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

January 19, 2011

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

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Panelists

Chairperson
Clifford Goodman, PhD

Vice-Chair
Saty Satya-Murti, MD, FAAN

Voting Members
Rene' Cabral-Daniels, JD, MPH
Roger Dmochowski, MD
Leslie Grammer, MD
Roger D. Klein, MD, JD
David M. Mintzer, MD
David J. Samson, MS
Ajay Singh, MBBS, FRCP, MBA
Robert L. Steinbrook, MD

CMS Liaison
James Rollins, MD

Industry Representative
Lester D. Paul, MD, MS

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Guest Panel Members
Jerry A. Holmberg, PhD
David Stroncek, MD

Invited Guest Speakers
James Bowman, MD
Jeffrey L. Carson, MD
J. Michael Cecka, PhD

Executive Secretary
Maria Ellis

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PANEL PROCEEDINGS

(The meeting was called to order at 8:11 a.m., Wednesday, January 19, 2011.)

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 comment, and make recommendations concerning the currently available evidence regarding the effects of ESAs on health outcomes in adult CKD patients predialysis and dialysis.

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 conflicts of interest during their introduction.

We ask in the interest of fairness that all persons making statements or presentations disclose if you or any member of your immediate family owns stock or has another formal financial interest in any company, Internet or E-commerce organizations that develops, manufactures,

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distributes and/or markets ESAs. This includes direct financial investments, 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 all speakers addressing the panel, please speak directly into the mike and state your name.

For the record, voting members present for today's meeting are Dr. Saty Satya-Murti, Rene' Cabral-Daniels, Dr. Roger Dmochowski, Dr. Leslie Grammer, Dr. Roger Klein, Dr. David Mintzer, David Samson, Dr. Ajay Singh, and Dr. 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 voting members and

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one for the entire panel.

I ask that all panel members please speak directly into the mikes, and you may have to move the mikes 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 personal identifiable information that you or others may disclose about you during today's meeting. Please do not disclose personal information.

If you require a taxicab, there is a 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.

And lastly, all CMS guests attending today's meeting are only permitted in the following areas of CMS single 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.

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Now I would like to turn the meeting over to Dr. Jim Rollins.

DR. ROLLINS: Good morning. My name is Jim Rollins and I'm the director of the Division of Items and Devices in the Coverage and Analysis Group here at CMS. MedCAC serves three main purposes for CMS to get input from experts in the field on the topic, and that information helps us strategize our efforts related to future activities on that particular topic. Number two, to help disseminate information to the general public. And a more immediate use of the MedCAC, along with an external technology assessment, is to help us craft national coverage determinations.

I would like to thank the members of the MedCAC, especially the chairperson and vice chairperson, for participating in today's discussion.

DR. GOODMAN: Thank you very much, Dr. Rollins, and thank you, Ms. Ellis.

We have just this day for a pretty full agenda on a topic that has considerable potential impact in the world dealing with Medicare beneficiaries, and with that in mind we expect that all of our guest speakers and those providing scheduled public comments and any who may provide open public comments, as well as my fellow MedCAC members, will be on point and concise today.

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When recognized, as Ms. Ellis mentioned, please speak into the microphone when recognized. If you don't do that, our court reporter will not be able to hear you, which means that the very important things that you're going to be saying will not be entered into the record.

We have today time for scheduled public presentations, I understand now that there are going to be 16 of them, which I think is an unusually large number,

each of which will be allocated a maximum of four minutes by CMS. And given our tight agenda, including the need to hear from all these speakers and to provide a full discussion, we're going to need to adhere to those four-minute limits. Later on we'll hear from some open public commenters who I believe will be signing up, each of which will be allocated one minute. So we kindly, though firmly, suggest that each scheduled speaker focus your presentations on the information that pertains directly to today's voting questions. So if you had planned to present material, this comes under the heading of friendly advice, if you planned to present material that you find would be repetitive of previous speakers or that is merely background information about the organization or interest that you represent, you might consider dispensing with that part of your presentation and focusing instead on what you want this committee to

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hear that is directly relevant to the questions. That will help you and all of us. In any case, please heed the traffic light system to which Ms. Ellis referred to earlier. Thanks very much.

Please do quiet your cell phones and other electronic gizmos now, that's a great idea. And as Ms. Ellis said, anyone who speaks today should have already, or will be required to fill out a disclosure form as per FACA regulations, as I understand it.

So we're going to move now to some brief disclosures. Mine happens to be a little longer than most, and I apologize for that. We're going to recite our name and any disclosures that you may want to put on the record.

I am Cliff Goodman, a senior vice president of the Lewin Group, that is a healthcare policy consulting firm. Lewin is part of Ingenix, which is a health data analysis and IT firm. Ingenix in turn is one of multiple subsidiaries of United Health Group. I have no interests to declare pertaining to today's topic, but I do want to disclose that as a Lewin employee I have worked on several studies during 2007 and 2010 that concerned reimbursement mechanisms for the care of end stage renal disease, such as bundled pain approaches and the like, including for a major dialysis firm and for a major biotech firm that

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happens to manufacture ESAs. I've also spoken at and moderated health policy meetings for a major biotech firm that also happens to manufacture ESAs. Any honoraria for those activities were paid directly to my employer and not to me. With that I would like to turn to our cochair, Dr. Satya-Murti.

DR. SATYA-MURTI: Saty Satya-Murti. I am a neurologist and health policy consultant. I have no conflicts of interest to declare for this topic and today's MedCAC.

MS. CABRAL-DANIELS: Hello. Rene' Cabral-Daniels, National Patient Advocate Foundation, and likewise, I have no conflicts to disclose at this time for this MedCAC.
DR. DMOCHOWSKI: Roger Dmochowski, I'm a urologist, and I have no conflicts related to this topic.
DR. GRAMMER: Leslie Grammer, allergist immunologist. I have no conflicts related to this topic.
DR. KLEIN: Roger Klein. I'm a pathologist and have no conflicts.
DR. MINTZER: David Mintzer. I'm a hematologist. We have previously received for our practice group some small educational grants from one of the manufacturers for summer internship grants, and participate in clinical trials with reimbursement for

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entering patients in study and costs.
MR. SAMSON: David Samson, Blue Shield Blue Cross Association, no conflicts to declare.
DR. SINGH: I'm Ajay Singh, I'm a nephrologist with Brigham and Harvard Medical School. I receive research and consulting income from Johnson & Johnson, AmGen, and consulting fees from GSK and Sandoz.
DR. STEINBROOK: Robert Steinbrook, I'm an internist, I have no conflict of interest to declare.
DR. PAUL: Les Paul, I'm a pulmonologist and senior vice president of medical affairs for Caris Life Sciences, and I have no conflicts to declare.
DR. HOLMBERG: Jerry Holmberg. I'm the senior advisor for blood policy, and also the executive secretary for the advisory committee on blood safety and availability. The committee, the advisory committee of blood safety and availability was asked to discuss ESA a couple years back.
DR. STRONCEK: Dave Stroncek, a hematologist trained in transfusion medicine and histocompatibility. I am with the department of transfusion medicine clinical center, NIH. I have no conflicts to declare.
DR. GOODMAN: Great, thank you all, thank you very much.
We are not going to move to the CMS presentation

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of the voting questions, and this will begin with Kimberly Long. Ms. Long, welcome.
MS. LONG: Good morning. My name is Kim Long, and I am an analyst for the Coverage and Analysis Group. CMS has called this meeting of the panel to review the available evidence on the use of ESAs for the treatment of anemia in adults with CKD, including patients on dialysis and patients not on dialysis, and more specifically the impact of ESA use on renal transplant graft survival. ESAs are used with the intention of reducing the need for red blood cell transfusion and thereby minimizing immune sensitization as detected by panel reactive

antibody, PRA assays. PRA may be predictive of renal transplant graft survival. Some have proposed, therefore, that ESAs increase the survival of renal transplant grafts.
For the voting questions, use the following scale identifying level of confidence, with one representing the lowest or no confidence, three representing intermediate confidence, and five representing a high level of confidence.
The MedCAC will be asked to vote on the following questions.
Question one: How confident are you that there is adequate evidence to determine whether or not current

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PRA assays predict renal transplant graft survival for individual patients (in contrast to populations).
If the result of question one is at least intermediate, mean vote greater or equal to 2.5, how confident are you that current PRA assays predict renal transplant graft survival for individual patients?
Discussion for question two: How do PRA assays relate to more specific tests of HLA sensitivity, and whether titer levels predict specific organ HLA sensitivity?
Are the various proprietary PRA assays clinically interchangeable? For example, would the treating physician's management of a patient differ depending on a specific assay?
Do current PRA assays provide the same clinical information as older assays? For example, do historical data on performance of PRA assays apply to currently available assays?
Question three: Donor-specific blood transfusions were frequently employed prior to renal transplantation for immune modulation and improved graft survival. These differ from therapeutic blood transfusions, which are performed for anemia and blood loss management.
How confident are you that there is adequate

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evidence whether or not therapeutic blood transfusions decrease renal transplant graft survival?
Question four: If the result of question three is at least intermediate, mean vote greater than or equal to 2.5, how confident are you that the therapeutic blood transfusions decrease renal transplant graft survival?
Discussion for question four. The relative roles of sensitization as opposed to underlying comorbid conditions in affecting renal transplant graft survival.
The adequacy of the evidence base on the relationship, if any, between the number of units transfused and renal transplant graft survival. For example, is there a threshold number of units that predicts renal transplant graft survival, or is there a linear or exponential

relationship between the number of units transfused that predict renal transplant graft survival? The relative roles of blood transfusions, pregnancy, prior renal transplant, and other factors that cause sensitization. Question five: How confident are you that there is adequate evidence to determine whether or not ESA use for anemia blood loss management improves renal transplant graft survival? Question six: If the result of question five is at least intermediate, mean vote of greater or equal to 2.5, how confident are you that there is adequate evidence

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to conclude that ESA use to maintain hemoglobin levels greater than or equal to ten grams per deciliter is necessary to improve renal transplant graft survival? Question seven: What significant evidence gaps exist regarding the clinical criteria, including hemoglobin level of patients who should receive blood transfusions for chronic anemia with the intent of improving renal transplant graft survival? Question eight: What significant gaps exist regarding the relationship, if any, of number of units transfused, screening PRA assays, more specific HLA assays, immune suppressive regimen, and the timing of rejection to determine the role various factors play in transplant graft survival outcomes? Now Dr. Koller will present the background. Thank you.

DR. GOODMAN: Thank you very much, Ms. Long. Dr. Koller.

DR. KOLLER: Good morning. My name is Dr. Elizabeth Koller, and I will be presenting background information for this disease. Various services and supplies for endstage renal disease, ESRD, are covered by Medicare as mandated by law. These include chronic dialysis, blood transfusions, drugs for anemia management, and transplantation.

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Well, as we proceed through this meeting, it's important to consider what is actually known about the causes of anemia in patients with renal disease, about the need to intervene in the setting of anemia, about the impact of various interventions for anemia, about transfusion reduction by ESAs, about who receives a transplant, about the causes of transplant rejection and how this knowledge has changed, about the causes of sensitization, about the assays for sensitization, how they have changed and what they measure, about therapeutic advances to mitigate sensitization.

As this slide shows, anemia associated with renal disease is multifactorial and not always erythropoietin mediated. In addition, especially older patients may have coincident anemia of chronic disease or anemia from other hematologic disorders.

Radtke, in a 1979 longitudinal study, showed that anemia cannot be attributed to renal disease unless the creatinine clearance is under 30. As patients further approach the need for dialysis, hemoglobin levels drop, and a compensatory rise in endogenous erythropoietin. At this point, uremia is the cause. With removal of uremic toxins by dialysis there is marrow recovery, a rise in red cell production and a compensatory fall in erythropoietin. With further loss of renal tissue in the subsequent six or

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so months, erythropoietin production capacity is lost in most ESRD patients.

What do we know about the criteria for anemia management? What are the physiologic requirements? The just released European manual for optimal blood use codifies what is known. The Alliance endorsed the 2009 analysis performed by the German Medical Association, which found that there was reasonable evidence for transfusions in the setting of hemoglobin levels below six grams per deciliter in the absence of any risk factors, and with hemoglobin levels between six and eight for some patients with cardiovascular decompensation. Transfusion levels in patients with hemoglobins greater than ten was not supported.

The data have their gaps and limitations, available data applied primarily to acute care settings. Complicating matters are the compensatory mechanisms for anemia in the chronic setting. For example, two, three DPG levels rise and result in better oxygenation in the tissue than would otherwise be expected for a given plasma hemoglobin level.

Well, what are the reasons for transfusion in renal patients in particular? Transfusions may be done for chronic anemia management, but they may also be performed for other reasons, including bleeding diathesis

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secondary to uremia and renal disease-related procedures. A recent survey conducted in the United Kingdom for blood use showed that transfusions in general were administered for other than renal indications and that most transfusion recipients were older. An earlier ten-year survey of renal patients in the U.S. revealed that fewer than 20 percent of renal patients had more than five transfusions, and that this number decreased to under 10 percent by 1996. A persistent 30 to 40 percent, however, appeared to require one to five transfusions.

Well, what the are the indications for ESAs? ESAs do not improve survival or cardiovascular morbidity. They do not improve exercise tolerance. And health-related quality of life was removed by the FDA in 2007.

Do they reduce or eliminate the need for transfusions? What are the transfusion data from the registration studies? The protocols in the trials did not

utilize any validated criteria for anemia intervention. There were no specific criteria for transfusion. This absence of an established treatment algorithm complicates interpretation of open-label or uncontrolled trials. There is also little publicly available information about for whom, why and when transfusions were administered, and if there were longitudinal changes in sensitization.

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Data, where available, were limited to the numbers of patients who received transfusions. For example, the Canadian group conducted the randomized pivotal six-month registration study in 118 non-diabetic, relatively young and very anemic dialysis patients. Fewer patients from the erythropoietin arms appear to have been transfused, but little else is known about the nature and need for transfusion, as is indicated by these blank cells delineated in yellow. In another randomized pivotal study that enrolled 117 pre-dialysis renal patients without GFR inclusion criteria, no transfusions were given to any patient during the eight-week study. We are aware of at least three registration studies with possible transfusion data but these are not within the public domain, and we call attention to study 8701, which is frequently cited. Other ESAs, darbepoetin and polyethylene glycol-epoetin have been approved for anemia management, but neither carries indications for transfusion reduction. The registration studies were equivalent studies with active and not placebo controls. One of the blinded studies, 211, which remains unpublished, showed more transfusion in the darbepoetin arm. Well, how are ESRD patients managed? Most are

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treated with dialysis. The proportion of patients who have a functional transplant is relatively higher amongst the prevalent patients than the incident patients. This likely reflects the demographics and relative good health of the population selected for transplantation. As can be seen here, patients under 20 are primarily managed with transplantation, whereas patients older than 45, are managed with dialysis. The likelihood of transplantation within three years of ESRD registration is just under 70 percent for those who are under age 20. It is less than ten percent for those who are 60 and older. Well, what are the causes for transplant failure? As you'll hear in more depth later, there is both cellular and humeral mediated rejection. Organs may also fail because of donor characteristics, recipient traits, surgical experience, and patient compliance with immune suppression. Well, Patel and Terasaki attempted to tease out some of these factors. They developed the PRA, the panel reactive antibody test, which is a global assay of

antigens to which a patient was sensitized. The number one cause of sensitization is thought to be prior transplant. Multiple pregnancies and transfusions are thought to be the other major contributors to sensitization. PRA assays do, however, have false

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positives, and PRA results may be affected by whether the sample is collected before or after a dialysis session, and the use of statins. Also for unexplained reasons, PRA levels have increased over time despite the extensive use of ESAs. Unfortunately, it is not possible to assess the current relationship between transfusion parameters and PRA results from the various assays, because UNOS, the organ sharing network, no longer collects substantive transfusion data.

