean, is there such information which might inform what's happening as compared to what the label

might suggest would be an appropriate way to achieve what can be achieved in an individual patient in an efficient fashion?
DR. GOODMAN: You're asking what goes on in practice?
DR. STEINBROOK: Well, I'm just asking, we haven't specifically heard

00265

information or evidence presented about ways in which things are dosed. We've heard something about what the label says, we've heard something about in the U.S. versus other countries, and I'm wondering if there's a next step beyond that.
DR. GOODMAN: Thank you. Dr. Agarwal.
DR. AGARWAL: I can answer that question in a broad way. A minority of patients need a large volume of EPO dosing in analyses here. In other words, the sicker your patient is, the more EPO he requires to reach a certain target. The way I remember it is that 20 percent of your patients need 80 percent of the EPO that you spend in a month, that's my broad, you know, statistic, rule of thumb statistic. I think if we look at the management of these 20 percent and ask the question, these people are hyporesponsive, should we keep pushing the dose as high as, you know, the dose that they have been using, that is the fundamental question that we are struggling with.
The practice banners, I don't know if they have been adopted from the package insert

00266

to the clinical practice. At least that's not what we are doing. I mean, we look at the final dose of EPO, but I don't know if it is common practice, I can't speak to that.
DR. GOODMAN: Okay, thank you.
Dr. Coyne.
DR. COYNE: I think at that point, to move toward policies or issues, my experience in reviewing dialysis change and anemia protocols is they do not take into account the point of hyporesponsiveness and stop increasing the dose after 12 weeks. They also tend to set relatively high targets, the higher the target, the less likely a poorly responding patient is to get to that target, and consequently they're going to get higher and higher doses. A good example of that is Dr. Lazarus's mean hemoglobin in that population was 12 at a time where the target was 11 to 12. If you were really shooting for the middle, you might

actually have your mean there. And thirdly, when we look at incident dialysis patients, they tend to start on rather high doses, because these patients have a very high incidence of being, hemoglobins below ten,

00267

frequently in the eights. Even if they're increasing at an appropriate rate of, say, half a gram to a gram every month, because they're below target they get another increase in dose, even though they're going up. So consequently, at least an analysis by Cotter showed that by month four, 95 percent of the patients who had received at least 15,000 units per week of EPO during the first three months overshot a hemoglobin of 12. I don't think that's very rational management. So one policy, or one thing to focus on for CMS would be, is it appropriate to set a lower limit for EPO and have that individual fail that over a three-month course before you're allowed to proceed to these higher doses.

DR. GOODMAN: Dr. Coyne, have you seen anything in the evidence and particularly the RCT evidence that could answer that question?

DR. COYNE: Well, with regards to whether you could achieve that? I mean, to take the CHOIR study as an example, the maximum dose in the CHOIR study, and incidentally it was a CKD population, was 20,000 units. So those patients were managed and did in general

00268

increase their hemoglobin, and did in general have a very low transfusional rate, which was the goal of both arms. In the -- I will stop there.

DR. GOODMAN: Okay. I want to quickly just address two questions, and then we will address the next step. Does anybody have a concise comment or observation about this matter of whether the CKD patient has been evaluated to determine the etiology that is the cause of anemia, has that ever entered into a consideration for what the impact of the treatment has on outcomes? That is, whether the patient has been evaluated to determine the cause of the anemia? Any evidence of that that anyone can put on the table for consideration? Dr. Messana?

DR. MESSANA: Weak evidence, but in our observational trial and in others, people used claims diagnoses for a variety of conditions have been mentioned as part of the statistical adjustment, or the covariates in

the models. And that, to the extent that those could reflect diagnoses, have been searched for.

00269

DR. GOODMAN: And we could conclude what, if anything, from that?

DR. MESSANA: Well, the results that Dr. Koller showed this morning showing associations between achieved hemoglobin and ESA doses were adjusted for GI bleeding, hyperthyroid, a couple other things that Dr. Silverstein mentioned.

DR. GOODMAN: So they were adjusted?

DR. MESSANA: Yes.

DR. GOODMAN: Okay. Dr. Coyne, on that point?

DR. COYNE: Most of the randomized trials had minimal entry criteria to try to minimize the proportion of patients who were iron-deficient, which is a common cause of hyporesponsiveness, and also someone that's on uncontrolled hypertension or high PTH values, and so there was some attempt to avoid that. And obviously if there had been recent GI bleeding, they were also excluded. So, the trials are trying to look at populations who have already had those addressed.

DR. GOODMAN: Okay. And then question G had to do with whether the CKD patient

00270

demonstrates cardiac, cerebral or other vascular comorbidities, whether that's had a bearing on treatment options. I think we've heard a little bit about that today, did we not? Comments or additions on that? No? Dr. Singh.

DR. SINGH: I think one possible concern we should have is based on data from the TREAT study, and if patients have a very high risk of stroke, in the TREAT study the question is, should those patients who have an underlying history of stroke be treated the same way as patients who don't have an underlying history of stroke. So I think that speaks to this issue of whether there's underlying cerebral vascular disease, whether we should treat them similarly. I wanted to see if Dr. Pfeffer could comment on that. And then the second issue is that in the patients in the Normal Hematocrit study, those were high-risk dialysis patients who had evidence of cardiovascular disease when they were enrolled, both heart failure and coronary disease. They seemed to have worse outcome

than another population of patients that was
00271
also included in a randomized trial, the Canada-Europe study, who were asymptomatic, who when the results came out, they didn't have the same mortality risk. So I think there may be some consideration we have to give to the underlying protoplasm and how we then treat these patients with respect to underlying cardiovascular disease.
DR. GOODMAN: Okay, thank you. Dr. Steinbrook, on that?
DR. STEINBROOK: Could I just ask Dr. Singh to go the next step and say how he would advise beyond consideration? And I would also add malignancy in chronic kidney disease.
DR. GOODMAN: We're not looking at practice guidelines, of course.
DR. STEINBROOK: No, no, no, but just what the evidence says, does the evidence say anything about going to the next step, or is this something we need to be concerned about?
DR. SINGH: I would be concerned about treating patients who have a history of, underlying history of stroke with ESAs, because of the potentially higher, you know, potential risk of having another stroke. I think that
00272
would be an area of significant caution in my mind.
DR. GOODMAN: Was that derived from the evidence, that statement, or something else?
DR. PFEFFER: May I?
DR. GOODMAN: Dr. Singh is indicating Dr. Pfeffer.
DR. PFEFFER: Okay. Dr. Singh is yielding the floor, that's never happened. We have many multiple risk factors for having an event, but really what you're asking is an interaction between the therapy and that risk factor.
DR. GOODMAN: Yes.
DR. PFEFFER: And the only interaction that we've observed for a cardiovascular event, any cardiovascular event, is a prior history of a stroke. Those who have prior history of stroke behave differently and were more likely to be adversely affected, so for me that's a very important finding.
DR. GOODMAN: Thank you, and I thought you had mentioned that a little bit earlier today. Ms. Atkinson was next.
00273