As such, PRA is a relatively nonspecific assay and will not determine the likelihood of susceptibility of a specific organ. New technology has enabled a determination of antibody profiles specific to the patient, and a calculated PRA takes advantage of some of this information and reduces the likelihood that a patient will be offered an unacceptable organ.

Only 10 to 20 percent of patients wait-listed for a transplant are significantly sensitized, in other words, with a PRA of 80 percent or greater. Even sensitized patients have options. In addition to better characterization of sensitization, transplant programs employ induction therapy, antibody capture with IVIg, antibody clearance with plasmapheresis, and experimental agents.

This chart shows the numbers of transplants in highly

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sensitized patients. 300 to 350 transplants occur in such patients annually. This could be up to 12 percent of highly sensitized incident patients or up to four percent of highly sensitized wait-listed patients. To put this in perspective, 2.3% of all incident patients are transplanted in year one.

Although there are research gaps in transfusion use and criteria for anemia intervention, the data do not support therapeutic intervention with transfusions for patients with hemoglobin levels greater than ten grams per deciliter and for most patients with hemoglobin levels between six and ten. Although physiologic replacement levels of ESAs may have a role in ESRD patients with significant anemia and ESA responsiveness, the data in support of the transfusion reduction indication are limited. ESAs do not eliminate the need for transfusions in renal patients because the transfusions are given for a variety of reasons.

PRA are nonstandard. Nonstandardized and nonspecific tests, which have changed over time. Patient characteristics other than PRA impact on transplant suitability. Most transplant patients are young and

without comorbid conditions. The relationships between transfusions, PRA, and renal transplant outcomes are not straightforward and cannot be explored because the
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appropriate data are not currently collected by either CMS or UNOS.
Lastly, I would like to point out that there are options for sensitized patients and these are growing in number. Thank you very much.
DR. GOODMAN: Before you go back down, can we have the next to last summary slide back up again? It would be the first of the two summary slides. I just note, panel, before we go on, we're seeing a lot of data from studies thrown at us today, and I want to make sure just before you move to the EPC presentation at least of this juncture, if anybody has any kind of high level concise questions at this point. We will obviously have a chance to get back to Dr. Koller during our question period later today, but I just want to make sure we get a good look at least at her summary slides now, and make sure we at least understand or have heard what she has presented, at least on a high level at this point.
So just do take a minute, as I am, to make sure I am reading this carefully, and I know all of you have this in hard copy as well. So, among the summary points, if you don't mind, Dr. Koller, the first point addresses research gaps. The second point addresses when there would be therapeutic intervention of transfusion or not. The third point deals with replacement levels of ESAs,
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whether or not they've got a role in these patients. The fourth bullet addresses whether or not ESAs eliminate the need for transfusion in patients. Those are the first four summary points, and then the next slide, please. This deals with PRA, makes the point, the assertion that PRA are nonstandardized and nonspecific tests. The next point is that patient characteristics other than PRA impact or affect transplant suitability. The third point on this slide regards the relationships between transfusions, PRA and renal transplant outcomes, where it is asserted that the outcomes are not straightforward based on current data. And the final point suggests that there are options for sensitized patients.
So those are the main summary points. I just wanted to allow those to sink in for a few moments. I know we've got a lot of material left for today. Okay. Seeing no questions now, but I'm sure there will be some later, once again, thank you very much, Dr. Koller, we appreciate you presenting a lot of material in that amount of time.
Next up is Dr. Michael White, he's with the University of Connecticut EPC. For those of you who don't understand how this works, it is often the case that when CMS is looking at coverage decisions or potential ones,

that they will contact the Agency for Healthcare Research
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and Quality, AHRQ. AHRQ has a set of, I believe, 13 evidence-based practice centers, of which U.Conn-Hartford is one, and these EPCs will prepare basically systematic reviews, they're sometimes called evidence reports or TAs, technology assessments, to address the availability and quality of evidence on certain questions, and these questions more or less match up with the questions that the MedCAC is to address. Now sometimes because of the lag time and some adjustments in questions, by the time the TA appears to us, its set of questions may not entirely align with the questions that we're addressing, but the content is almost always quite relevant.
And so with that, again, Dr. White, welcome, and we look forward to your presentation. Thank you, sir.
DR. WHITE: Great, thank you. Welcome, everyone. None of the people that were involved in this technology assessment have any financial or other conflicts of interest in regards to the TA report or this presentation.
So, about 450,000 people in the United States have endstage renal disease and a very small subset of those, around 14,000 patients as of 2009, ended up getting transplants annually. The alternative to renal transplant is chronic dialysis. So, human leukocyte antigens are a set of human major histocompatability complex derived
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glycoproteins that are expressed on cell surfaces, and this allows for auto recognition, the ability to discern yourself from non-cell.
There's two main classes, there's Class I and then there's also Class II HLA. Allorecognition is the recognition of antigens displayed on transplanted cells. There is a direct pathway where donor antigen presenting cells migrate to the recipient lymph nodes and present antigens to the T-cells. There's also an indirect pathway where the recipient antigen presenting cells migrate into the allograft, get hold of the alloantigens and then present them to T-cells. So you need this allorecognition plus a costimulatory signal in order to be able to activate T-cells and initiate rejection.
So, there's four main types of rejection.
There's a hyperacute rejection, which is an immediate recipient immune response against the allograft, and this is due to preformed recipient antibodies. This is humeral mediated.
There's acute rejection, which generally occurs between five and 90 days after a transplant. This is due to alloreactive T-cell mediated rejection.
There is a type of acute rejection which is called humeral rejection, which is similar in terms of the time course, but is instead of being conducted by
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cytotoxic T-cells is humerally mediated. And then chronic rejection can be caused by a myriad of different causes, immunologic processes, and can be cell mediated, humerally mediated, or drug induced. There is immunosuppressive therapy that's available. There's three main types. There's induction therapy, which is usually initiated intra or immediate postoperative period and then continued for several days afterwards. This is often given to patients who have preformed antibodies, a history of previous organ transplant, multiple HLA mismatches, or a transplantation of organs with prolonged cold ischemia times. Then there's maintenance immunosuppressive therapy, and there's common classes. So one of the things that you're going to see is that the calcineurin inhibitors, here talking about cyclosporin in particular, was unavailable before 1983, and had more common use after 1984 so you'll see later on, we're going to do a cut point and look at data after 1984. Antiproliferatives are also available, and then target with Rapamycin inhibitors, and then the old standby, corticosteroids. And usually, two or more medications from different categories are used together. And then there's acute rejection therapy, which includes usually corticosteroids with or without other

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immunosuppressive therapy. So what did we do in our technology assessment? Well, what we did is a systematic search of the literature from MEDLINE and Cochrane CENTRAL from the earliest possible date through August of 2010, and then a targeted search of EMBASE, specifically looking for foreign language articles over the same time period. We did backwards citation tracking, which means that we went through the references of book chapters and the citations that we had in order to be able to identify additional citations that were not readily apparent in our literature search. For a study eligibility it had to be studies in humans, either clinical or observational studies. The patients needed to receive transfusion prior to kidney transplant, and we allowed people who had a pancreas transplant at the same time as a kidney transplant to be included in this data set. We reported on the relationship between transfusion and renal allograft outcomes, and these studies had to report on outcomes of interest. Here we're talking specifically about rejection, graft survival, and then patient survival. And then outcomes of interest, looking at the impact of predictability of PRA on renal transplant rejection or

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survival. So those are the studies that ended up getting included from our literature search.

Now we looked at each individual study and we rated each individual study for its quality using the following definitions. We had good studies which had the least bias, and the results could be considered valid. There was fair, which was data that's susceptible to some bias but not sufficient to invalidate the results. And then poor data, substantial flaws that imply biases of various types that may invalidate the results.

This data set has severe clinical and methodological heterogeneity. The retrospective nature of virtually all the studies and the apparently poor quality of individual studies upon validity assessment meant that we could not pool the results together, we could not perform meta-analyses. So what are some of the areas of heterogeneity? Different definitions of outcomes, different subpopulations, different etiologies of renal failure, the role of HLA matching, living donor versus cadaver donor, or a mixture of those two. The use of perioperative transfusion, previous transplant and pregnancy, history of previous random transfusion with donor-specific transfusion trials, differing time periods of follow-up, ABO compatibility. And then a variety of other things that we couldn't even discern, like simple

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hypothermic storage versus pulsatile, perfusion, and factors such as that.

So we graded the strength of the body of evidence and you could have three possible choices, high confidence that future studies would not change the results, moderate confidence that future studies would not change the results, or low confidence. We also had a category of insufficient evidence.

Now we created the body of strength of evidence based on the risk of bias, the consistency of the different studies that evaluated that endpoint, the directness of the endpoint, is it a terminal endpoint or is it a surrogate/intermediate outcome, and then the precision was evaluated, and that's how we determined our strength of evidence.

So after we did our literature search we ended up with 1,195 citations after duplicates were removed. Ultimately 280 studies were available for inclusion based on qualitative evaluations. That means that they met the inclusion criteria. However, a number of those studies were multiple publications from the same data set over a similar period of time, so we had to go through and tease those out to make sure that we weren't overrepresenting the data by the inclusion of those studies. So we ended up including 172 studies that provided analyses that met

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our inclusion criteria.

Let me give you some insight to the body of literature that we have today. 83 percent of the studies were retrospective observational studies. 84 percent used

concurrent control groups, which is a good thing, but almost 80 percent of studies did not account for confounding, and that's very very important when you're looking at retrospective data studies, so that's a negative for the quality of this data set.

Demographic data in both groups, yes in 74 percent of the cases, but that meant that in over a quarter of the cases they didn't provide demographic data. And this doesn't mean complete demographic data, this means demographic data of any kind reported in two individual groups.

And then studies that were conducted entirely from 1984 to present were what we're calling the post-cyclosporin era or the cyclosporin era. 83.4 percent were not, so we're looking at an older data set for a lot of the studies we will be looking at today.

In terms of its applicability, a good representative sample of studies were conducted in the United States or Canada, but more importantly the validity of individual studies in about 88 percent of studies, the individual studies were rated as poor.

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So Key Question 1.A, do red blood cell transfusions prior to renal transplant impact allograft rejection or survival, and what is the magnitude of that effect relative to other factors?

So here we looked at the impact of packed red blood cells, whole blood, leukocyte-depleted, leukocyte-free, matched blood, donor-specific blood together, versus no transfusion. Data were evaluated regardless of the number of transfusions, the number of units transfused or the number of donors, so this was our collect-all with the greatest power in the analysis.

Data were evaluated regardless of the time period, but keep in mind that in 1.B which we will be talking about next, we will go through many of the individual subgroups exploring some of these different facets separately.

So for rejection let me just orient you, because we're going to see a lot of slides that are going to be like this as we go along. So for the data set looking at a significant reduction in rejection, no significant effect on rejection, or significant increases in rejection, so this is the significance evaluation.

There were 25 trials that had evaluated rejection. Nine of the 25 showed a significant reduction in rejection, that was 36 percent. 13 out of 25 showed no

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significant effect on rejection, that was 52 percent of the overall literature base. So what we can say is that transfusions, based on this data, had either a beneficial to neutral significant effect on rejection outcomes, but the strength of evidence is low.

Then we looked at the directionality of effect,

because maybe some of the trials were underpowered. When we looked at the direction of effect, we looked at whether it was a decrease, whether there was no change or whether there was an increase, and you can see that there's 47 individual analyses. And our conclusion based on this data is that transfusions had a beneficial to neutral effect on rejection outcomes, but this data set is insufficient because it was very hard to gauge the magnitude for any of these rejection analyses.

Now let's move on to survival outcomes, first looking at graft survival. And I just want to orient you just for a second that patients can have multiple rejection episodes but they may or may not lose their graft, all right? So when we're talking about rejection we don't mean loss of a graft, loss of a graft would be here when we're talking about graft survival. So we looked at the data based on one-year graft survival for studies that had presented one-year data, or the maximum duration of graft survival looking at the maximum duration

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that was reported in any of the individual studies.

Again, we looked at the significance of findings first, and we saw that in all cases transfusions had a beneficial to neutral effect on one-year maximum duration of graft survival, the strength of evidence being low. When we looked at patient survival, you can see the vast majority of data were showing a neutral effect on either one-year or maximum duration patient survival, strength of evidence being low.

Now here we look at magnitude, and as we go along you will see that for both graft survival and patient survival we break things up into these categories. A greater than 10 percent increase in survival, a very small change in either direction, a positive or a minus 10 percent change in survival, or a greater than 10 percent decrease in survival. And when we looked at that, we saw that transfusions had a beneficial to neutral effect on one-year and maximum duration graft survival, strength of evidence being low.

When we looked at patient survival, we saw that transfusions had a beneficial to neutral effect on one-year and maximum duration of patient survival with a strength of evidence that is low.

We also looked at multivariate analyses and we looked at rejection outcomes, and there were six analyses,

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three analyses had evaluated for retransplantation, two evaluated for the impact of transfusion, and one evaluated for the impact of prior pregnancy. In two-thirds of the cases multivariate analyses showed retransplantation to be an independent predictor of an increasing chance of rejection. In contrast, both of the multivariate analyses showed transfusions to be an independent predictor of decreasing rejection. The one analysis that evaluated

prior pregnancy found it to be an independent predictor of decreasing rejection.
We then looked at graft survival outcomes and here the data set was larger, there were 30 overall analyses. You can see that 57 percent of these multivariate analyses showed retransplantation to be an independent predictor of worsening graft outcome, 50 percent of the multivariate showed transfusion to be an independent predictor benefitting graft outcome, the other showing no effect, not a predictor of worsening outcome. And 25 percent of the multivariate analyses showed prior pregnancy to be an independent predictor of worsening graft outcome, in the other cases it was not an independent predictor.
And then patient survival outcome. Here we're looking at eight analyses, seven for retransplantation, one for transfusion, and then none for prior pregnancy.

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And we can see that 14 percent of the multivariate analyses showed retransplantation to be an independent predictor of worsening patient survival outcome. No multivariate analysis showed transfusions were an independent predictor of those outcomes.
Now let's go to 1.B. Is any such impact of red blood cell transfusions on renal transplant outcomes altered by variables such as planned and donor-specific transfusions versus either no transfusion or therapeutic-specific transfusions, the number of transfusions, the number of units of blood transfused, and/or the number of donors?
So we're going to present the number of transfusion data. We have the number of units of blood transfused data that we can present during the question and answer session. The data is very similar to the number of transfusions data, but there are many fewer analyses. No data for the number of donors.
We looked at the use of leukocyte-depleted blood. There was scant data, it's not going to be reported, although we have slides for those if you want to talk about those during the question and answer session.
And then for four and five we grouped them together into different time periods to account for changes in either immunosuppressant regimens or other changes in management

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that had occurred over time, and we'll talk about that when we get to that slide.
So graft rejection if you have donor-specific transfusion versus non-donor-specific transfusion, so everyone in these studies had received transfusions, just different types. Donor-specific transfusions had received transfusions from the people who they were going to be getting their organ from. And you can see that when you look at rejection in the significance evaluation, that donor-specific transfusion had a beneficial to neutral

significant effect on rejection outcomes, with the strength of evidence being low. When we looked at the directionality of effect we found also that it had a beneficial to neutral effect on rejection outcomes, but of course again, the strength of evidence is insufficient because we couldn't gauge the magnitude.

Looking at survival outcomes, first looking at graft survival, both one-year graft survival data and maximum duration graft survival data, in all cases showed either a beneficial to neutral significant effect on one-year and maximum duration of graft survival, strength of evidence being low. When we looked at patient survival, looking at one-year and maximum duration patient survival, it was a neutral effect was what we had found, no significant effect on one-year or maximum duration

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survival, only two trials, so the grade of evidence here was insufficient.

When we looked at the magnitude of effect, in all cases whether we were looking at graft survival or patient survival, okay, we ended up not finding a large magnitude decrease in survival. For graft survival it was either beneficial to neutral, and then when you look at patient survival, just like it was for the significance finding, it was a neutral effect.

Multivariate analyses for rejection outcomes, there was only one analysis. Donor-specific transfusion was found to be an independent predictor of decreasing rejection. For graft survival outcomes there were four analyses that assessed for donor-specific transfusion, one found it to be an independent predictor in benefitting graft survival. There were no studies looking at multivariate analyses that evaluated patient survival.

Now we will move on to 1.B, graft rejection based on the number of transfusions, the number of units of blood, and then the number of donors data had no analyses and was not reported. So here we're going to focus on the number of transfusions and what you see is that for graft rejection, the use of a larger number of transfusions versus a lower number of transfusions had a beneficial to neutral effect on rejection outcomes, and

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when we looked at the directionality of effect we found the same conclusion of beneficial to neutral effect, strength of evidence being low to insufficient.

When we looked at graft survival based on the number of transfusions, the intensity of transfusion versus no transfusion, we broke things up into several different categories. First we looked at one to five transfusions versus no transfusions, then we looked at five to ten transfusions versus no transfusions, and then we looked at greater than or equal to ten transfusions versus no transfusions. And in all of these cases, whether we looked at graft survival, okay, in any of these

three sub-cases, it always came up with either a beneficial to neutral effect on graft survival, the strength of evidence being low. When we evaluated based on the magnitude of the effect, in virtually all of the cases within these analyses, whether you had one to five, five to ten, or greater than ten transfusions versus no transfusions, you ended up with a beneficial to neutral effect on graft survival.

So now we're looking at higher versus lower number of transfusions, and you can see when we look at one-year graft survival and maximum duration graft survival, if you had greater than five transfusions versus one to five transfusions, it was a beneficial to neutral

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effect, a neutral effect was seen for one-year graft survival for greater than ten transfusions versus one to five, and the same kind of thing held true when the number of transfusions were greater than ten transfusions versus five to ten. Okay? So the use of a higher number of transfusions versus a lower number of transfusions had a beneficial to no significant effect on graft survival, but as you had more transfusions versus a lower number of transfusions it was going from a more significant benefit to a more neutral effect as it had progressed.

Looking at the magnitude of effect, the same kind of thing, the data is showing either a beneficial to neutral effect on graft survival. Now we're looking at patient survival looking at increasing number of transfusions versus no transfusions and here what we see is a neutral effect down the line, okay, strength of evidence being low. We looked at the magnitude of the change in patient survival and what we saw was predominantly a neutral effect. Some beneficial effects were seen in some trials, although the number of trials evaluating this for a higher number of transfusions were pretty low, again, strength of evidence being low.

Now we looked at higher number of transfusions versus lower number of transfusions. Whether we looked at greater than five, greater than ten, okay, versus one to

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five transfusions, or greater than ten transfusions versus five to ten transfusions, we're seeing a neutral effect in both the significant effects and in terms of the magnitude of effect.

Multivariate analyses. Seven analyses evaluated the number of transfusions or the number of units that were transfused. In three of five multivariate analyses, they showed that the number of transfusions was an independent predictor of fewer rejection outcomes, so this is similar to what we have been seeing up to this point.

However, this data set included patients who may have received zero transfusions, so it was more transfusions versus less, but when it was less it could have included zero. There were two analyses, both were for the same

study, that evaluated higher intensity, greater than five transfusions versus lower intensity, either one to five transfusions, here not including zero. So they analyzed these separately and in this analysis, one of the two analyses found that greater than five transfusions was an independent predictor of increasing risk of rejection with living donors but not with cadaver donors.

Multivariate analyses looking at graft survival, 18 analyses. 61 percent did not find transfusions to be an independent predictor of graft survival, 33 percent found it was an independent predictor of worsening

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survival, 5.6 percent found it to be an independent predictor of benefitting graft survival, so the dominant one here being the one showing that it was not an independent predictor. There were two analyses that found transfusions of higher intensity to be an independent predictor in both living and cadaver allografts versus lower intensity, same study that we had talked about on the last slide.

Patient survival outcomes, seven analyses. 57 percent did not find the number of transfusions or the number of units transfused to be independent predictors of patient survival in either direction. 50 percent were limited to five or fewer transfusions, okay? So three of seven multivariate analyses, or 42.9 percent, showed the number of transfusions to be an independent predictor of worsening patient survival outcomes. Two analyses were from the same study and examined either six to ten transfusions versus no transfusions, or greater than ten transfusions versus zero. One study examined transfusions of greater than 40 units of blood. Okay.

So now we're going to look at the impact of when the studies were conducted in terms of the time period. Studies conducted after 1984 looking at cyclosporin, studies after 1992 more reflecting contemporary practice. And what we can tell you, up to the year 1992, while

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transfusions may have a significant beneficial to neutral effect on rejection, thereafter transfusions may or may not provide this effect. When we looked at the directionality, we can say that up to the year 1992 transfusions may have a beneficial to neutral effect on rejection, but thereafter they may or may not provide this effect. So you see that in that 1992 to present time frame, things become more dichotomous.

Let's look at graft survival and look at the same time periods. What we see when we look at graft survival is that it goes from, in an earlier time period before 1984 where the majority are showing beneficial effects, to a majority of studies showing neutral effects, to all the studies showing a neutral effect from 1992 to present, both in terms of the significance analysis and in terms of the magnitude of effect analysis.

So for the time period, what we don't feel like we saw with rejection was a large number of studies showing a significant decrease in survival or a large constituent of studies that were showing a large magnitude of decrease in survival in that 1992 to present time period.

We looked at patient survival. Across the board we're seeing a neutral effect on patient survival regardless of the time periods. This is transfusion

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versus no transfusion over these three time periods, a neutral effect, strength of evidence being low.

So Key Question 2.A. How have PRA assays changed over time, do all PRA assays measure the same thing, what things contribute to intra-assay variability, and then how correlated or independent of one another are these measures?

PRA testing seeks to evaluate who's most at risk of antibody rejection. Patients with preformed antibodies against HLA antigens are at risk of hyperacute or humeral rejection. If you have a PRA of 80 percent what that means, just to orient you, is that a patient is supposed to be incompatible with 80 percent of donors. A PRA of greater than ten percent is considered sensitized. A PRA of greater than or equal to 80 percent is considered highly sensitized, although many institutions have their own takes on what is considered highly sensitized, some people say it's above 40, some people say it's above 60.

The PRA system has been used since the 1960s. One of the first tests for determining PRA that we're going to talk about is the complement-dependent cytotoxicity test, and this is the oldest test for determining PRA. They take serum-containing antibodies against HLA antigens, the antibodies will bind to the lymphocytes, and then when they add complement to the

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serum the lymphocytes will be killed and then will be detected by stain.

But there's some problems with using the complement-dependent cytotoxicity test. It only detects Class I antibodies, it can detect non-HLA antigens, it depends on lymphocyte and complement quality, and then it's limited by the cell panel that you use. So it cannot be used as the only test to determine sensitization.

There is an ELISA test, which is a solid phase assay which is supposed to be more sensitive than the CDC.

There's also a flow cytometry test, and with this assay there's two different flavors, there's the house method where you use whole lymphocytes, or the more commonly employed method using microbeads which identify Class I and Class II antibodies, but also specify which HLA mismatches occur. So the CDC is thought to be inferior in terms of sensitivity and specificity to both the ELISA and the microbead flow cytometry tests, which are supposed to

be roughly equivalent to each other, so these different assays have varying sensitivities and specificities. There are different PRAs and one PRA is not another PRA, and currently 44 percent of centers are using peak PRAs, while 56 percent of centers are using current PRAs. So if you do something that raises PRA and then you measure your PRA at a future time point the PRA may

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decrease; however, it would not change your peak PRA. Composition of antigen panels vary depending on the kit that you use or whether you're using locally procured cells, and it may differ from the potential donor population.

Let's talk about calculated PRA just for a moment. UNOS on October 1st of 2009 recommended against the PRA system and through a calculated PRA strategy. CPRA, or the calculated PRA, is based on the unacceptable HLA antigens to which patients are sensitized, but rather than a global assessment, looking at the specific HLA antigens to which patients are sensitized to, and which if it was present in a donor would represent an unacceptable risk for the candidate. CPRA is computed from HLA antigen frequencies among 12,000 kidney donors in the United States between 2003 and 2005.

So this much more closely represents the potential of actual organ donors that expressed one or more unacceptable HLA antigens. If an HLA antibody is identified in a patient, a kidney with that antigen would not be offered. The higher the CPRA, the fewer kidneys that would be offered to the patient. By March of 2009, only 13 of 256 kidney transplant centers did not enter specific HLA antigen incompatibilities into the UNOS system, showing good adoption by transplant centers. 90

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percent of the patients with a PRA of greater than 80 percent also had high CPRA in the same range.

Let's look at correlations between the assays. If you look at ELISA versus ELISA, or if you look at ELISA versus flow cytometry, so looking at different kits of ELISA or kits of ELISA versus different kits for flow cytometry, they are generally well correlated, R values around 0.78, 0.80. When you look at ELISA versus CDC, they are reasonably correlated for Class I antigens, but again, CDC does not evaluate for Class II. They were reasonably correlated in two of the three analyses that we had found.

Analysis in patients with graft failure, okay, here is something that I think is very important. This study did something different than what the other studies did, and they looked for correlation specifically in patients who had graft failure. Here what you see is that there was significant correlations, but look at the correlation coefficient. Instead of being around 0.78, 0.79, the correlations between ELISA and flow cytometry

are down to 0.49, and the correlations are even lower when you look at CDC tests versus either flow cytometry or ELISA, the average scores around 0.28 to 0.30.
Key Question 2.B. How useful are PRA assays in predicting sensitization from blood transfusions,

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donor-specific antigen sensitization, and renal transplant rejection or survival in the setting of 2.A that we just described?
So let's look at rejection outcomes. Here we're looking at PRA, and we're looking at higher and lower PRA. So when we looked at rejection, what we found was a neutral effect, lower PRAs may not significantly impact rejection. When we look at the directionality of effect, all the studies were showing a directional effect showing a decreased risk of rejection, it just wasn't high enough to reach statistical significance. When we looked at graft survival what we see is either a beneficial to neutral effect for having a lower PRA for failure. The same thing was true for the magnitude of effect that you saw, a good magnitude or a small magnitude of beneficial effect for a lower PRA. When we looked at patient survival, though, we saw that there was a neutral effect of having a lower PRA in either the significance or the magnitude of patient survival, strength of evidence for all of these analyses for 2.B being low.
So in summary, the data is generally weak, the strength of evidence is low to insufficient. There is a reasonable chance that future research could alter these conclusions. Transfusions generally have a beneficial to neutral effect on renal allograft outcomes. Over

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differing time periods there's a shift away from beneficial effects and more towards neutral effects. A potential confounder, though, is that in some of these studies patients were originally enrolled, and when they looked at patients who had subsequently developed high PRAs, they did not allow those patients to undergo transplantation.
Lower PRA generally had a beneficial to neutral effect on renal allograft outcomes, but the studies did not assess the impact of higher PRAs from transfusion alone versus any cause, so was it due to prior transplantation, was it due to mothers receiving grafts from their children, was it due to viral infection.
PRA varies based on the assay that's used. When PRA is determined in relation to stimuli, okay, things can be different than, if a time period happens after the stimuli had occurred. And then there's also the use of modulators, giving immunosuppressants, giving statins, using plasmapheresis, or using a combination of those strategies.
And there's a strong movement now towards the CPRA system where specific incompatibilities are

determined, but the impact of transfusions on the CPRA are not well described.
What kind of future studies need to be done?

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Multi-institutional studies are needed. Each individual institution had their own way of doing things, so it's very hard to know whether or not the data from one institution can be extrapolated to other institutions. Adequate reporting of demographics, very poor reporting of demographics in this data set. Randomization would be very important, or at least adjustment for confounders, adjustment for all the important confounders. Standard definitions of outcomes. Standard follow-up times, and the longer the better. Transfusions should not just be counted in the dialysis or the transplant center like they commonly are. People can receive transfusions for a variety of different reasons. And finally, CPRA testing, so that specific HLA antigen sensitivities resulting from transfusions can be identified.
And then taking the next step and seeing what the impact of immunosuppression is on those outcomes in sensitized patients due to the transfusion is desperately needed. Thank you.
DR. GOODMAN: Thank you, Dr. White. Dr. White, if you could just remain at the podium for a few minutes if necessary. Panel, if we do have a top line question or two at this point, we're going to take it, and then we'll move on. And before I get to Dr. Klein, I wanted to point something out. Charlie, could you go back to slide 14,

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please? Thank you.
And Dr. White, his team presented just a lot of great information, but I thought it would help me and perhaps others, just to go back to this. With regard to the overall body of literature, I think you came down to about 172 studies that met your inclusion criteria. This picture kind of gets the terminology up there insofar as the overall body of evidence. There were three types of studies, there were CCTs, controlled clinical trials, prospective observational studies and retrospective observational studies.
DR. WHITE: Yes.
DR. GOODMAN: And the panel notices that 83 percent of that whole body of studies were typically the least strong design, i.e., retrospective observational studies. Only eight percent were controlled clinical; most of the controlled clinical trials did have concurrent controls, which is usually a good thing. Among the prospective and retrospective observational studies, gosh, four out of five did not account for confounding, three out of four did not provide demographic data for both groups studied, and what, 84 percent were conducted since 1984.
But in any case, this is not what I would call

the strongest airtight body of evidence. Now there are a
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lot of reasons why that occurs, not everybody designs with MedCAC, or for MedCAC to review them in 2011, but this is not a particularly strong body of evidence as you've characterized it, and I see you nodding your head. Charlie, could you move to, try slide 18. I just want to make sure that I'm detecting a pattern actually, and the pattern might look a lot like slide 18. Basically when it comes to your conclusions, you found a lot of things saying that the intervention, in this case transfusion, was beneficial to neutral, but the quality and strength of evidence was low to insufficient. And this slide is probably not a bad example, it could be a good example, and all the conclusions and strengths of evidence here were beneficial to neutral effect, low evidence.
DR. WHITE: Yes.
DR. GOODMAN: And it seems to me that we saw a lot of that in that series of slides, correct?
DR. WHITE: Yes.
DR. GOODMAN: I just wanted to make sure I understood that. A couple of questions if we could, Dr. Klein first.
DR. KLEIN: Although most of the evidence that you've presented, the studies were rated or graded as poor or fair quality, and most of the evidence was
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observational. There were a number of clinical trials and there were studies that were rated as good. And I'm wondering if you independently analyzed that body of data versus the larger body of data, and whether or not there were differences.
DR. WHITE: We didn't look at that, we didn't evaluate for good quality studies separately from the overall body of evidence.
DR. GOODMAN: That's a fair question, just because the overall body of evidence may not be entirely impressive, that doesn't reflect on any particular study. Good point, thank you, Dr. Klein. Dr. Grammer.
DR. GRAMMER: I just want to be sure that I was correct that you didn't look at the relationship between transfusions and renal allograft eligibility, or the likelihood that a patient would receive a transplant?
DR. WHITE: Yes, and it's not one of the key questions that we were given. So, here's one of the dilemmas. Whether or not a patient in a specific center is given a transplant in the face of higher PRA or not does not mean that that's what the case would be in another institution, so some institutions would give those patients induction therapy. Other centers would not give them transplantation. Other institutions would do different things, they wouldn't give them a cadaver, they
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would only give them living, and the variability is such that it's very difficult to be able to tease out that information. It's important that people recognize that there were some patients who didn't receive transfusions who did hit those institutions' cutoffs, and were not being given a transplant because at that institution they were above their overall cutoff for PRA.