MS. ATKINSON: Dr. Singh, correct me I'm wrong. This morning when you presented the four studies, the exclusion criteria for the majority of those studies were congestive heart failure, prior stroke, or recent stroke, recent MI, and uncontrolled hypertension; correct?
DR. SINGH: Well, not for all the studies. So for example, in the Normal Hematocrit study the investigators deliberately aimed to recruit patients who were high-risk patients who had a history of coronary disease, had a history of heart failure. Even in the patients who were enrolled in the studies, you have certain entry criteria, but it turns out that these patients developed those, some of those, some evidence of cardiovascular disease during the course of the study.
Cancer, for example, you know, in the TREAT study there were patients who had a history of cancer who were enrolled, and those patients ended up having, it appeared, although the numbers are small, an increased risk of having a cancer-related death.
There were exclusion criteria here. For example in the CREATE study, serious

00274

cardiovascular disease was excluded, but that doesn't necessarily mean that all cardiovascular disease was excluded. In the CHOIR study angina was excluded, uncontrolled hypertension was excluded, but it doesn't mean that hypertension itself was excluded.
MS. ATKINSON: Thank you.
DR. GOODMAN: So Ms. Atkinson, that means there was or was not enough to go on with regard to the stroke risk?
MS. ATKINSON: It just helps understand, you know, if you're not looking at that subset of population, then are these findings based on that.
DR. GOODMAN: Thank you for that. Dr. Agarwal.
DR. AGARWAL: So, I want to come back to the stroke risks. There are two risks that we've seen in these higher targeted hemoglobin trials, one has been heart failure, the other has been stroke. Both these events are fairly modifiable with blood pressure and, you know, actually the risk is doubled if you increase the diastolic by five. In the TREAT trial there was an increase in blood pressure, in the

00275

CREATE trial there was an increase in systolic blood pressure. So when you're seeing these

events that are very blood pressure modifiable, the message is use the drug in a more sensible way than fixing a target. I disagree completely that we should limit the drug to a person with a blanket statement, if you had a stroke, don't use the drug. What if I have a facial droop, and you know, I'm playing golf. I would rather die of a stroke on the golf course than in my bed feeling like a bag of worms, you know? I think it's really important, the patient's decision is really important there, and if we make a blanket statement it should not be done, it's a bad thing we are doing for the patients.

DR. GOODMAN: Thank you, Dr. Agarwal, for reemphasizing, as you are, the importance of patient references. Dr. Pogach, and then we'll wrap it.

DR. POGACH: A response to Dr. Agarwal. Is your statement about the decrease (inaudible), is that associational data from epidemiologic trials, or has that been tested in randomized trials?

00276

DR. AGARWAL: That's the data which is a meta-analysis of one million people who have participated in any hypertension trial in the world. It's out of Oxford, it's published by Lewington and Lansing, about five or six years ago, and that's where the hypertension guidelines also included that statement.

DR. GOODMAN: Is that helpful, Dr. Pogach? What are you concluding from that?

DR. AGARWAL: It is randomized controlled --

DR. POGACH: Based on the recent ACCORD trial, I have some suspicion of associational studies and meta-analyses.

DR. AGARWAL: These are randomized controlled trial data. I know what the ACCORD trial shows, and that is a separate issue altogether.

DR. GOODMAN: Okay, thank you. Dr. Kewalramani, to make a brief statement on this?

DR. KEWALRAMANI: Yes. I did want to make a brief point about the stroke finding in TREAT, and that is to say that the package insert for the ESAs has been updated for all

00277

patients. There's no differentiation made in this risk of stroke when targeting hemoglobin levels of 13 or greater, which is what TREAT did, and it's included in the package insert.

DR. COYNE: Do you think that your drug, that targeting 12 or less increases the risk of stroke? Can I tell my patient it will not increase your risk of stroke if I target less than 12, or 12?
DR. KEWALRAMANI: I think if we follow evidence-based medicine and try to be true to our patients about the evidence that we have and the knowledge that we know, when we practice medicine there are lots of things that we don't know and then there are things that we do know. If I was guiding my patients about stroke risk and they asked me their risk of stroke at 12, I would let them know that there are no randomized clinical trials that have evaluated that or shown harm at that level.
DR. GOODMAN: Are you satisfied with that answer, Dr. Coyne?
DR. COYNE: I guess. Could we also ask Centocor that question, if they feel that use of their drug to a hemoglobin of 12 does

00278

not increase the risk of stroke?
DR. GOODMAN: Is that Dr. McKenzie on that?
DR. MCKENZIE: Right, an excellent question, and I would agree that there is no randomized controlled data to inform the absolute answer in that ten to 12 grams per deciliter range. Having said that, you know, clearly in the TREAT trial where you targeted higher hemoglobins, that was a finding of that trial.
DR. COYNE: Well, it was also seen in the Parfrey trial of healthy dialysis patients, where four percent of the patients receiving Epogen had an increased risk of stroke at the higher hemoglobin target versus the lower target. So, can we feel confident when we target a lower hemoglobin that we in fact are not increasing the risk of stroke?
DR. MCKENZIE: Right, and I don't think we have the randomized controlled data to respond to that.
DR. COYNE: Are either of you doing any studies to address the risk in, whether stroke is increased when we target hemoglobin

00279

at, say 12? Are there any trials going on in that direction?
DR. MCKENZIE: Specifically, or Marcie, would you like to answer --
DR. GOODMAN: Hold on a moment, please. Dr. Coyne, ask your question. Dr.

McKenzie, are you going to ask someone else to answer?
DR. MCKENZIE: Dr. Wolfson is actually our medical director.
DR. GOODMAN: All right. So Dr. Coyne is going to pose a question.
DR. COYNE: Are there any trials going on to determine whether ESAs increase the risk of stroke at our present target of ten to 12, say, or 12?
DR. GOODMAN: And this is Dr. Wolfson?
DR. WOLFSON: I'm Dr. Marcia Wolfson, the medical director for Centocor Ortho Biotech. We just recently completed and published two trials looking at targeting hemoglobin at a true labeled range of ten to 12. In those studies the incidence of stroke over the exposure adjusted stroke rate was about 1.1 percent, which I think is very

00280

similar to that seen in the placebo arm of TREAT. So while we haven't actually carried out a study to answer your question directly --
DR. COYNE: Was that in a hundred percent diabetics like the TREAT trial?
DR. WOLFSON: It was about 68 percent diabetics.
DR. COYNE: So you don't have a control arm.
DR. WOLFSON: No, no control arm, everybody got treated with a different regimen, but the target was the same.
DR. COYNE: Okay.
DR. WOLFSON: So that's the information we have to date.
DR. GOODMAN: Thank you very much. I've learned that when I look at my watch at this point, if I think that we're going to be done at 3:30, we don't take a break. I don't think we're going to be done at 3:30, so it's probably a good idea to take a short break so we can be a little more focused on the matter at hand rather than other matters. We're going to take a ten, ten-minute break, and then reconvene for the questions. Thank you.

00281

(Recess.)
DR. GOODMAN: Let's take our seats. What we'll do now is the following. We're going to go and start with our questions one and two, see how far we get, but we will reserve time, mind you, for that question six, which has to do with basically filling evidence gaps. So we're going to start on questions one

and two at this point, see how far we get with those, and then save time for identifying in a summary way what the main evidence gaps are and how we might fill those.

Now, it's quite clear to all of us that this is really a multivariant problem, yes, this is quite complex, yes, there are many unknowns and so forth. And of course when there are unknowns, that tells me anyway that there's not a lot of evidence and there may not be enough evidence to go around.

We're going to ask you to be flexible about your interpretation of question one, and we'll start with that. And the flexibility has this in mind. Yes, we understand quite well that there are some differences with regard to the impact of being on dialysis or not being on

00282

dialysis. Yes, we know that things like where you start in your hematocrit or hemoglobin may or may not have some impact, as was discussed. We know that the protoplasm issue may pertain as well, as we've heard. But we do want to give back to the Agency some notion about what we think about the available evidence, at least at a high level, for some of these main issues.

And so, question one and two go together, and the main difference between question one and question two is the first one asks about the sufficiency of available evidence, it doesn't ask what the impact is, that's for a later question. Is there enough evidence available to draw some finding or conclusion, and it asks that question with regard to four outcomes. So question one asks, how confident are you that there is sufficient evidence, so this is the confidence in the sufficiency of evidence, not what it says, to determine whether using a medical intervention, blood transfusion, iron or ESAs, that it's using some medical intervention to maintain or raise the hemoglobin or hematocrit levels of anemic CKD patients, affects each of the health

00283

outcomes below? So the question is worded in a way that you're intervening through one of these measures hematocrit or hemoglobin, you're working through those to achieve an outcome in anemic CKD patients. And I recognize there are multiple factors going on here.

Dr. Perfetto?

DR. PERFETTO: I just want to make sure that I'm understanding that. I had interpreted this question as it would be some

combination of these therapies, it wasn't going to be only one that was driving this question, it's a combination of the therapies.
DR. GOODMAN: It could be one or multiple. The idea is a medical intervention, e.g., blood transfusion, iron therapy or ESAs, not limited to those. So it could be one or more of those, or others. It's a medical intervention. The idea is, can you manage the hemoglobin or hematocrit in these patients, the anemic CKD patients, to affect those four main types of outcomes below. And our first question deals with the sufficiency of the evidence. I know this is not a perfectly worded question, I don't know that there is

00284

one, but we'll do our best. Dr. Messana.
DR. MESSANA: Just for clarification, so, I think it simplifies, how confident are you that there's sufficient evidence to determine whether raising the hemoglobin or hematocrit levels of anemic CKD patients affects the health in each outcome below; is that correct?
DR. GOODMAN: That is another way of stating the question, right. Why don't you just say that again to make it, if that helps other people understand it better.
DR. MESSANA: I'll try. How confident are you that there is sufficient evidence to determine whether raising the hemoglobin or hematocrit levels of anemic CKD patients affects each of the health outcomes below?
DR. GOODMAN: It does say maintain or raise.
DR. MESSANA: Excuse me. Maintaining or raising the hemoglobin or hematocrit levels of anemic CKD patients affects each of the health outcomes below. So it's neutral in terms of the method.
DR. GOODMAN: That is correct. It

00285

also isn't asking you to make some appraisal of what the evidence says, it's just asking to appraise at this point the sufficiency of the evidence. Dr. Satya-Murti.
DR. SATYA-MURTI: Regardless of the level you start with and achieve, it applies across the board. It doesn't refer to where you start and where you end up.
DR. GOODMAN: Thank you. Yes, Dr. Agarwal.
DR. AGARWAL: I think intervention is an important word there, because if you remove

the word intervention it might become observation.
DR. GOODMAN: The word is medical intervention. We're not just watching, Dr. Agarwal.
DR. AGARWAL: Right, exactly. If you replace the word medical intervention with spontaneous variation, it's a completely different meaning. So I think we should focus on using a medical intervention, it's an intervention that we're performing, not a spontaneous variation in maintaining or raising hemoglobin.

00286

DR. GOODMAN: It is about an intervention, yes, sir.
DR. AGARWAL: So it's important to retain that word, intervention.
DR. GOODMAN: Dr. Messana.
DR. MESSANA: By lumping the three interventions together, we're not voting on each intervention, if I understand it, we're voting on the results of the intervention.
DR. GOODMAN: Whatever intervention was made, yes. It doesn't have to be any one in particular, but it is an intervention. Are you okay with that, Dr. Messana?
DR. MESSANA: Yes.
DR. GOODMAN: Thank you. Dr. Jacques.
DR. JACQUES: If I could provide just a little bit of comment on there, this gets a bit to whether or not you believe hemoglobin, hematocrit and/or anemia is simply a signal versus being a lever. By analogy, if you saw a car that had an open air bag, one might assume there had been an accident; one wouldn't assume that cramming the airbag back in would prevent the accident.
DR. GOODMAN: But Dr. Jacques, we are

00287

talking about an intervention having been made. Dr. Pauker, on this.
DR. PAUKER: Are we on one or two?
DR. GOODMAN: Right now we're talking about one.
DR. PAUKER: I'll wait for two then.
DR. GOODMAN: Okay. And number one is going to have obviously parts A through D. And panel, we recognize that this is sort of a variable situation, a lot of factors to consider, so this is, as I said earlier, kind of a high level consideration about the sufficiency of evidence. Does anybody have any further

questions about this obviously difficult question before we ask for your vote? And I will add that, listen, there's not an NCD on the table, we are not setting policy, we are not stating anything about a practice guideline, we're not practicing at all. What we are doing is providing our best input, insight, appraisal about the sufficiency of the evidence here, so as to supply CMS with some greater insights for their potential consideration. Okay? Any other points on