DR. GOODMAN: Thank you. Was there another question? Mr. Samson.

MR. SAMSON: I just wanted to be clear about the summary tables where you grade the evidence. The columns on the left that describe the patterns and results for statistical significance and then the columns on the right either deal with the magnitude of the effect or the direction, or both, and in the columns on the right there are larger numbers of studies. And I assume that it's due to a lot of studies not reporting on statistical test results; is that correct?

DR. WHITE: It's one of two things, either they didn't report the significance or they did not say that it was significant or not significant, okay? Or there are -- or they showed no -- so if you're looking over here on my right, I guess it's your left --

DR. GOODMAN: All on the right.

DR. WHITE: Yeah. Looking over here at the

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data, this is just the directionality of effects. Some studies may not have shown significance, or they may have shown no significant effect, but the effect was greater than 10 percent. So here we're looking at a lot of studies that may have been underpowered to be able to show differences, so we're looking at were the changes due to chance or were they due to some kind of real effect, but we wanted to give them the opportunity to look at the data in two different ways.

MR. SAMSON: Right, but I also wanted to clarify whether the studies in the left-hand columns are a subset of the studies on the right.

DR. WHITE: Yes, unless they did not report their effect but they said that there was a significant benefit. So pretty much in all cases what you're saying is true, that the significant ones are a subset of the magnitude ones, but it might not have been true in every case.

DR. GOODMAN: Thank you for that question, Mr. Samson. We'll go with Dr. Singh and then Dr. Dmochowski, and then we'll move on. Dr. Singh.

DR. SINGH: In the data you presented regarding panel reactive antibodies, PRA, you stated it was a narrative review. Could you tell us how were these studies graded, were they graded as good quality or poor

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quality?

DR. WHITE: Are you talking about 2.A?

DR. SINGH: The questions related to 2.A and 2.B.
DR. WHITE: For 2.B we did grade individual studies, for 2.A we didn't grade quality of individual studies, because 2.A was not part of a systematic review, it was just a narrative overview. But I believe we have in the backup slides, don't we have a slide looking at study quality?
DR. GOODMAN: We don't need to have it posted now, but Dr. Singh can refer to it.
DR. WHITE: Yes. For each key question we do have a slide, and then also in the report we do talk about individual study quality for each of the key questions and sub-questions individually.
DR. SINGH: Just one final additional question related to this. In those statements related to PRA, were these studies after 1992 or before, because it seems like 1992, with the introduction of calcineurin inhibitors is a breakpoint, and so the significance of those data may change based on that.
DR. WHITE: Right, and it is a smattering going all the way from 1972 up to the present year, so this is not contemporary data versus older data, it's pretty much

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a similar representation of the type of data that you've seen before.
DR. SINGH: For 2.A there were only two studies; were those two studies after 1992 or before 1992?
DR. WHITE: For 2.A?
DR. SINGH: Yes. There were only two studies -- I'm sorry. For Question 2.B, it says there were a very limited number of studies. I'm just curious about whether these studies on PRA were contemporary studies, and what I understand from your answer is that they were across the board, right?
DR. WHITE: Right. Let me look at -- let me look for the ones in 2.B.
DR. GOODMAN: Let's do this. You can do that offline, and we'll have time to return to this issue, Dr. Singh, once the Connecticut folks get a chance to check it out, but that's a useful question. There's that threshold, the potential breakpoint in magnitude about which you're inquiring.
Dr. Dmochowski, keep these brief, please, and into the mike.
DR. DMOCHOWSKI: Right, two brief questions. One, and this can be answered later, you used the term several times, magnitude of rejection. I'm not sure what that means, how you determine whether that's an over time

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thing, or if you had a predefined definition of magnitude of rejection.
Number two is, we're talking about numeric studies included, and especially when we get to your

latter slides, we were talking about two or three studies. I would be interested if you had in your quality of data, if you set a baseline number for included patients, and how many patients were in those very small numeric trials, the two trials we talked about, 40 total patients.

DR. WHITE: So, magnitude was whether or not the change between the two groups that we were evaluating was greater than 10 percent in one direction, greater than 10 percent in the other direction, or was within that plus or minus 10 percent threshold.

DR. DMOCHOWSKI: So with rejection of allograft, I guess is what I'm asking, is that how you viewed it?

DR. WHITE: For rejection, no. It was only the directionality of effect, and that's because in a majority of the studies that's the way they reported the data. We would have liked to have had, and in the methodology that we originally put out, we had said we're going to need greater than 10 percent in either direction, but we would have had nothing to present for rejection, and we thought that this would be more informative than not.

DR. GOODMAN: Thank you, Dr. Dmochowski.

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Dr. Steinbrook.

DR. STEINBROOK: Briefly, and this again can be addressed later. I think you had 112, give or take, studies which you found met your criteria?

DR. WHITE: It was like 156, and then there were 13 studies that -- 156 publications, or 154 publications, and then there were 18 supplemental studies, which were studies from the same data set but reported a different outcome that wasn't in another one of the publications.

DR. STEINBROOK: So with that approximate number of studies, to follow up on the earlier question about individual studies rated as good or better than low, or insufficient, is there the possibility to give us a sense of all the studies that you included, how many of them, or at least on one aspect of a relevant key question had good or excellent components, to give us a sense as to how widely distributed the good was? I understand some were good, but how many, particularly if they were good on one point and not another point.

DR. WHITE: Yes, and we have backup slides, and in the backup slides we show each of the individual studies. So if you look at Key Question 1.A, 81.8 percent were poor. For Key Question 1.B, 81.5 percent were poor. For 2.B, 88.2 percent were poor. So now we'll look at the good studies. Key Question 1.A, 7.5 percent were good.

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1.B, 4.2 percent were good. And for 2.B, none of the studies were rated as good.

DR. GOODMAN: Does that help, Dr. Steinbrook?

DR. STEINBROOK: I guess.

DR. GOODMAN: Okay. Dr. Satya-Murti.

DR. SATYA-MURTI: It's a variation of the same

question. Let's take, on our left, the panel's left, significant improvement on survival, and in some of the slides a higher percentage is noted, for instance this one here, 52.7. So a variation of the question that others have asked, is are these, were you impressed that a large percentage was from high quality studies with the least bias?

DR. WHITE: No, we don't have a sense that the results were different based on whether the study was of high quality or what we would say is good quality, versus studies that would be rated as poor quality.

DR. SATYA-MURTI: And you rated all the retrospective observational studies as lower quality consistently throughout your analysis?

DR. WHITE: I think pretty much they all were, and the reason why is because in virtually all the cases there was no accounting for confounding, so when we looked at risk of bias, that shot it. When we looked at consistency and we saw that there were a lot of outcomes,

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even splits between significant benefits and no significant effects, that that ended up hurting, you know, the consistency measures.

DR. SATYA-MURTI: And was it leaning towards one time period, the early time period?

DR. WHITE: No.

DR. GOODMAN: Last question before we move on. Dr. Paul.

DR. PAUL: I was just curious. Did you analyze separately patients with chronic kidney disease who received transfusions that were not on dialysis from those that were on dialysis?

DR. WHITE: No.

DR. GOODMAN: Okay, very good. Dr. White, thank you. We thank your full team from Connecticut-Hartford, we very much appreciate that, and appreciate the contribution of the RTPC program overall. Next is Dr. Bowman, Dr. James Bowman. He's the medical director for the division of transplantation and healthcare systems for HRSA, which is the Health Resources and Services Administration, part of the Department of Health and Human Services. Welcome, Dr. Bowman.

DR. BOWMAN: Good morning, and welcome to the panel and to the members of the audience. Wow. After Dr. White's presentation, it's

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amazing that we get any good results at all in kidney transplantation. I want to compliment Dr. White and his group for an outstanding review and a very lucid and comprehensive presentation on the questions that they addressed. I'm going to provide, hopefully, a clinical context for some of the information you've already heard, and also subsequent by Dr. Carson and Dr. Cecka, and hopefully any of my misstatements or errors will be kindly

and gently corrected by the subsequent speakers. As surgeons, as you noticed, we do not, are not known for our wealth of literature and randomized prospective double blinded clinical trials, that's nothing new in the surgical field. There are a number of reasons for that, going all the way back to surgical egos, some people say the quality of the surgical literature in general in surgical journals are not necessarily as high as some of the more erudite medical journals. And quite frankly, everybody likes to get a paper published, and so surgeons will put together three or four cases and report a series. The transplant surgical field is no different and in fact it's all, it was often done, and hopefully less so today, by the seat of the pants, because there were no alternatives in many cases to some of the treatments that the surgeons were using, and I'll try to provide some of that clinical context.

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I'm going to move forward very quickly through the first several slides. Please don't focus on the numbers, I'm just going to provide some context for endstage renal disease today. Ignore that slide, this is an earlier slide before it got cleared by my agency. Just in general, the number of ESRD patients in the country is about half a million, 80 percent of those are under the Medicare program. This represents one percent of all Medicare beneficiaries, approximately. However, if you look at the bottom of that slide, you'll see that these patients represent six percent of all the Medicare expenditures in this country. So it is an important component of the Medicare program even though it is only a half a million out of the 43 million Medicare beneficiaries in the country. Currently about two-thirds, a little more than two-thirds of ESRD patients get treatment through dialysis, and a third of them are treated by transplant. This includes transplants from previous, because this is a prevalence number, not incidence. In terms of the people that are, have ESRD, approximately half are white, about a third are black. For context, 13 percent of the American population is black, so the black population is disproportionately represented in the ESRD population. As you can see, less than, approximately one

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percent are what we would call children or infants, so the majority of the statistics relate to adults. I tried to tease out some of the adult statistics in the presentation but it's not always available to get that. Again, half a million patients. Every year about a hundred thousand new patients come into the ESRD program. Half of those approximately, a little less than half have diabetes mellitus. Every year about 87,000 patients die who have ESRD, and this includes some transplantations obviously. The people that get

transplanted every year with kidney is about 17,000 or so, it may be a little more than that right now, since these are 2007 numbers.
As you can see, there are not nearly enough transplants to go around for everybody who comes into the ESRD program. And as we will see, not everybody who has ESRD is appropriate for a kidney transplant. This just goes to show that the transplant waiting list is growing, just as the ESRD population is growing. Approximately 15 percent of patients get, are waiting for a repeat transplant, they've already had a transplant that has failed. These people are at higher risk for acute rejection and they're also at higher risk for graft loss after a second or third transplant.
In general, waiting time for transplants is as

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shown in the slide, it's sort of equally divided roughly between the first year, one to three years, and three to five years, and then there are a small portion who wait more than five years. This is due to some geographic variations around the country since this is an average of all the U.S., and also there are other reasons that people wait more than five years for transplant, not just geographic disparities, and high sensitization, as we'll get to in a little bit, and Dr. White already discussed, is one of those reasons.
Just to give you, and I don't want you to focus on the numbers, but about a third of the patients who get transplanted each year are from cadaver or deceased donors and one-third are from living donors. As you can tell, the living donors have increased remarkably in the past 10 to 15 years. The cadaveric donor population and number of transplants has started to level off over the past four to five years. This is a problem for those people who are now waiting for transplants.
In general the people who get transplants, again, about half are white, about a quarter are black, and if you remember from the previous slide, of the people who get kidney disease, the proportion of people with kidney disease, ESRD that were black, are actually more than the 26 percent as shown here.

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These represent fairly accurate numbers for current survival rates, these are 2007 results. This is for patient survival. This represents unadjusted, non-risk adjusted survival. By and large, deceased and living donor transplants have equivalent patient survival. Patients on dialysis obviously have less survival outcomes. There are a number of reasons for this and a lot of speculation. One of the reasons, quite frankly, is that people on dialysis represent a sicker population than ones who get transplanted, and we'll go over that just a little bit more.
In terms of the graft survival rates, this

presents the current survival rates for grafts. The most important thing to notice is that not only is there an across-the-board increase in graft survival with living donors, what's more important is that down the road at 10 and even 15 years, there's a significant difference in improvement in living donors compared with deceased donors. This has been true for the last 30 years and it's still true today.

In terms of why people lose their grafts, 20 years ago, 25 years ago the most common reason for graft loss was rejection. Nowadays people lose their graft because they die with a functioning graft. There's a couple of reasons for this, and very quickly it's related

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to the better immunosuppression, better treatment of rejection episodes. Also, older patients are getting transplanted and the medical care in general has improved. So we are transplanting an older group of patients, we are using better, more potent immunosuppressive drugs, we are able to treat acute rejection better and because of that, patients tend to die because of other reasons, just as in the general population, and their grafts are still working.

A corollary to this is that the most common cause of death is cardiovascular disease, and that's not surprising nowadays. Historically that was not the case. Again, historically, most grafts were lost due to acute rejection and the most common cause of death was infection, and a lot of those infections were a direct result of either immunosuppressive drugs or the increased drugs that were used to treat the acute rejections, which were much more common in those days than they are now.

There are other causes of graft loss. In the first year, approximately half are due to a combination of medical and surgical reasons, technical surgical reasons and medical reasons. Medical reasons in this group include infections that occur. Again, this is a percentage of the grafts that are lost, excluding those patients who died with a functioning graft, so I don't

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want to give you the wrong impression that this is a percentage of grafts that are lost during the first year after transplant.