00288

that?
Great. Let's take them one at a time, then. And the first one is going to be exercise or activity tolerance. Exercise or activity tolerance, this is on the sufficiency of evidence. If you've got low confidence, the lowest is a one; if you've got high confidence, that's a five. So one through five, low confidence, high confidence is five, how confident are you that there is sufficient evidence to determine whether using a medical intervention to maintain or raise the hemoglobin or hematocrit levels of anemic CKD patients affects each of the health outcomes below? Exercise and activity tolerance. Please put up your card, everyone. And I'll state as was stated earlier, that we're recording votes of all of our members, but the guests -- go ahead.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Can you please hold your numbers up so that I can see them, please.
DR. GOODMAN: All votes are being recorded but there will be a distinction

00289

between the voting panel members and the others later.
MS. ELLIS: Also, there's a pre-score sheet inside your packets. Please make sure you record your scores on those also. Thank you. I have everyone.
DR. GOODMAN: All right. Same question for B, this is the vascular events, stroke, myocardial infarction, congestive heart failure. How confident are you that there is sufficient evidence to determine whether the interventions, an intervention to maintain or raise hemoglobin or hematocrit levels in CKD patients affects vascular events?
(The panel voted and votes were recorded by staff.)

MS. ELLIS: Thank you.
DR. GOODMAN: Same question, this is for patient-perceived quality of life. This is sufficiency of the evidence for patient-perceived quality of life, is there enough evidence to go around here to show, to draw some finding?
(The panel voted and votes were recorded by staff.)

00290

MS. ELLIS: Thank you.
DR. GOODMAN: And then finally, survival. Is there sufficient evidence to make that determination for survival, the sufficiency of the evidence, survival?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you.
DR. GOODMAN: So those are the four parts for question one. Just to iterate, Dr. Jacques, the two sets of votes will be recorded?
DR. JACQUES: Yes, both sets of votes are recorded, both from the entire panel as well as the voting members only. In order to move to the next question, though, we are looking only at the votes of the voting members in terms of is there at least intermediate evidence.
DR. GOODMAN: And that threshold will be 2.5, a mean score of 2.5.
MS. ELLIS: All the scores were above 2.5.
DR. GOODMAN: Okay. Since all scores were 2.5 or greater, now as opposed to asking

00291

about the sufficiency of the evidence, rather than sufficiency, we're going to ask you -- well, I'll read it. For any health outcome listed in question one for which the panel indicates at least intermediate confidence, which was all of them, how confident are you that maintaining or raising hemoglobin or hematocrit levels of anemic CKD patients does indeed improve each such health outcome? And remember, this was any intervention. Dr. Messana, did you have a question on that?
DR. MESSANA: How confident are you, does that include experiential, or are we still talking about medical evidence basis?
DR. GOODMAN: We are asked to look at the evidence, that is what we're asked to do, yes. Thank you for bringing that up. Yes, Dr. Pauker.

DR. PAUKER: I have a confusion. The question talks about improvements, and B talks about adverse vascular events, so how do I score going the other way?
DR. GOODMAN: Yes. We realized that earlier. Dr. Jacques.
DR. JACQUES: Okay. If you believed

00292

that the use of the intervention would in fact reduce vascular events, i.e., improved outcome in vascular events would be reduced stroke, reduced myocardial infarction, improved congestive heart failure in that light.
DR. PAUKER: So in other words, if we believe that it produces more adverse events, it would be a one; is that correct?
DR. GOODMAN: Yes. Dr. Danis.
DR. DANIS: How would you like us to respond if we believe there's a J-shaped relationship?
DR. JACQUES: Well, you could either vote three if you wanted to, or if you have high confidence in fact that there is a J-shaped relationship, I guess, you know, deal with it as best you can, put an asterisk on there. And as was said, there is no open national coverage determination on this, and in fact, if we note that the panel struggles with certain types of questions, that is in fact very informative to us if we were to take a look at this later, using potentially a different set of questions.
So if you feel that you can't answer

00293

it at all, go ahead and leave it blank. Otherwise, please do your best and if you want to, asterisk and write in the margin, and we will take note of that.
DR. GOODMAN: Is there any particular one of these A through D that you'd like to break out, Dr. Danis, or should we just go with what Dr. Jacques said, and then I'll ask for comments thereafter.
DR. DANIS: Well, I am tempted to say that it would be great to have the opportunity to answer these questions with regard to hemoglobin above and below 12 or 13. I think there's -- if we could answer the question twice with regard to that break point, I think it would be useful.
DR. GOODMAN: Dr. Jacques?
DR. JACQUES: The panel does have the ability to split this question if you want to. You could vote once on, for example, less than

12, and then again on 12 or greater than 12, if you believe that that's the appropriate cutoff, but what we would like to avoid doing is having an hour discussion on what that cutoff might be, since it seems to be all over the place in

00294

terms of people's comments.
DR. GOODMAN: Dr. Satya-Murti.
DR. SATYA-MURTI: Marion's question is crucial, because this keeps coming back to me too, as to the answers will depend on what level we are. And yet as Louis says, we can keep splitting it into further numbers and decimals. So either we can say high level or low level and leave it binary and not put a number to it, in which case the answers will double, but it's all right if the panel wants it that way, high and low level, we can do it.
DR. GOODMAN: I will put on the table under 12 or 12 and greater as a proxy for what that is. Would anybody object to that? Dr. Coyne?
DR. COYNE: Well, I guess in looking at this question, my concern is I would probably categorize the data for dialysis patients, I would characterize the data for dialysis patients, for CKD nondialysis patients.
DR. GOODMAN: Now, the good thing is that we've had that discussion that's recorded in the record and I think, at least I'm

00295

confident that our consideration of that matter has been raised and discussed at least as well as we could do.
DR. COYNE: Okay.
DR. GOODMAN: Any objection to the less than 12 versus the 12 or greater for this question? Dr. Satya-Murti.
DR. SATYA-MURTI: Yeah, may I object to that, because I really think by fixating on a number, we would run into the same issues we did most of the day today. So leave it as high and low, and leave the numbers to the researchers and workers in the field to determine what that number would be. So I would like to go for high and low.
DR. GOODMAN: Okay. Dr. Steinbrook.
DR. STEINBROOK: My concern about that is many of us may have different views about what high means and what low means, and if we just ask it in the eyes of the beholder, I think that would be less informative, but I would be happy with whatever is decided.

DR. JACQUES: I mean, if the panel believes that the evidence base is so scattered, then maybe the best thing to

00296

indicate is that there is somewhat limited confidence overall about the body of evidence to answer this question in its entirety. And again, this is simply advisory to us, okay? I'm not going to go back to my computer and write some policy this afternoon based on what you guys have voted today. So if the best sense of what you actually conclude is that this stuff is all over the board, no matter what number we pick we will potentially be interpreted in a way that we don't intend, okay? And I can understand why people might have difficulty even saying 12 is a cutoff, I think some people might even want nine as a cutoff, some people might want to say below nine, above 12, and below nine and 12, who on earth knows, okay? That's sort of the sense that I've gotten. So it really is up to the panel and as I said, we've listened to all your comments, so we understand the nuances in whatever you might vote.

DR. GOODMAN: Dr. Satya-Murti.

DR. SATYA-MURTI: If it's acceptable for you that the scatter that's impressing many

00297

of us would lead to a lower confidence level, so it doesn't mean that we are unconvinced, but it's more a reflection of the scatter of the evidence.

DR. GOODMAN: Let me just take the chair's prerogative here, and I'm going to give it to you in two steps. Because ambiguous though it may be, the literature does talk a lot about various levels and various cutoffs. Imperfect though it may be, let's take one for the purpose of these votes and then when we're done with this vote, I'll start at the far end and ask you if you have a single qualifying comment that you would like to add about what you think is high or low, or why you might have voted that way. I just think that will provide a little bit more clear help to the Agency. So with all due respect to my co-chair, whom I will ask for the final comment on this, let's do the 12 thing, because it is an anchor, although imperfect, and then we'll ask for comments.

DR. AGARWAL: Are we voting twice, or simply voting once with the 12 or greater?

DR. GOODMAN: I had intended on voting
00298
twice, okay? So we're going to vote below 12 now, and we recognize it's imperfect, all right? So for these health outcomes, and they're all of them, we'll start with exercise or activity tolerance, at a level below 12. How confident are you that maintaining or raising hemoglobin or hematocrit levels of anemic CKD patients improves each such health outcome, exercise activity tolerance below 12, and this is the hemoglobin.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you.
DR. GOODMAN: Same outcome, exercise and activity tolerance, 12 or greater, how confident are you that maintaining or raising hemoglobin in this case, anemic CKD patients, improves exercise activity tolerance at 12 or greater?
(The panel voted and votes were recorded by staff.)
DR. COYNE: So where do we put these answers?
DR. GOODMAN: So indicate on your score sheet whether it was 12 or below 12.
00299
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Thank you. Now we're going to go to vascular events, and I'm going to ask Dr. Jacques one more time to clarify the direction of this answer.
DR. JACQUES: An improvement in outcomes related to vascular events would be a reduction in those vascular events, i.e., do you feel that treatment or intervention that would raise or maintain the hematocrit would reduce the likelihood of stroke, heart attack, et cetera?
DR. GOODMAN: And we'll ask that question for the below 12. So how confident are you that maintaining or raising hemoglobin below 12 for anemic CKD patients improves the health outcome, where Dr. Jacques identified that improvement in reduction of that rate, of vascular events?
DR. MESSANA: I'm sorry, but I'm confused. As opposed to what, maintaining or raising the hemoglobin to less than 12 as opposed to what?
DR. JACQUES: As opposed to not raising it to 12. So in other words, is there
00300

advantage to a patient regarding vascular outcomes if you maintain or raise their hematocrit to this particular target.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Thank you. Same question, 12 or greater hemoglobin.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Thank you. Next is patient-perceived quality of life. For hemoglobin below 12, how confident are you that maintaining or raising the hemoglobin to below 12 for these patients improves that health care outcome, patient-perceived quality of life?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Thank you. Same question with hemoglobin 12 or greater. How confident are you that maintaining or raising hemoglobin to 12 or greater for these patients improves patient-perceived quality of life?

00301

(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Great. The last one here is on survival, hemoglobin below 12. How confident are you that maintaining or raising hemoglobin to below 12 for anemic CKD patients improves survival?
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: And again I'll remind you, and it won't be the last time, we're always thinking about the evidence that is available.
MS. ELLIS: Thank you.
DR. GOODMAN: And finally, the same question on survival for hemoglobin 12 or greater.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Dr. Pauker, did you have a point, sir?
DR. PAUKER: I'm confused as usual. Are we talking about this as a target that

00302

we're aiming for or a target that's been achieved?

DR. GOODMAN: The question is to maintain or raise.
DR. PAUKER: Of a patient whose target is greater than 12?
DR. GOODMAN: Well, it's maintain or raise with this target in mind, correct?
DR. JACQUES: Yes. Essentially if you're aiming at something under 12, which is anything under 12, the panel's not being specific, you could have decided nine was fine, but that's under 12. So it's simply as a place to go to maintain a, let's call it a desirable hematocrit, should that be under 12 or over 12.
DR. PAUKER: So this is a target.
DR. JACQUES: Right. I don't know that anyone is recommending initiating ESAs in a patient whose native hemoglobin is greater than 12.
DR. GOODMAN: Thank you for asking the question, Dr. Pauker.
Now before we leave it, as promised, does anyone have, starting at the far end with Dr. Messana, does anyone have any concise

00303

one-sentence remarks to qualify your responses to this question and the chair-used prerogative to set this thing at 12? We understand that we could have handled it otherwise.
DR. MESSANA: My only comment relates to my generally low confidence scores which are driven by lack of certainty about whether hemoglobin is the marker or, the effector or a marker of these outcomes.
DR. GOODMAN: So, you have a question about the physiology?
DR. MESSANA: Low hemoglobin may be a marker of disease state which leads to reduced exercise tolerance, et cetera, and I'm not convinced by the data that's been presented that hemoglobin is the target that we should be measuring.
DR. GOODMAN: Right, although the question did phrase it in terms of using those markers. Whether that's right or wrong maybe is a separate point, but the question is phrased with regard to using those.
DR. MESSANA: Well, it was phrased in terms of my confidence in using those.
DR. GOODMAN: Point well made, thank

00304

you. Any other comments that anyone would want to make with regard to how you answered this question posed the way we had to pose it?
Dr. Agarwal.