In subsequent years after the first year, the reasons for graft loss change as noted, and the cyclosporin and calcineurin inhibitors have been implicated. However, there is a lot of debate about the precise role of those drugs in the transplant group in this case.

Now getting to the point of blood transfusions, like Dr. White pointed out, we don't have good data nowadays on blood transfusions and the impact in the transplant population for several reasons. Number one is there are much fewer blood transfusions because of the use

of EPO. Also, we do not collect data on how many transfusions people have when they come to a waiting list. This is very difficult information to get because many many patients have blood transfusions and are not either aware of it or do not realize how many transfusions they have had by the time they go on dialysis, and also by the time they go onto the waiting list.

Probably the most astounding observation in the transplant field in the early to mid '70s was when Dr. Opelz and his group identified an improved outcome of acute graft rejections, I mean in graft survival, in

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patients who had blood transfusions, and in particular it was that group of patients who had five or more blood transfusions that had the most impact, or most increase in their outcomes.

A corollary to this was when Dr. Salvatierra and his group, which was a collaboration of others around the country, also discovered that in living donor transplants, patients who had blood transfusions from their living donors or their intended living donors actually had similar results.

The reason this is so important is back in those days in the early '80s and mid '80s in particular, graft outcomes were not really as good as they are today, a one-year graft survival of 75 percent was very good at that time, and so an impact of 20 percent improvement was quite astounding at the time. So it was adopted in many centers for the living donors to have a series of three donor-specific blood transfusions. Similarly, the patients, there was no reluctance to give a dialysis patient, especially one on the waiting list, a blood transfusion prior to transplant, because of the perceived improvement that that patient would get.

Now in fact there was a problem, as has been noted by Dr. White, of sensitization. Let me -- I think I've already covered this, but the graft survival of 20

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percent improvement was initially what was experienced in the late '70s and '80s. Subsequent to that, that effect was less pronounced, and went down about 10 percent, and currently there is no percent for improvement. However, it's hard to get at that data now because the history of transfusions in the current cohort of patients getting transplanted is very murky at best.

DR. GOODMAN: Just a couple more minutes, Dr. Bowman.

DR. BOWMAN: Okay. Incidentally, the product to get those transfusions primarily has to be fresh blood, it cannot be frozen or recalled, it has to be either whole blood or packed cells, but it is probably due to leukocytes within the blood. It has to be a minimum of three for donor-specific transfusions, and a minimum of five for random donors to get the sweet spot, so to speak.

If you went more transfusions after that, you would probably get some increase in sensitization. The effect is apparently related to either a haplotype match, which is similar to what you would get from a brother or a sister in a living donor, or an HLA DR and an HLA B match. Full sensitization is in parentheses, primarily because not everybody has an agreed upon consistent definition of sensitization. Some people call it more than 10 percent, some people call it more than 50 percent,

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some people call it more than 80 percent, and in fact I'm hoping that some of the other speakers will address this, but the real clinical impact is probably on those patients who are probably more than 90 percent sensitized. The real sensitization rate is fairly low, as you can see from the slide, and in fact the donor-specific transfusions it actually reduced that 30 percent down to about 10 to 15 percent.

I'm going to skip this slide, I hope that Dr. Cecka will discuss this in a little more detail. This is just a breakdown of the PRA levels on a current waiting list right now. The vast majority are not, in quotes, sensitized, as you can see, and about eight percent have sensitization rates over a level of PRA of 80, and over a PRA of 90 is even less than that. PRA does affect the number of, percent of patients who are transplanted within three years as you can tell. It does go down as you get into the upper PRA levels of 90 and above.

There are options for sensitized patients. They are not perfected yet, they're not available to all patients yet and it's still a work in progress, but is clearly a work that is ongoing and offers some reasonable hope, whereas previously there was very little hope for patients who were highly sensitized, and I'm talking about

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patients with PRAs of 90 or above. Obviously one option is to wait for a long time for that sweet kidney that does not have a positive crossmatch, and that's like winning the lottery, quite frankly.

The desensitization protocols are being done right now by expert research centers. There are a number around the country that are doing this, but they are not available to everybody obviously, because of geographic reasons.

And then the kidney paired donations or kidney paired exchanges where you have multiple clusters of living donor pairs who in and of themselves, each pair is incompatible, either because of ABO incompatibility or more likely now is the highly sensitized patients. In fact, algorithms have been developed to actually match up strangers who are members of other pairs, and those patients in turn get compatible kidney transplants. This is, again, still a work in progress, but OPTN UNOS has a

pilot project right now for a national kidney pair donation project, but in fact several systems have been ongoing in this country for the last six to eight years, and that has been the instigating impetus for this activity.
DR. GOODMAN: You may want to wrap up, Dr. Bowman.

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DR. BOWMAN: So then, the final slide is just to point out that there are a number of causes of anemia in the renal transplant patient, and I would add as a corollary that there are a number of causes of anemia in the ESRD dialysis patient. It's not all due to the lack of EPO, there's obviously many causes, and I'm not a hematologist and I'm running out of time, so some of these other issues can be addressed maybe in the question and answer session, and I think I will close with that since I believe I'm out of time.
DR. GOODMAN: Thank you very much, Dr. Bowman, that's very helpful. Among many things you noticed is the disproportionate impact of the Medicare ESRD population of about half a million out of 43 million Medicare beneficiaries, but they still account for six percent of Medicare program expenditures, so that is a disproportionate count there.
We're going to move now to Dr. Jeffrey Carson. Dr. Carson is the Richard C. Reynolds professor of medicine and the chief of the division of general internal medicine at UMD New Jersey Robert Wood Johnson Medical School. Dr. Carson, welcome, sir.
DR. CARSON: Thank you. It's a pleasure to be here. So, I was asked to talk about what information we know about transfusion triggers in general to try to

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comment on how this information may relate to the use of EPO. So what I plan to do is go through for you just briefly an approach that I think about that I use to approach transfusion decisions, very briefly touch on side effects, talk to you about, show you a little bit of data on the effect of anemia mortality and morbidity, and what evidence, emphasizing clinical trials, which demonstrate the effect of blood transfusion on outcomes. And then I will give you my view on how this information relates to the questions at hand today, the ESA story.
So if one goes to the bedside, which of course is not what we're doing here, but nevertheless, if you're making a transfusion decision, like every other medical decision, there's a risk benefit. The risk side relates to the side effect of transfusion and the risk related to anemia. If you give blood, you're hoping it would improve mortality, morbidity and function.
So the side effect story -- and I'm going to be skipping slides to try to stay within the time constraints. I'll just simply say that the side effects

which I think are well known to this group are infrequent, and I have in my slides a description of the event rates associated with transfusion.

So what about the risks of anemia? Well, if you were to go to animal data, what you find is that if you

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let the hemoglobin drop in normal animals, you begin to see serious events between three and five grams per deciliter. And if you experimentally tie off coronary arteries in animals you begin to see changes of myocardial ischemia at higher blood counts. This is relevant because coronary disease is common in the endstage renal patients.

So if we look at human data, we've done a retrospective cohort study of patients who declined blood for religious reasons, there were 2,000 patients in this particular analysis, and you can see here that most patients in the surgical population had normal and near normal hemoglobins and low mortalities, but as their preoperative hemoglobin falls, their risk of death rises dramatically. The main finding from this analysis is that it's not only the effect of cardiovascular disease on outcome.

Here is the preoperative hemoglobin by the odds of death. Here in yellow are patients without cardiovascular disease, here in red are patients with cardiovascular disease, and this data suggests that as the preoperative hemoglobin falls, patients with cardiovascular disease have more higher odds of death than patients without cardiovascular diseases, with this red seeming to take off around ten grams per deciliter.

So I would summarize here in terms of the risk

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of anemia, this is in a surgical setting, not in an endstage renal disease setting, is that mortality and morbidity rises as the creatinine hemoglobin falls, and animal and human data suggests that patients with cardiovascular disease may be less tolerant of anemia than patients without cardiovascular disease. So to emphasize again, cardiovascular disease is a very important problem in patients with endstage renal disease.

But what this data does not tell you is whether or not transfusion modifies those risks. So what evidence do we have from clinical trial data? This is a summary slide of a systematic review that is current short of one trial. What you can see here is there's been 3,600 patients who have been randomized either to what's called a restricted group which is less transfusion, versus a liberal group which is more transfusions. The definitions of these transfusion thresholds vary among the trials, but you can see that there's about 3,600 patients randomized, and there's another trial published in JAMA that has about 500 patients. That's the number of people that have been studied up to this point in published literature.

This is a summary of the 30-day mortality in

people who got less blood versus more blood, and overall you can see here that the odds ratio is .83, the confidence intervals overlap once, so there's no

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significant effect on mortality based upon this data, but keeping, emphasizing again and again that what you need to demonstrate is using more blood improves outcomes, and there is certainly nothing to suggest that.

What you can see here is the majority of the evidence comes from one trial called the TRICC trial, which was published by Paul Hebert in the New England Journal in 1999, in which they took consecutive ICU patients with hemoglobin less than nine, randomized them to a restrictive group which was defined as a seven-gram threshold, versus a liberal group which was a ten-gram threshold. They looked at 30-day mortality as their primary outcome. There were about 800 patients in this trial. The group that got less blood did somewhat better, although not statistically significantly better, than the group that got more blood.

And if you were to look overall, these are Kaplan-Meier curves which plot survival by time. You can see here that the group that got less blood looks slightly better but the P value is not significant, but in a subgroup analysis of patients with ischemic heart disease, what you see in fact is a reversal of these curves. This top curve is the group who got more blood, versus the group that got less blood. So once again, following the theme of maybe patients with cardiovascular disease are

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different.

They also looked at other clinical events, including classically recognized myocardial infarction, which were low event rates, but nonetheless the group that got less blood had fewer MIs, fewer episodes of pulmonary edema, and a trend towards less ARDS as well. So nothing in this published data suggests that using more blood is beneficial.

What I'm now about to show you is unpublished data in a trial funded by the NIH that is called FOCUS, which is a transfusion trigger trial that's undergoing peer review at this moment. This was a randomized clinical trial of hip fracture patients who had cardiovascular disease or risk factors and a hemoglobin less than ten postoperatively within three days of surgery. Patients were randomized to liberal, which was a ten-gram threshold, a restricted group which was defined as having hemoglobin less than eight or having symptoms, prespecified symptoms that surgeons thought was an indication for transfusion.

Our outcomes included function, mortality, myocardial infarction and morbidity. When we randomized 2,016 patients from 47 centers in the U.S. and Canada -- where are my other slides? This is not the other slides.

Well, I had a presentation set of slides, which this is
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not, so let me tell you what the trial showed.
The first thing it showed was, though our primary outcome was function, the ability to walk without human assistance at 60 days or death, about 35 percent of patients in both arms of the trial had this event, there was no significant differences, they looked almost exactly the same. We also looked at a shorter time of functional recovery at 30 days, the same basic results, no effect.
The second thing is we looked at mortality, we looked at mortality in three time periods, one was during in-hospital mortality, the second was 30-day mortality, next was 60-day mortality. In general the mortalities were almost exactly the same, with approximately a one percent increase in mortality in the group got more blood, the less blood not significant, generally low event rates.
Third set of outcomes, myocardial outcomes. Those included isolated elevated troponin levels. So while these patients went through a screening for these events with four troponins, three EKGs, there was a blinded classification of acute myocardial infarction. Isolated troponins were almost exactly the same in both arms of the trial. Myocardial infarction was slightly less frequent in the group that got more blood than less blood but the differences were less than one percent.
Mortality in hospital was slightly more frequent in the
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group that got more blood than less blood, evening out the effect. And our primary cardiac outcome, which was defined as in-hospital death, myocardial infarction or unstable angina, the differences were tiny, less than one percent difference between the two arms of the trial. Also, the results were not statistically significant, but in general these were low event rates, and the study was large enough to pick up about a 50 percent effect in outcomes.
The last set of outcomes were infections, length of stay, congestive heart failure, pulmonary embolism, all low event rates, and once again the events were relatively infrequent, but nothing to suggest a positive effect of using more blood than less blood.
So overall, the FOCUS trial found no significant effect of using a liberal transfusion versus a restrictive transfusion.
So, the last issue is generalizability to ESAs, because that's what the question is here. I emphasize that none of these trials were done in the setting that's under discussion today. When one looks at the transfusion trial that primarily focused on acute anemia compared to the ESAs where you're looking at the effect of chronic anemia, to the time course that we wrote about in the setting of trials looking at transfusion trials are
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primary short-term effects, and the issues that you're worried about when thinking about ESAs are long-term effects.

The relative importance of these outcomes, I think you will find many opinions on this. My personal opinion is that when you think about transfusions, you're trying to deal with short-term issues, you're trying to get people to survive, to avoid medical complications, you want to improve their function if possible. You would like to reduce the amount of blood they get, but symptoms like fatigue are much less important in this clinical setting because in general this is a short-term problem that resolves as the patient picks up.

In contrast to an ESA study where you're trying certainly to reduce the use of blood, and that some of the symptoms such as fatigue function become more important because this is a chronic disorder, people feel terrible for a long period of time and you want to try to reduce these symptoms if you can, but of course it's not to minimize morbidity, MI, heart failure, infection or mortality, and we certainly would not suggest that. The side effects, I think, are well known between the transfusion group, and the ESA side effects are very very different of course.

And finally, to emphasize to you that the red

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cells that are being transfused in red cell transfusion trials have been stored and may not function the same as the red cells that are produced by ESA, which of course are fresh.

So to summarize here, the risk of transfusion appears to be low. Patients with cardiovascular disease appear to be less tolerant of anemia. Clinical trials have been performed in patients undergoing cardiac surgery and now in postop surgical patients undergoing hip repair with cardiovascular disease and risk factors, and there's no evidence that the liberal transfusion improves outcome.

And then lastly, that the generalizability of the transfusion data to ESA is uncertain because of differences in potential benefits, risks and time course of anemia. Thank you very much and I'll be happy to answer questions.

DR. GOODMAN: Dr. Carson, we don't have time at this point for questions, but I need a clarification. Your first point in your overall summary, the risk of transfusion appears to be low, this to me is an incomplete thought. Can you complete the thought for us, please, the risk of what with transfusion appears to be low?

DR. CARSON: Just in general. The risks of transfusion, and I didn't go through all that, but the risks of transfusion acutely, the things that everyone

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talks a lot about is things like HIV, Hep-C, hepatitis C, and thank goodness those things have become extremely

uncommon. Then more moderate -- do you want me to stop?
DR. GOODMAN: No, I understand. I just wanted to know insofar as in this context or just in general.
DR. CARSON: Just in general.
DR. GOODMAN: And your third point, clinical trials, in a sentence, could you just say what you said in several sentences a minute ago, clinical trials, what about them?
DR. CARSON: The clinical trials up to this point have demonstrated that there is no demonstrated benefit of a liberal transfusion approach over a restricted transfusion approach. And that these trials, I'll give you one more sentence, these trials have tested a seven-gram threshold and eight-gram threshold. That's where the restricted groups have been tested up to this point.
DR. GOODMAN: And they found?
DR. CARSON: They found no significant benefit by using more blood than less blood.
DR. GOODMAN: Thank you very much, Dr. Carson, that's very very helpful.
Dr. Cecka, if you could just hold on, I think many folks would probably appreciate that we take our

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break now, and if you wouldn't mind holding off, we will do that. We have a scheduled ten-minute break. Since the federal government is so generous these days, we will call it a 12-minute break. Take a look at your watch or your timepiece, add 12 minutes to it, and Dr. Cecka will be starting then. Thank you very much.
(Recess.)
DR. GOODMAN: Next up is Dr. Michael Cecka.
Dr. Cecka is the director of clinical research, the Immunogenetics Center at UCLA, and Dr. Cecka, you're up and you've got 15 minutes, and I see your slides are ready. Yes, sir.
DR. CECKA: Thank you very much. I'm going to tell you a little bit about some of the tests that we use for sensitization and transplant under evolution, because part of the difficulty in analyzing what happens with blood transfusions is how we measure some of these effects.
In the early days of transplantation in the early 1960s several groups independently noted that sometimes when you transplanted a kidney, that catastrophic acute rejection was irretrievable or irreversible, and this was summarized in this paper from Terasaki and Patel that you heard about earlier. I just wanted to show you the actual data, that if you tested

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patients who have had antibodies and HLA with the donor and were positive, 80 percent here, 24 out of 30 patients experienced these hyperacute rejections. This was based on this cytotoxicity test that was used in HLA typing

early on. It wasn't completely sensitivity, because sometimes patients that were negative still had hyperacute rejection.

Over the early years of this test that evolved to extended incubation times and addition of antiglobulin that increased the sensitivity, starting in 1971 or '72, hyperacute rejection was pretty rare. Every patient who got a kidney transplant was tested with this crossmatch test before transplantation to avoid these antibodies.

Now you didn't have to wait for an actual donor, though, you could do a test on a surrogate panel of donors that represented people who could be potential organ donors and discover how limited a patient's access to transplant would be based on the formation of these HLA antibodies.

Now if you didn't test these patients at all, you could see that six out of 23, about a quarter of these patients had this kind of reaction. So sensitization to HLA antigens was relatively common in these patients who were awaiting transplantation.

The test itself was done by adding the patient's serum to a bunch of wells on a very small tray, and then

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adding a series of donors, cells from one individual donor to each of these wells, and you would add complement to the test, add a vital dye, and then see whether the cells were alive or dead. After an incubation period we look at common donors that had cells that were killed by the patient's serum. So this was the cytotoxicity test that we felt would give us an estimate of panel reactive antibody, this was a panel of donors, and we can see here that 16 of these donors would result in a hyperacute rejection if he were transplanted with a kidney from that donor.

So the issue that sensitization raises here is access to transplantation. We don't transplant patients who have these antibodies against the donor. And even today, 30, 40 years later, we don't cross this barrier very often. It's been retested a few times in the recent past and it can be done with certain modifications in certain patients, but in general no one will transplant in this situation. So these patients who have antibodies that react to many of these donors have very limited access to transplants.

This is the test. If you have these HLA molecules among the other cells, when you add the patient's serum, it would bind if it was an antibody agent, the B-27 antigen, for example, it would bind, it

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opens holes in the cells, and when you add the vital dye, you can measure dead cells here which look big and dark against bright and shiny live cells, here where the green ones are live and the red ones are dead. And if you had a small amount of killing, 20 percent or so, that was considered a positive reaction.

Well, these tests were modified, as I said, to become more and more sensitive, so the hyperacute rejections nearly disappeared in the early 1970s. But still patients who were transplanted that were sensitized against the donor with measurable antibodies, but had antibodies in general, also had problems with delayed graft function after the transplant, which complicated the management of the patients.

So we have acute rejection, which you heard about earlier, chronic rejection, which you also heard about earlier, but importantly, prolonged the waiting time for a transplant for patients who had these antibodies, and if they had a lot of antibodies, in fact it would bar them from transplantation so they would have no access to this lifesaving treatment.

The problem, though, was to avoid donor-specific HLA antibodies, and the crossmatch test evolved from this complement that demonstrated toxicity to presensitivity by addition of antihuman globulin, flow cytometry, and they

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used the addition of these cells to test for these antibodies, and each of these had an increasing sensitivity, and these different sensitivities lead to the confusion about what sensitization means.

The panel reactive antibody tests were designed to be at the same level of sensitivity as the crossmatch tests that they were meant to predict, so you have the same sorts of approaches here.

Now in the 1990s a new set of tests came along that were solid phase tests, where you could isolate HLA antigens and place them on solid support media and avoid a lot of the problems of doing cell-based tests. The cell tests were very complex because as we began to appreciate the increasing complexity of the HLA system, we realized that some of the antigens were only on one subset and not another so you had to measure them separately, so we altogether had 10 or 15 different tests with these antibodies that were being used. But today we are using these solid phase tests all across the United States and around the world in fact, and crossmatching has gone to a virtual crossmatch, at least preliminarily, in almost all cases in the U.S.

The effect of sensitization on graft survival, you can see here in the survival curves from the early days based on data from the UCLA registry of transplant

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recipients, you had an immediate reduction in graft survival for broadly sensitized patients that occurred early on and amounted to about a six percent difference in survival rates, and these were thought to be cases where we had not detected the antibodies because we were using these relatively insensitive tests. You can see that in more recent data here we have reduced this incidence of early graft loss for sensitized patients, so we're really

much better with the more sensitive tests at detecting these antibodies.
How do people become sensitized to HLA antigens? Well, one is a natural transplant that occurs, and that is pregnancy, because the fetus inherits one chromosome from the father of the HLA antigens and one from the mother, and the difference is, the HLA types between these chromosomes can stimulate an immune response of the fetal cells in the circulation in the mother, or at birth when blood is exchanged.
In this case, I have made this a very simple difference between the father and mother, the A3 antigen father and the B18 antigen father are different from the HLA antigens in the mother, and so she can have a response to these antigens. And in this case I've said that she chose to make an antibody against the A3 antigen on the fetus. Now because these HLA types, these HLA antigens

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are structurally very similar, these antibodies may react with the specific antibody to a structure on A3 may also recognize a structure on A31 in the laboratory. So these can become, even from a single difference in the immunization event, sensitized to a large number of HLA antigens.
Now, you heard that pregnancy is one of the major stimulators of HLA antigens, and of course if you actually have a transplant and lose it and immunosuppression is taken away, this is probably the most effective immunization event. But blood transfusion when they're given to these patients, particularly to these patients, the ones that have lost a graft or who have been pregnant, will restimulate the immune response even if it were generated many many years ago.
So this shows you the time line of an immune response where primary exposure to an antigen IgM type antibody response, and the generation of memory cells, a repeat exposure usually causes a rapid rise of IgG, and that's the antibody that we're most concerned about. If your test is oversensitive at a level here, that you can measure IgG at this point, you're going to miss IgG as it goes down with time. So if your patient has a pregnancy here and some blood transfusions, and then over here comes on the transplant list, if you have this insensitive test

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for antibodies, you're going to think this is not a sensitized patient, and as you increase the sensitivity of this test, you will be able to detect that sensitization more and more accurately.
DR. GOODMAN: Dr. Cecka, you've only got about two or three minutes, and I want to make sure you get through your slides.
DR. CECKA: Yeah, I'm almost finished here. So looking at a cross section on this, there are different clones making antibodies, and you will also see that the

tests with different sensitivities may detect different numbers of antibodies, even in any one individual instance in cross section. The flow cytometry crossmatch did not require a complement fixation or measurement, and you could actually look at a normal serum with low antibody versus a patient's serum antibody and look at how much shift there was in fluorescent intensity from the second antibody and determine more or less quantitatively how much antibody was on that cell.
Luminex technology is one where you're using plastic particles that have a combination of dyes that allow you by flow cytometry to distinguish about a hundred different beads at a time, so you can stick different antigens on these beads, and there are a number of types, but the most precise is one where we use recombinant

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antigens with only one antigen stuck to each bead, and by looking at which antibodies bind to those antigens, you can identify here exactly what HLA types there are.
So today we can identify antibodies very specifically, and the new way of measuring sensitization is this. In UNOS for a transplant patient, to identify a patient who has anti-A2, you list that as an unacceptable HLA antigen because that's going to cause problems, and what happens is if you have all these donors coming up that would be compatible with that patient, the ones that have the A2 antigen are not offered to that patient anymore, and that turns out to be 50 percent of the possible donors. So a patient who develops an antibody to A2 now has a 50 percent calculated PRA, and you heard that this is based on actual donors.
If the patient also has antibody DR4, you see that you have a 60 percent CPRA, but all the patients who have A2 or DR4, all the donors, I'm sorry, are not offered to that patient. And if you also happen to have antibody DQ5, the PRA goes up to 70 percent, but now of those 14 donors, only two would be available for that patient.
Now we do give highly sensitized patients extra points in the kidney allocation algorithm, so we give them a little advantage for when a probable compatible donor arises, he's able to receive that kidney, so this is a

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part of the final rule.
So just to summarize, the HLA antibody tests have evolved over the years. You've heard that the CDC was the least sensitive, AHG was a little more sensitive, the effects shown in about ten percent more sensitized patients. Flow cytometry a little more sensitive, maybe another ten percent more sensitized patients. Then we moved to ELISA and some single phase assays, and then the most sensitive are these single antigen tests that we use today. The precision has improved for a lot of these sensitized patients so we can essentially identify what HLA antigens are there and which donors are not going to

be appropriate for those patients. There's still some controversy about the importance of weak HLA antibodies, but these are very individually specific in many cases. A patient who has been sensitized by a previous graft, for example, may have memory that those weak antibodies carry that might have more importance than for a patient who has never been, an unsensitized male who might have a weak antibody of their own. So we're learning still about this, and the main problem I think is that the memory is not quantified in these patients. So with regard to -- can I just have one second?

DR. GOODMAN: You can have two seconds.

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DR. CECKA: Okay. There were three reasons that people thought transfusions helped transplants. One was the tolerance, that it created tolerance. Two was that it allowed for total deletion, where you would stimulate in a patient those clones that were responsive to the HLA antigens of the transfusion donor, and that these would appear at the time of high immunosuppression to be killed. But the third was that this was a selection process, and that is that if you were responsive, you would make antibody against a transfusion, and the more transfusions you got, the more HLA antigens you were exposed to, and the more likely you were to find when they would recall your memory that you would not be transplanted. So patients who were transfused and made antibodies were not transplanted. If you were transfused and didn't make antibodies, you were probably not very responsive to those HLA antigens, and you did better when you were transplanted. And if you were not transfused at all, a percentage of those responders at the time of transplants lost their grafts.

DR. GOODMAN: Thank you very much, Dr. Cecka, we appreciate your insight on those tests. Now we're going to move to our scheduled speakers, of whom there were 15 at last count, and so as noted before, we will only be able to allow four minutes

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per speaker, I'm sorry about that, but we can't allow more time because the FACA rules have us ending at 4:30, and so that fits. Dr. Bryan Becker is up first. Among other things he's professor of medicine, the senior associate dean for clinical affairs at the University of Illinois at Chicago College of Medicine, and today he's representing the National Kidney Foundation. Welcome, Dr. Becker.

DR. BECKER: Cliff, thank you. Good morning, committee members and distinguished guests. I'm a transplant nephrologist and immediate past president of the NKF. Our goal is to provide the best possible therapy for our patients, and for kidney failure patients that is transplantation, and to do so mitigating the most risk

possible. In thinking about the concept of transfusion and what it may or may not do, we have data from the United States Renal Data Systems that certainly demonstrates in a contemporary cohort with contemporary factors involved that there is an elevated risk associated with transfusion and an increasing PRA, especially in men, and women who have been pregnant, as well as in the best constructed types of studies, some evidence that transfusion, even with contemporary leuko reduction techniques, can lead to allosensitization in this unique population that is kidney failure.

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And we know patients continue to get transfused on the wait list, and those with higher PRAs are actually the ones that seem to get more transfusions over time. These individuals, those with higher PRAs are the ones who linger longer on our transplant waiting lists. And access to transplantation, the best therapy possible, is important. There's an association here that is clear, though not necessarily causative.

As important is recognizing that rejection is approaching events, but an outcome is graft loss, and we know that elevated PRA levels are commonly used tests as you have heard, though maybe not the best, and is associated with reduction in graft loss, not at one year where we know that graft survival rates are excellent, but over the time frame that is important for the benefit of that recipient.

Given the lack of Level I evidence, we are focused more and more on the transient relationship between transfusion and PRA and what happens to our patients in terms of access to this therapy and in terms of their outcome, and I as a clinician am left with that relationship as the cornerstone for how I honor my oath in making a judgment with what's good for my patients in their best possible interests. Thank you.

DR. GOODMAN: Thank you very much, Dr. Becker, a

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point well made. Next is Dr. Ruben Velez, who's a nephrologist from Dallas, Texas. He's representing the Renal Physicians Association. Welcome, Dr. Velez.

DR. VELEZ: Thank you, Mr. Chairman. I'm Ruben Velez, I'm a practicing nephrologist in the Dallas area, and I'm here representing the Renal Physicians Association. That is an association of over 3,000 practicing physicians in the care of patients with CKD and transplantations.

As the MedCAC considers the issues surrounding the impact of ESA use on renal transplant survival, RPA urges that the panel recognize the significant advances in renal transplant care over the past two decades. In particular, transplantation offers patients with kidney failure the best quality of life when compared to lifelong dialysis treatments. Blood transfusions given to patients

awaiting transplantation may reduce the likelihood that those patients will receive a kidney. This is because blood transfusions often increase the HLA antibodies, as we already heard, reducing potential matches for transplantation.

Those patients with high ELA have longer waiting times pretransplant, and increased mortality while they're waiting, and lower graft survival. It is therefore critically important to prevent available use of

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transfusions whenever possible.

Further, the RPA is concerned that an overly restrictive ESA policy revision that does not account for the need to minimize the use of transfusions will have an unintended detrimental impact on transplant recipients waiting list, and organ survival. Fortunately, since ESAs became available in 1989, blood transfusions in outpatient hemodialysis patients have significantly decreased. We urge the panel to recommend policies that preserve this advancement in kidney care.

RPA shares the safety concerns associated with ESA prescriptions that result in high hemoglobin levels or very high ESA doses, but we're also concerned about our patients at the lower end of the treatment range.

Importantly, the current nephrology standard of practice guiding the administration of ESAs does not target hemoglobin lower than 13. The current practice in use is to achieve a hemoglobin between 10 to 12 while keeping hemoglobin around 10 to avoid transfusions and improve patient quality of life. We believe that this practice results in safe and appropriate use of ESAs. Therefore, the RPA recommends that the panel not allow policy revisions that could create serious patient care issues at the lower end of the hemoglobin range.

We also urge MedCAC to preserve the ability of

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physicians and patients to make individualized treatment decisions that incorporate not only the physician clinical expertise but also the patient's preference and resulting quality of life. An effective process for determining appropriate administration of ESAs to kidney patients will include a discussion of the risks and benefits of ESA therapy.

DR. GOODMAN: You have less than a minute, Dr. Velez.

DR. VELEZ: Yes, sir. As the panel is aware, the Food and Drug Administration cardiovascular and renal blood advisory committee recently reviewed evidence on the risks and benefits of ESAs, and the panel found no reason to recommend any change to the current labeled hemoglobin range of 10 to 12 in dialysis patients.