DR. AGARWAL: The answers reflect the targeted goal, not achievement goal.
DR. GOODMAN: Thank you. Dr. Pogach.
DR. POGACH: My answers reflected, primarily reflected hemoglobin for the exercise and patient quality of life, and that's what I considered in my responses, due to the heterogeneity of the studies.
DR. GOODMAN: I don't understand. Did you not consider all the four outcomes?
DR. POGACH: What I did is when I was thinking about the range, I was clarifying that I was trying to, for the ones that were patient-centered and exercise, I started at lower levels, moving it up a bit higher, and I felt that there were unanswered questions in the ten to 12 range, but since you just asked for less than 12, I wanted to clarify that I had more certainty at the lower levels than the intermediates.
DR. GOODMAN: Good, thank you for the

00305

clarification. That's helpful for the record. Dr. Danis is next.
DR. DANIS: Yes. I just wanted to say that my answers don't include my thoughts on children because there's really very little data there.
DR. GOODMAN: Thank you for making that point. We may want to revisit that before the bottom of the hour when we talk about evidence gaps. Any other points on this question? Dr. Satya-Murti, did you want to add?
DR. SATYA-MURTI: No. I think on either extreme, we seem to agree on quality of evidence and level of evidence, and I also am quite suspicious of using hemoglobin, so that's the reason my scores were also low.
DR. GOODMAN: Okay, thank you. I know this felt a bit laborious, and my reward to you is that we're not done yet. We're going to move to question 3.A, which I believe requires us asking about the 2.5 or greater.
DR. JACQUES: Right. There were only three of the eight votes in question two that achieved at least a 2.5. All three of them

00306

related to a target below 12 and they were A, exercise activity tolerance; C, patient-perceived quality of life; and D, survival.
So question 3.A in that regard would then say, for any health outcome addressed in

question two for which the panel indicates at least an intermediate confidence, a mean score of 2.5, how confident are you that there is sufficient evidence to determine whether the use of ESAs to maintain or raise hemoglobin or hematocrit levels to a target less than 12 in CKD patients improved each such health outcome, and that would only be addressed for A, C and D.

DR. GOODMAN: Thank you for that clarification, that simplifies things. And I further appreciate the clarification of your using the word target, given the earlier question about that.

Okay. So we're going to be looking at only A, C and D here, and this is in particular use of the ESAs. Dr. Steinbrook.

DR. STEINBROOK: And targets less than 12, right?

00307

DR. GOODMAN: Correct. So let's look at first exercise tolerance, this is exercise tolerance, it's about ESAs, target under 12, and how confident are you that there is sufficient evidence -- remember, this is sufficient evidence, not the answer -- sufficient evidence to determine whether the use of ESAs to go with that target less than 12 improves exercise tolerance? This is sufficiency of evidence again, not whether it in fact improves or not, but the sufficiency of evidence to make the determination later of an improvement or not.

(The panel voted and votes were recorded by staff.)

MS. ELLIS: Thank you.

DR. GOODMAN: Okay. Same question for patient-perceived quality of life, target under 12, sufficiency of evidence regarding ESAs. Sufficiency of ESAs, target under 12, patient-perceived quality of life.

(The panel voted and votes were recorded by staff.)

MS. ELLIS: Thank you.

DR. GOODMAN: And then D is survival,

00308

sufficiency of evidence, use of ESAs, target under 12, survival. And please hold your cards high.

(The panel voted and votes were recorded by staff.)

MS. ELLIS: Thank you.

DR. GOODMAN: Okay. And as Dr. Jacques pointed out, we don't have to deal

right now with 12 or greater. So now we're going to question 3.B; is that correct?
DR. JACQUES: Yes, and we're totaling those now. All three of them were above 2.5.
DR. GOODMAN: Thank you. So we will do all three again, and this time instead of sufficiency of the evidence because we already discussed sufficiency, we're asking whether or not there is an actual improvement. So, how confident are you that the use of ESAs to target under 12 hemoglobin improves exercise tolerance?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Thank you. Same question for patient-perceived quality of life.

00309

Use of ESAs, target hemoglobin under 12, improves patient-perceived quality of life.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Thank you. And then finally for question 3.B, survival, how confident are you that the use of ESAs to target hemoglobin under 12 improves survival? Hemoglobin under 12, ESAs, survival.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Okay. So, can we proceed to question 4.A then? And question four, this is another sufficiency of the evidence question and we start again with all four of the outcomes. And I think we're going to do the 12 thing again, are we not?
DR. SATYA-MURTI: We have to if we have done 12 or under before.
DR. GOODMAN: We'll do 12 again, so this is going to require eight votes on your part. So, how confident are you that there is sufficient evidence to determine whether the

00310

use of ESAs to target hemoglobin below 12 worsens exercise tolerance? So this is sufficiency of the evidence, not what the evidence say but the sufficiency of the evidence, use of ESAs, target hemoglobin under 12, worsens exercise tolerance.
DR. POGACH: Could you --
DR. GOODMAN: It's sufficiency of the evidence if you're using ESAs and targeting under 12, how confident are you that it would

worsen exercise tolerance? Bear with us.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them.
DR. GOODMAN: Thank you. Same question, now you're targeting 12 or greater, sufficiency of the evidence. Same question, sufficiency of the evidence, using ESAs, target 12 or greater, worsening exercise tolerance, how good is that evidence, do you have low confidence or high confidence in it?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them.
DR. GOODMAN: Thank you. We will move

00311

now to vascular events, stroke, MI, congestive heart failure, and we're back to below 12. So sufficiency of evidence, use of ESAs, target hemoglobin under 12, worsened vascular events. How good is that evidence, do you have low confidence in that evidence relative to that question or do you have high confidence?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Same question, except now we're looking at target hemoglobin 12 or greater, vascular events, sufficiency of evidence, use of ESAs, target 12 or greater, does it worsen vascular events?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them.
DR. GOODMAN: Thank you. Now on C, patient-perceived quality of life, again, sufficiency of evidence, use of ESAs, target hemoglobin lower than 12, worsen patient-perceived quality of life.
(The panel voted and votes were recorded by staff.)

00312

MS. ELLIS: Okay, I have them.
DR. GOODMAN: Thank you. Now patient-perceived quality of life, target 12 or greater, sufficiency of the evidence now, not what it says but sufficiency of the evidence, using ESAs, target 12 or greater, does it worsen patient-perceived quality of life?
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you.
DR. GOODMAN: Let's move to survival. Sufficiency of evidence, using ESAs, target

hemoglobin under 12, does it worsen survival? Sufficiency of evidence, is there enough evidence to go on, low confidence, high confidence.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Good, thank you. And finally, target 12 or greater. Sufficiency of evidence, use of ESAs, target 12 or greater hemoglobin, does it worsen survival?
(The panel voted and votes were recorded by staff.)

00313

MS. ELLIS: Thank you.
DR. GOODMAN: Thank you. Now in our parallel question, we're going to wait for a little calculation with regard to any of those in 4.A which achieved a score of 2.5 or greater, and we'll focus on those in question 4.B.
DR. JACQUES: For the first set, the less than 12, the two questions receiving a score of at least 2.5 were B, vascular events, and D, survival. For the second round of voting, on an outcome that was not less than 12, all four received votes of at least 2.5. So there are six remaining questions.
DR. GOODMAN: Thank you for that. So in question 4.B, that means that the outcome we're going to look at first is vascular events. And this time, instead of the sufficiency of the evidence, we're looking at what you think the evidence says about whether or not it does worsen the outcome. So for 4.B now we're asking, how confident are you that the use of ESAs to target hemoglobin under 12 worsens vascular events?
(The panel voted and votes were

00314

recorded by staff.)
MS. ELLIS: Okay.
DR. GOODMAN: And while you're thinking about vascular events, let's do the same thing for target hemoglobin greater than 12. Use of ESAs, target greater than 12, worsens vascular events, this is the greater than 12 for hemoglobin. B, vascular events. We are going to come back to A. We're still on vascular events.
MS. ELLIS: I have them, thank you.
DR. GOODMAN: Let's now go back to A, I probably should have started with A, but we'll cover all these. We're going to look at

exercise tolerance, which is A, and this is going to be hemoglobin greater than 12. So, how confident are you that the use of ESAs at hemoglobin target greater than 12 worsens exercise activity tolerance, which is A? This is about exercise activity tolerance, hemoglobin target greater than 12, 12 or greater.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them.

00315

DR. GOODMAN: So we've got A for greater than 12, B for less than 12, and B for 12 or greater, and now we're going to look at patient-perceived quality of life for the greater than 12, right? So this is confidence in using ESAs to maintain hemoglobin for patient-perceived quality of life greater than 12. This is patient-perceived quality of life, 12 or greater hemoglobin.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them.
DR. GOODMAN: Thank you. You have them all so far, is that okay? Good. Now we're going to talk about survival under 12. So, how confident are you that the use of ESAs to maintain or raise hemoglobin under 12 worsens survival. Starting under 12, first under 12, yes. D is for both. Under 12. This is survival, hemoglobin under 12.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: Thank you.
DR. GOODMAN: And then finally, still with survival, but 12 or greater. Using ESAs,

00316

maintaining hemoglobin 12 or greater, survival.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: I have them, thank you.
DR. GOODMAN: So those are the current voting questions, correct, those are all the voting questions so far.
Two orders of business. As Dr. Pauker suggested, we want some feedback from you on the matter of transfusion, number of transfusions, is that correct, Dr. Pauker? Discussion or voting? I think discussion would probably work better on this, Steve, don't you?
DR. PAUKER: I gave it to you.
DR. GOODMAN: The question, I think just given our time, some brief discussion

about this, which has to do with the confidence that there is sufficient evidence to determine whether the use of ESAs decreases the number of transfusion patients with CKD. Is that correct, Dr. Pauker?

DR. PAUKER: Yes.

DR. GOODMAN: Dr. Pauker, would you just make an introductory statement for the importance of this question, just briefly?

00317

DR. PAUKER: We heard discussions here from a number of presenters and public comments about the fact that use of ESAs would reduce the number of transfusions, so I thought it would be remiss for that not to be addressed under questions, so I suggested the question about the use of ESAs to decrease the number of transfusions.

DR. GOODMAN: Okay. Any comments by panelists on this? And Dr. Pauker, if you have a brief comment yourself on this, we would take that, rather than making it a voting question, which may cause some other difficulties. But would you or any other panelist care to comment on that matter of transfusions?

DR. PAUKER: From my perspective, I think (inaudible).

DR. GOODMAN: Okay. Dr. Perfetto.

DR. PERFETTO: I don't have a specific comment about transfusions, but I do think that it's very related to something that I was thinking about as we were voting, that we're voting on some of these endpoints that we really didn't review a lot of evidence on, and I know that there's a lot more evidence on

00318

these endpoints like there is on transfusions that we didn't talk about, because our earlier discussion today was predominantly focused on some studies that were looking at the use of high doses and the safety issues related to those use of high doses. But I think there's a lot more evidence that exists on endpoints like transfusion, and exercise activity and quality of life that we didn't really talk about.

DR. GOODMAN: That's right. Yes.

DR. POGACH: My own sense is clearly for the pre-EPO era when hemoglobin was quite low, EPO certainly had an impact there, but in the trials that were discussed today, it seems to me that there is no sufficiency of evidence as to why transfusions were done or not done, despite findings in some studies to understand what was behind it. So I don't feel that I

would concede the point that EPO improves, avoids transfusions in people who are very very low, but once you get above a certain threshold, it's not answered by any studies, certainly not in the ranges that they addressed, for example the TREAT study.
DR. GOODMAN: Okay. Yes, Dr. Agarwal.

00319

DR. AGARWAL: I don't know exactly what the comments refer to, but the TREAT study showed a twofold difference in transfusion rates between the placebo arm and the treated arm, and the label has in it that it's indicated for avoiding transfusions.
DR. POGACH: I have no idea what the reasons are behind it, so surviving it was noted to be a non-major outcome finding, so I have concerns.
DR. GOODMAN: That was Dr. Pogach, by the way, for the record. Yes, Dr. Coyne.
DR. COYNE: Certainly I think in the dialysis population, the data strongly supports that it reduces transfusion risk. I think the stability of the percent of patients receiving transfusions in the EPO era since the mean hemoglobin has reached about 11, which was a decade ago, indicates that transfusions that are now occurring are in acutely old patients, and that managing above that doesn't seem to be impacting it.
In the TREAT study, although there's a dramatic difference, I think we have to remember it really was salvage therapy for

00320

individuals who fell less than nine to bring them back above that. So I think it remains to be proven if in that population, if you were to treat patients to a hemoglobin level of say ten or 11, whether there would be any substantial difference in transfusion risk. And as a correlate to that, I point to the very small differences in transfusion that were observed in the CHOIR study where both arms got active treatment, and the low arm target and achieved value was 11.3.
DR. GOODMAN: Thank you. Due to the time, we do need to try to vacate as close to 4:30 as we can. Rather than filing further questions, what I want to do is this. And we'll start at the far end with Dr. Messana.
So, as a closing question then, and what we're going to try to do, and I mean this, is try to answer it in a sentence, okay?
So, given your understood purpose for

this meeting, then, where do you see the greatest evidence gaps for informing any kind of coverage decision, national coverage determination, if there ever is to be one, with regard to this question? And I understand we

00321

covered a lot of territory here, but on the matter of using these interventions for the types of outcomes that we discussed today, where are the greatest evidence gaps? And we'll start with you, Dr. Messana.

DR. MESSANA: In order to avoid reducing quality of life and increasing the risk for adverse events related to inadequate treatment, we need to better understand whether the targets that have been used in the randomized controlled trials to date, i.e., hemoglobin, are appropriate or whether they are inappropriate surrogates for appropriate anemia management.

DR. GOODMAN: Thank you very much, Dr. Messana. Dr. Coyne.