On behalf of the Renal Physicians Association, I thank you for the opportunity to speak today. Thank you, Mr. Chairman.

DR. GOODMAN: Thank you, Dr. Velez, and we appreciate you insights about individual patient management, much appreciated. Next is Mandy Trolinger, who represents The Renal Support Network. Welcome, Ms. Trolinger.
MS. TROLINGER: Thank you. My name is Mandy Trolinger, I am a former renal dietitian, currently a

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physician's assistant, and two-time kidney transplant recipient, and also I was on hemodialysis. At two years old I was diagnosed with kidney disease and underwent my first kidney transplant at 14 years old. My mother was generous enough to donate this kidney, which allowed me to not have to undergo dialysis. This transplant allowed me to pursue my bachelor's and master's in nutrition, and become a renal dietitian. Unfortunately, during graduate school I was diagnosed with chronic rejection and had to change immunosuppressive regimens.
I had an adverse reaction to medication and had to receive several transfusions throughout one year, and then I was able to maintain my hemoglobin with ESAs alone and have not received another transfusion to this day. I remember going to my various doctor appointments to manage my anemia, and he would always joke that he didn't need to see my labs, he could just ask me how I felt, and I pretty much was within a half point on my hemoglobin all the time.
During graduate school I was very physically active, I taught aerobics, but then I found myself where I could barely walk a half mile to get to class, and I was always looking for the elevator instead of taking the stairs. It felt like I ran a marathon all the way uphill just walking to class. Concentrating on my studies was

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also difficult, I would read a paragraph and not remember what I read. And I stopped teaching aerobics as a result of anemia, and so now I was also losing the cardiovascular benefits and the bone building benefits which I needed due to longtime steroid use.
12 years after my first transplant I found myself once again in endstage renal disease. I had hoped to go straight to transplant once again and skip dialysis. I had more than ten people, family members and friends willing to donate; however, nobody was a match. My PRA level at that time was drawn, it was 87 percent; it was thought that was mostly due to the prior blood transfusions that I had.
I began dialysis and once again did not have to receive transfusion because of the use of ESAs. Over the next few months my levels did drop more than 20 points and I received a deceased donor transplant. This transplant allowed me to go back to school to complete my physician's assistant degree. And I think back to graduate school and how it took all of my energy just to keep up with my

studies, research and work. I compare it now to the physician's assistant school and realize how much easier P.A. school was for me mentally and physically, even though it was a hundred times more stressful than my undergraduate work ever was.

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I remember one rotation leaving the hospital at two a.m. thinking I have to be back here in four hours to meet my supervising physician with a smile on my face and acting like I had all of the energy in the world, regardless of how tired I was.

DR. GOODMAN: You have about a minute, Ms. Trolinger.

MS. TROLINGER: Thank you. I realized at that point how grateful I was for having a successful transplant and no further problems with anemia. I would like to think I would have managed P.A. school well even though, if I did have to deal with the situation of anemia again. And I would like to think I would have been able to do this because of my attitude of being very persistent and stubborn at times. Just ask my mom about what she thought of me growing up as a child, how to raise a strong willed child. That determination to achieve my personal goals has always been a driving force in my life. I am where I am today because of my family support, excellent medical care, and my drive to pursue what I enjoy. It also helped that I had a physician that thought we could work outside of protocol and justify my ESA dosage when needed. I'm asking you today to take into consideration of course the use of ESAs in transfusions, but also that every patient is unique. One thing I keep

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in my mind as a patient and P.A. is guidelines are for populations, the doctor is for the patient. And of course it goes without saying as we all sit here, that we need more research in this area before changing guidelines, which are where I believe we stand today. Thank you.

DR. GOODMAN: Thank you very much, Ms. Trolinger. We very much appreciate the dual view that you bring as a patient as well as a P.A. and healthcare provider, that's very much appreciated, thank you. Next is Nancy Spaeth, from Seattle, Washington. Ms. Spaeth.

MS. SPAETH: My name is Nancy Hewitt Spaeth and I'm a nurse, and I'm one of the longest surviving kidney patients in the world. In the summer of 1958 as a ten-year-old I was stung by a swarm of yellow jackets while at camp. When I was 16 I won my beginners ski school slalom race, I beat the boys. Two years later I couldn't walk from the lodge to the lift. Soon after that my kidneys failed. I was accepted by the admissions and policy committee in Seattle and with the help of Dr. Scribner began dialysis in 1966 at 19. I've had four transplants and waited through four episodes on dialysis,

a total of 15 years of dialysis and hundreds of blood transfusions. I'm a carrier of hepatitis C and cytomegaly virus because of those.

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My sister-in-law called me one morning after I had gotten the children off to school and asked me what I was doing. Becky, I said, what can I do, my body has me in prison. I'm crawling up the stairs on my hands and knees, it's so hard to breathe, and I am so cold.

It was now 1987 when my daughter Sarah was ten and my son Josh was 12. Dr. Tong called Dr. Ashwa asking if I could be considered for the erythropoietin study, and oh, that EPO, what a difference it made. I took my kids skiing, I played in the yard, I volunteered at school. I didn't need those naps anymore that I never really got, because Sarah would keep coming into my room to check on me to make sure that mommy was okay. It's a frightening thing to have a sick mommy. But now mommy was up and moving, going places and doing things, and I was a lucky mommy.

So lucky that when my aunt, a retired RN, came to visit, she asked me in amazement what had happened to me. She couldn't believe the change in my energy. I told her I was testing a new drug for a company called AmGen. She went out and bought ten shares. I have worked these past 23 years, I have been productive, raised my children to be responsible adults, volunteered in my community and for the Northwest Kidney Centers. It's a gift to be able to baby-sit my grandson. I have had this transplant for

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11 years. I waited five years for it. I've had no transfusions since 1980. I am safe with my Epogen and Aranesp still today, which allow me to work, pay taxes, contribute to Social Security, society and Medicare.

I understand your concerns about ESA and hemoglobin. It should not be so low that one ever needs a transfusion. The lowest it should ever be is 10, because otherwise one may need a transfusion, which as we've talked about, can increase antibodies and preclude transplant. This probably happened to my second transplant.

Please don't paint all renal patients with a broad brush. We are all different, we have different type blood vessels, different amounts of plaque in those vessels, some have heart disease and some don't. When I had breast cancer in 1999 I was given the risks and benefits of treatment by my doctor. It was I who chose the treatment after considering the risks. The ESA dose needs to be decided between the doctor and the patient, weighing the risks and benefits, to increase productivity and quality of life, as I did with my cancer treatment. Otherwise, what's the point of living without the energy to be productive?

I challenge each of you to donate a couple units

of blood, try to climb a flight of stairs, and then go
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back to work without falling asleep at your desk. Thank you.
DR. GOODMAN: Thank you very much, Ms. Spaeth, and certainly you're a pioneer in multiple ways. It sounds like you're an athlete too, a healthcare provider, and apparently a swell mom, so it's great to have you. Thank you very much.
I believe next is Dr. Tracy McGowan, from Centocor Ortho Biotech, which is a Johnson & Johnson company. Welcome, Dr. McGowan.
DR. MCGOWAN: My name is Dr. Tracy McGowan, I'm a nephrologist, and I'm here today to present on behalf of Centocor Ortho Biotech. Today I would like to leave you with four points.
The first point is that chronic kidney disease is a continuum, from early renal insufficiency through endstage renal disease, and throughout this spectrum all at these patients are at risk for the development of anemia and the potential need for blood transfusions.
As we've heard, blood transfusions are associated with increased panel reactive antibodies. Increased panel reactive antibodies are associated with longer waiting times for renal transplant, as well as untoward outcomes in those transplant recipients.
The only way to avoid renal transplantation is
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to maintain adequate hemoglobin levels proactively. ESAs are indicated to maintain adequate hemoglobin levels for patients with chronic kidney disease. ESAs are not a substitute for transfusions. Therefore, the trigger to initiate ESA therapy needs to be higher than the trigger for blood transfusions.
And lastly, in a recently convened FDA CRDAC, the majority of expert panel members voted to maintain the current ESA label for chronic kidney disease as written.
The following slides will support these four points. I'll merely focus on the ones of interest to the panel that I think are most impactful.
In a recent USRDS report it was noted that over a quarter of the patients who received transplants were exposed to blood transfusions. This is important because the patients who are exposed to blood transfusions had a longer waiting time on average than the patients who were not, as noted in this graph from the same USRDS report.
Why is that? As you heard, blood transfusions are associated with increased PRA. Increased PRA is associated with increased waiting time for renal transplant patients, and worsened outcomes in those transplant recipients.
This relationship is noted in this study where patients with high PRAs who were receiving transfusions
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had significantly higher PRAs than those patients who were no longer receiving transfusions. Why is that important? As you can see from this slide, the higher your PRA, the longer you are likely to wait for a renal transplant. In fact in these studies from 2005 you can see that patients with PRAs of greater than 80 percent, they were not able to calculate in the final analysis what their median waiting time for transplant would be because many of these patients were still waiting for a transplant.

In a study of almost 100,000 patients, being exposed to pretransplant transfusions is associated with having a PRA of greater than 10 percent. Having a PRA of greater than 10 percent in the same study was associated with worsened outcomes for those patients in the subsequent six years.

In another study by Lietz, you can see that not only was blood transfusion associated with worse outcomes in these patients, but the patients who did not need blood transfusions, patients who were only managed with EPO, had the best outcomes in these studies.

To the four points I'd like to leave you with, chronic kidney disease is a continuum and all patients along this continuum are at risk for development of anemia and the potential need for blood transfusions, blood transfusions which as you know now are associated with

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increased PRA, which is associated with longer waiting times and worsened outcomes. The only way to avoid blood transfusions is to maintain adequate hemoglobin levels. FDA indicates adequate levels for hemoglobin of 10 to 12 grams per deciliter, an indication that was recently reported at the CRDAC meeting.

In closing, I would like to thank you for allowing me to present this information to the panel today on behalf of Centocor Ortho Biotech. I would like to ask as we are here today, that hopefully this panel will make a choice, a choice to allow physicians, healthcare providers to continue to have a choice to provide their patients with ESAs to maintain adequate hemoglobin levels, so that those patients aren't faced with one choice, which is transfusion. Thank you.

DR. GOODMAN: Thank you very much, Dr. McGowan. We have a choice today, but only after examining the evidence, which we will phrase very carefully. Thank you very much. Next is Dr. Barry von Hartitzsch, with Nephrology Specialists of Oklahoma, in Tulsa, Oklahoma. Dr. Von Hartitzsch.

DR. VON HARTITZSCH: I have studied anemia and renal failure for 40 years. ESA agents are the only way we can prevent the need for dialysis. I have had seven years experience in raising hemoglobin levels to the

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normal range of 13 to 16 in dialysis patients, and in predialysis patients, and that was in the years 2000 to

2007, before the FDA lowered the levels to 10 to 12. This is a patient, nine-and-a-half years. These are predialysis, 52 -- five-and-a-half years. 70 -- I'm sorry. 70 was there, but this is nine-and-a-half years. These are stage four patients. This was a 78-year-old woman, still going strong after eight-and-a-third years. Comparison of hemoglobin and erythropoietin, the trials, ACORD settled at 11.9, CREATE 11.6, 10.1 in the American trial, CHOIR. You see the increase in erythropoietin is related to erythropoietin resistance, and renal failure patients are confounded by the fact that they have hypertension, smoking, anemia, diabetes, cardiac disease and obesity, all which affect oxygen delivery to the tissues. So you have a compound aspect of hypoxia, this is a classification of hypoxia, COPD, and smoking and anemia decrease the oxygen-carrying capacity of the blood. Hypertension and cardiac disease, and non-steroidals affect, distribution of blood slows up, and cardiac disease slows up the ability to compensate by increased heart rate. Diabetes is a block at the tissue level because if you don't get glucose into the cells, you can't oxidize the glucose perfused energy, and ATB production in the cells is the basis of life. All these factors

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collectively increase hypoxia, cause oxidative stress, the phagocytic response and seeing an increased number of aging cells dying, some of them dying because of an anaerobic respiration due to oxidative stress. This is a list of erythropoietin resistance. The greater the number of risk factors, the greater the dose of the erythropoietin required to raise the hemoglobin to 13.5. And in the CHOIR trial, this was another range of hemoglobin levels. I'm concerned about people out in the lower levels, you know, one standard deviation down there, both the creatinine and hemoglobin levels are going down to parallel. This is erythropoietin resistance in dialysis patients. I can raise the hemoglobin levels to normal in everybody as long as I give them as much as it takes. These are specters that you see when hemoglobin levels fall predialysis. Anemia, less than 13 grams, versus angina and intractable congestive heart failure. This is my clinical practice. Anemia less than 12 grams causes angina, congestive heart failure in women, myocardial infarction in men, ischemic limb and gangrene and amputations, particularly in diabetics. Transient ischemic attacks, stroke at anemia less than 11 grams, frequently leading to death. Erythropoietin trials in the United States start

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too late. We watch everybody develop heart disease and they develop heart disease beforehand, and 800,000 of them die each year of cardiac disease. Those that survive cardiac disease get to dialysis at 100,000 per year, and

most of them are dead because of the 20 percent death rate in five years.
DR. GOODMAN: Dr. Von Hartitzsch, you need to wrap up please.
DR. VON HARTITZSCH: This is Dr. Andrews' work from the FDA, where he looked at the achieved hemoglobin levels cancelling out erythropoietin resistance. These are the serious adverse events that occur, with death rates in those quintiles. They were divided not by group but by quintiles. You can see that people above 13.3 grams, 281 people had the best survival and the least events. People down in the 10 to 12 range where we are, they died, they had more events and they died faster.
DR. GOODMAN: Dr. Von Hartitzsch, you need to conclude, sir.
DR. VON HARTITZSCH: I'm concluding here with the CHOIR trial, the truth, the control trial maintaining normal hemoglobin levels when you take into account achieved hemoglobin levels. The clinical controlled trials are confounded by erythropoietin resistance.
DR. GOODMAN: Thank you, Dr. Von Hartitzsch,
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please step down now. We appreciate your comments about your clinical practice and the various case studies you shared with us. Next is Dr. Sue Leffell, who is a professor and laboratory director of the Johns Hopkins University immunogenetics laboratory, and today she is representing the American Society for Histocompatibility and Immunogenetics. Welcome, Dr. Leffell.
DR. LEFFELL: Thank you. I'm going to limit my remarks this morning to two issues, primarily because Dr. Cecka has so nicely covered the area of definition of sensitization to HLA, so I am going to concentrate on the impact of sensitization and the relationship of transfusion to sensitization, and I will give you more recent data that is based on the sensitive solid phase immunoassays that Dr. Cecka told you about.
The impact of sensitization, as you heard, is very profound. Currently 40 percent of the active candidates on the renal transplant waiting list are sensitized, 17.2 percent of the candidates are highly sensitized, with PRAs or a comparable CPRA of 85 percent.
The impact of sensitization is twofold. It reduces access, a severe limiting factor on access, and it impacts long-term graft survival. These are OPTN data, more recent data than some we've seen previously, showing the impact on access. It increases the median waiting
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time. The middle bars in the range of 10 to 79 PRA show that even moderately sensitized patients have increased waiting times, and for those highly sensitized patients the median waiting time more than doubles. The red X on the far right indicates that a more recent cohort, as was pointed out previously, there are very few highly

sensitized patients who ever make it to transplant, so you can't calculate an accurate median waiting time. With regard to the impact on long-term graft survival, these are some recent data from a very large study of over 5,000 renal transplant recipients in a collaborative transplant study, and this was based on the sensitive solid phase immunoassay. If you look at the graph on the left, these are over 4,000 recipients of first transplants. The solid bar at the top is graft survival of patients with no HLA detectable antibody by these sensitive assays. There is a highly significant difference in the graft survival at 87.5 percent, to that of patients with antibodies, even low levels, to both Class I and Class II HLA antigens shown by the lower dotted line, with graft survival of 76.5 percent. A similar breakout was seen between patients with and without HLA antibodies in the retransplant patients shown in the graph on the right. Because there are limited data available on the

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impact of transfusions with leukoreduced blood products in the current era, we pursued the option of trying to provide you with some more current data, and we looked at sensitization rates among males with no previous transplants, because transfusion is the most likely cause of sensitization in these patients. At my own center at Johns Hopkins among our renal candidates, we have a 23.5 percent incidence of sensitization among males with no previous transplants. And at M.D. Anderson, looking at candidates for hematopoietic cell transplants, there was an incidence of 12.1 percent. Another recent study from Emory looked at the impact of multiple transfusions of leukoreduced products among sickle cell disease patients, and these authors report an overall rate of sensitization of 34 percent. Even if transfusion induces only low levels of sensitization, because of the problem with memory cells, which Dr. Cecka alluded to, subsequent infection or inflammation can impact the level and the breadth of HLA antibodies, causing significant rises in types and expansion of the breadth of HLA antibodies, as was shown in this recent study.