DR. COYNE: I think the major gaps in our knowledge relate to the relationship of dose of EPO to harm. The trial isn't always focused on target hemoglobins, but as we've heard, there's a great variability in responsiveness. And in clinical practice the doses that we give in the U.S., because they're reimbursed, far exceed the typical doses that are seen even in the fifth quintile of these

00322

randomized trials that we've reviewed. So I have concerns about safety of higher doses and I don't think we have any trials that are really addressing safety related to dose.

DR. GOODMAN: Thank you for that point, Dr. Coyne. Dr. Agarwal.

DR. AGARWAL: In the EPO hyporesponsiveness patient defined as failure to reach hemoglobin of at least ten grams per deciliter after 12 weeks of titrated therapy per package insert, I would like to see a randomized trial do a strategy of planned EPO dose versus free titration, and follow for mortality and cardiovascular events.

DR. GOODMAN: Thank you, Dr. Agarwal. Dr. Perfetto.

DR. PERFETTO: I think I would follow and echo that. I think for me the issue of what is driving the refractory patient or the nonresponsive patient is something that's very important to understand, and to understand the relationship between that and adverse events.

DR. GOODMAN: Thank you. Dr. Steinbrook.
DR. STEINBROOK: Three things.

00323

Narrowing the range of nine to 12 to a range of one or two within that. ESA dosing, potential harm studies focusing on ESA as an independent variable. And finally, where there's enough information to support modeling to try to put everything in there, sensitivity related to kidney transplants, transfusions, all the risks and benefits, and that can inform decision-making even if it doesn't provide the answer.
DR. GOODMAN: Thank you. Dr. Puklin.
DR. PUKLIN: Well, Amgen's drugs have been around long enough to recognize -- when they first came out they actually played a significant role in the AIDS patients for whom there was no treatment who were highly anemic, and so in the early '90s that was one of their most significant roles. I think that these are vital agents in helping patients in chronic renal disease and who have cancer.
And I would encourage Amgen to get their scientific advisors together and try to figure out what the problems are for the patients who are nonresponsive to the increasingly large doses, which constitute the

00324

group of people who seem to be having the complications at the higher levels of target treatment, and I would suspect that with time they ought to be able to solve the problem of what the underlying resistance is to the drug, and if they could do that they could eliminate those patients from the trials, or from treatment, or they could develop some other technology or drugs to do away with the nonresponsive group. I would encourage them to do the research in that area.
DR. GOODMAN: Thank you. Dr. Pogach.
DR. POGACH: Three things. There appear to be no data on pediatric patients. Two, future RCTs really have to distinguish patients who are physiologically healthier with no comorbidities from those who have other major complications. And three, I think if transfusion is going to be used as an outcome, we have to understand why it's used and if there's any benefit of it, as opposed to just number of transfusions.
DR. GOODMAN: Thank you, Dr. Pogach. Dr. Pauker.

DR. PAUKER: I think we've clearly
00325
heard of this new multivariant problem. I think we need a multivariant model and we need to segregate the patients based on that prediction, not trying to lump them here and there. I would also say that I'm distressed after all these years that we do not have a better evidence base. I think it is a sad state of affairs for us to have gone this long and to hear inconsistent evidence, it ought to be better. I think that's a crime.
DR. GOODMAN: Thank you, Dr. Pauker.
Dr. Levine.
DR. LEVINE: In addition to the suggestions that have already been made, I would like to suggest studies that look at alternatives in terms of quality of life and exercise tolerance, particularly those outcomes because there are, as the triathlete brought up, cardiovascular training and other approaches to those outcomes, and I would like to see some comparisons of those.
DR. GOODMAN: Thank you. Dr. Danis.
DR. DANIS: I would support a lot of the other suggestions. I'd also argue for something that I commonly do, which is to have
00326
coverage with evidence collection, so that you can start to deal with the lack of very wide good data. And I think it would be great to do some cost effectiveness analysis looking at use of titrating, you know, the varying doses of EPO to clinical outcome and cost data involved. And I also think that, I was struck by the quality of life analyses, there are various measures that are being used, and I was wondering whether they really get at some issues like employment status with various treatments, and I think data collection on that kind of outcome would be useful.
DR. GOODMAN: Thank you, Dr. Danis.
Dr. Calega.
DR. CALEGA: As others have said on the panel, looking at the hyporesponders in terms of defining them as a group, identifying them as a group, and looking for what the most effective dose of EPO would be. Also, pediatric studies, data on pediatric patients would be very helpful. And then the health equity issue that I think was touched on but not really explored today, you know, are there subpopulations who are not being treated
00327

equally, such as African-Americans or women?
DR. GOODMAN: Thank you, Dr. Calega.
Ms. Atkinson.
MS. ATKINSON: Actually, I'm going to quote Dr. Singh, because I think he said it best in his January 13, 2010 editorial, that more studies need to be done looking at is there a toxic dose range for ESAs, is there a class effect of ESAs, and does the frequency of ESA administration make a difference.
DR. GOODMAN: Thank you, Ms. Atkinson.
Dr. Satya-Murti.
DR. SATYA-MURTI: While we are searching for a better alternative target to hemoglobin, I would like to make two points. One is quality of life, and exercise tolerance. We don't have a minimum clinically important difference among them, what is an MCID for renal patients, so we need to determine that, and that was brought up this morning, so further detailing of these two soft targets.
And the last point is as a neurologist, I know very often stroke is considered as a homogeneous entity, which it is not. There are major artery strokes due to

00328

major vascular disease, and end artery disease causing stroke and hemorrhages, so I think the next stage would be to determine what type of stroke they're talking about, the etiologies being different, so we should not misattribute a longstanding diabetic renal stroke to a drug-induced stroke.
DR. GOODMAN: Thank you, Dr. Satya-Murti.
Thank you all, panel, very much. I know that this body of evidence is somewhat uneven and so forth, and you've done a superb job.
I do want to point out that when we've looked at the epidemiology involved, the number of people involved in this, the costs involved and the impact on mortality, morbidity and quality of life, it is quite clear that we have gone pretty far in disseminating the use of these interventions without sufficient evidence, and the field owes all these patients about whom you heard today much stronger, better qualified, better documented ongoing evidence collection. There is too great a gap between what we're observing in practice and

00329

what we know about this important intervention for some severely affected Americans, and I

think that the experience that our MedCAC has had today calls great attention to not just what evidence we think we see, but to large gaps in evidence. And over the long run, I don't believe that's tolerable. We need to do a much better job of generating evidence for these various types of patients under these various types of conditions.

So thank you very much, panel, for a splendid job today. I very much appreciate your industriousness and stick-to-itiveness with a messy evidence base, but that's how it is, I guess in the real world, and we will turn it back to CMS.

DR. JACQUES: Thank you, and travel safely.

DR. GOODMAN: Thank you all.

(Whereupon, the meeting adjourned at 4:32 p.m.)