DR. GOODMAN: Dr. Leffell, you may want to start to wrap up.

DR. LEFFELL: I am wrapping up right now. I

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would like to leave you with three reasons for the continued use of ESAs for renal transplant candidates. First, as I have pointed out, HLA sensitization occurs today even with leukoreduced product. Secondly, even low levels of HLA-specific antibodies adversely impact renal transplant candidates. And finally, something that hasn't been mentioned before, for children and young adults, avoidance of sensitization is particularly important, for

these patients will very likely need a second transplant during their lifetime.
On behalf of ASHI, I would like to thank the committee for the opportunity to present this information.
DR. GOODMAN: Thank you very much, Dr. Leffell, and thank you for that very close look at this issue of sensitization and your noteworthy mention of the pediatric population. We appreciate that. Next is Dr. Lawrence Goodnough, who's a professor of pathology and medicine, and director of the transfusion center among other things, at Stanford University Medical Center. Welcome, Dr. Goodnough.
DR. GOODNOUGH: Thank you. I come to you as a hematologist today with 30 years of experience in publications and application of device strategies to avoid blood transfusions. By way of disclosures I have served or I am serving as a consultant for medical advisory

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boards to companies that provide products that are alternatives to blood transfusions including AmGen, which provided travel for me here today, and also Centocor Ortho Biotech, McLaughlin, Leopold, AMed, Bayer, and Eli Lilly, all of whom are in the field of alternatives to transfusion. I'm here to speak for myself, and on a personal note, my 86-year-old mother, who has stage four endstage renal disease, predialysis, whose anemia has been successfully managed for the last two years with an ESA and avoiding blood transfusions.
Slide one of three, and I show you these slides to directly refute two summary conclusions from Dr. Koller, which I'll address. Slide one is here to remind the panel of a blood shield law which has been legislated by 49 states that provide grants of immunity explicitly for blood banks, and in one they legislate blood as a medical service rather than as a product subject to warranty. The basis for the blood shield laws historically to the present is because blood is regarded as inherently risky and inherently dangerous, and that includes not only known, but unknown risks, including emerging pathogens.
Relevant to this, I disagree with the summary conclusion by Dr. Koller that transfusions for most patients with hemoglobins of six to ten is not warranted.

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WHO categorizes hemoglobin of six to eight as severe anemia. Best practices mandate that severe anemia be treated and the anemia be addressed. That also includes many, if not most patients with moderate anemias of eight to ten, as was supported by Dr. Carson's comment in this population, most of whom have cardiovascular disease.
Slide two presents the circular of information for blood and blood product which is issued jointly by the AABB, American Blood Centers, and the American Red Cross, under the auspices of the CDC and the FDA, and as such is

the equivalent of a USPI or package insert for blood. And in this pamphlet it says what is blood and how do we give blood, what happens when we give blood, what are the indications for blood, and what are contraindications for blood. And on page nine of the current edition it says directly under contraindications, that if the clinical condition permits sufficient time for one of four hematinic agents to promote erythropoiesis, these should be used instead of a blood transfusion. The industry circular says the blood is contraindicated if you can identify and track the sufficiency of folic, iron, B12 and erythropoietin. And directly to this, I disagree with the summary conclusion of Dr. Koller that data for PSA in reduction of blood transfusions are limited for this patient population in whom transfusions are elective, and

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blood transfusions are contraindicated.
Why do we have a national blood inventory? It's for people who cannot plan ahead, including Level I trauma patients, women with postpartum hemorrhage, and nonelective surgical patients, malignant hematology patients and so forth. For everybody else, blood is contraindicated and the alternative should be used instead.
I am happy to be here, and pleased to answer any further questions now or later this afternoon. Thank you for your time.
DR. GOODMAN: Thank you very much, Dr. Goodnough, for your comments about interventions. Next is Gail Wick, who is an RN and is a trustee to the American Kidney Fund Board of Trustees. Ms. Wick.
MS. WICK: Good morning. Thank you for the opportunity to speak here this morning representing the American Kidney Fund. I am a member of the Board of Trustees of the Fund. Additionally, I've been a nephrology nurse for the previous 40 years working in all modalities, and in numerous patients ranging from staff nurse to vice president of nursing. The American Kidney Fund is the nation's leading charitable organization providing treatment-related financial assistance to kidney patients, last year providing over $155 million in

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financial assistance to patients on dialysis.
It's been well established that CKD is complicated by anemia and potential blood transfusion requirements. Prior to the introduction of ESAs, patients suffering from anemia relied heavily on blood transfusions to maintain a healthy red blood cell count. I know because I was there. While blood transfusions are necessary for some patients, they carry known risks, which have been discussed here previously. And while helpful with anemia management, blood transfusions in patients with CKD have been associated with high PRA titers, which can preclude and delay time to kidney transplantation, as

well as complicate patient management, which is key. ESAs elevate hemoglobin levels and dramatically decrease transplantation needs for patients with CKD. Lower PRA levels have the ability to allow for a more successful transplantation process, and aside from the transplantation issue, there are significant health benefits associated with ESA use. With appropriate dosing and administration of ESAs and control of factors that importantly hinder the body's response to ESAs, patients require less medical attention and hospitalization, and rarely need blood transfusions. While there has been controversy over dosage administration practices, it's important to emphasize that

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each patient receiving dialysis responds differently. Because of this, it's important for the physician and patient to be permitted to decide on immunomanagement care plans that are best suited to the patient. The American Kidney Fund believes that all dialysis patients have the right to live normal and productive lives, and should have access to the best quality of care that allows them to do so. Studies have demonstrated that hemoglobin levels greater than ten are associated with improved survival and quality of life that's very important, when compared to hemoglobin levels less than ten. Receiving the proper dose has made normal life a possibility, as well as reducing the need for transfusions. AKF believes that any change in policy should take into consideration its impact on quality of patient care and not be centered on incentives. We believe that patients with CKD but not yet on dialysis should have access to ESAs when their physicians deem it an appropriate need. Healthier patients at the onset of dialysis are likely to help drive down first year mortality rates and realize decreased health risks associated with anemia. In conclusion, AKF encourages CMS to continue efforts to ensure that doctors have the flexibility to

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adjust medications based on patient needs, and that patients have access to the medications and treatments that provide the best health outcomes. I thank you again for the opportunity to speak.

DR. GOODMAN: Thank you very much, Ms. Wick, for your concise comments, in particular on the matter of medication adjustment, we appreciate those very much. And next is Dr. Glenn Chertow, who is a professor of medicine at the Stanford University School of Medicine, and is its chief of the division of nephrology. Welcome, Dr. Chertow.

DR. CHERTOW: Thank you very much. Thank you for the opportunity to speak. I will be here all day today to take questions if requested. I'm currently the

Norman S. Coplon Satellite Healthcare Professor of Medicine at Stanford University. Before joining the faculty at Stanford I served on the faculties at Harvard and UCSF. In addition to caring for patients with chronic kidney disease, I teach and conduct patient-oriented research, including clinical trials. Over the past several years I have been recognized for my contributions to clinical care, teaching and research. In 2004 I was elected to the American Society of Clinical Investigation. In 2007 I received a national torch bearer award from the American Kidney Fund in recognition of my contributions

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towards improving the lives of persons with kidney disease. I have authored more than 300 peer reviewed original papers, editorials, reviews and book chapters on topics related to kidney disease. The majority of my research has been funded by the National Institutes of Health, but over the past 15 years I've also performed research sponsored by pharmaceutical companies, including in alphabetical order, AmGen, Bayer, GelTech, GenCyte, Novartis, Smithkline Beecham.

I've also served as an advisor to AmGen, and am currently cochair of AmGen's EVOLVE study, a global clinical trial investigating the effects of toxic medications in patients on hemodialysis. I've also served as an expert witness addressing clinical issues in two of AmGen's patent infringement cases. In October 2010 I provided clinical commentary for AmGen at the FDA CRDAC meeting. AmGen has covered my travel expenses to this meeting. I emphasize that my statement has not been discussed or shared with any AmGen employees.

Virtually all patients on dialysis and a sizable fraction of persons with chronic kidney diseases or CKD have lower than expected hemoglobin concentrations, many have symptomatic anemia. While transfusion can be a lifesaving maneuver for patients with active hemorrhage or severe refractory anemia associated with hematologic

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malignancies, transfusion is not a viable approach for the management of anemia in patients with CKD.

In addition to the issues related to alloimmunization addressed by others before and likely after, transfusion occurs often with acute heart failure, hyperkalemia, iron overload and other complications in these vulnerable Medicare beneficiaries. These risks are accentuated in persons with CKD.

The role of transfusion in kidney transplantation in my opinion was inaccurately depicted in the technology assessment report prepared by the University of Connecticut group, in that persons who were transfused but never received a transplant were ignored. From the Normal Hematocrit Trial and TREAT, we have learned that overzealous correction of anemia with ESAs can precipitate adverse events in selected patients with

CKD.
In contrast, the judicious use of ESAs reduces the need for transfusion, abrogates sensitization, as we've heard, and prevents other transfusion-associated complications. In all instances, physicians should carefully consider whether anemia is the cause of symptomatic dyspnea, fatigue or other manifestations of chronic disease. Conditions other than CKD resulting in anemia should be investigated so that the risks associated
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with the provision of ESAs can be mitigated.
It should be noted that women compared with men, and African-Americans and Latinos compared with whites, are more likely to have anemia associated with kidney disease. Restricted coverage of ESAs for vulnerable Medicare beneficiaries with CKD would place these individuals at undue risk and sadly reduce their access to transplantation, the optimal therapy for kidney failure.
Finally, I would invite Dr. Koller, Dr. White, any members of the committee to join me for rounds at any of the seven dialysis units at which I see patients, and I believe you would find the experience informative. Thank you for your time.
DR. GOODMAN: Thank you very much, Dr. Chertow, for your comments, very much appreciated. Next up is Dr. Stephen Fadem, who is a clinical nephrologist and medical director at Dialysis Centers, in Houston, Texas. Welcome, Doctor.
DR. FADEM: Thank you for allowing me the opportunity to present before you today. I'm a clinical nephrologist and medical director for several dialysis units in Houston, Texas. I'm active in the transplantation program at St. Luke's Episcopal Hospital, and as well actively refer patients to Baylor as well as the University of Texas programs. I've participated in
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several research projects which were funded by either Ortho Biotech or AmGen, or several other companies. In addition, I was a research participant in the CHOIR study, and as well an active participant in the EVOLVE study.
I deal with a population of patients who are anemic because they lack the kidney mass due to erythropoietin. Their pathophysiology requirements differ from those of other populations, including cancer patients. In 1982 I was part of a team of physicians that demonstrated that patients with chronic kidney disease before dialysis lose an average of 3.15 cc's of blood per day, while those on hemodialysis lose approximately 6.27 cc's of blood per day. As a result of these two factors, patients who do not receive recombinant therapy with synthetic erythropoietin stimulating agents are going to develop severe anemia and will probably require blood transfusion. Although the incidence of blood transfusion has dramatically decreased since the advent of synthetic

therapies, it's still higher than ideal, with 15 percent of transplant recipients receiving at least one blood transfusion in 2008. About 28 percent on the transplant wait list received a transfusion within the first three years who were on the list.
Blood transfusion scarcity is a challenge to major trauma centers' surgery suites, not only because

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blood is a scarce resource, but also because the blood can transmit viruses such as hepatitis B and C, although less likely, it can happen. With respect to transplantation, a major factor is blood transfusions can sensitize patients so that they will induce a panel reactive antibody, and you've heard a lot about this already, and it will challenge the immunological stability of the transplanted kidney and this will create, of course, high C panel reactive antibody levels, and the percentage of the population that will match against these patients will be lower. Those who have a level greater than 80 percent can have a very high sensitization rate. In other words, the higher the sensitization rate, the harder it is to find a donor.
The USRDS report has demonstrated that the three-year cumulative incidence of blood transfusions in patients on the transplant list with panel reactive antibodies over 80 percent was around 41 percent, while those who had no antibodies was only around 24 to 25 percent. In a study in Ireland published in 2003, 100 percent of patients who were highly sensitized had received blood transfusions. Patients who were sensitized must wait at least one to three years longer on a list for kidney transplant. The survival rate is a fraction of what it would be without a higher PRA --

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DR. GOODMAN: You've got about one minute, Doctor.
DR. FADEM: -- and you do not receive a kidney, but they have a 90 percent higher risk of death. In all likelihood, patients who have a high panel reactive antibody may never receive a kidney transplant, they spend the longest time on dialysis.
The AAKP recently demonstrated that patients who receive a kidney transplant had the highest level of satisfaction. Thus as a clinician, I want what's best for my patients, and that is the opportunity for a kidney transplant. In order to achieve that, I want to maximize all conditions that allow them this chance, and likewise, to minimize challenges. It's convincingly observed that blood transfusions sensitize patients with high level cytotoxic antibodies, which will diminish their opportunity to receive transplants.
Perhaps equipoise obviates the ability to study this further, but in the interim, it appears that the kidney patient's best interest is to avoid a blood

transfusion. Thus, we need to ensure that patients who have been on a waiting list for a transplant have sufficiently high hemoglobin levels that they do not require a blood transfusion. Thank you very much.

DR. GOODMAN: Thank you very much, Dr. Fadem,

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thank you for those insights. Next up is Dr. Reshma Kewalramani. She's the nephrology therapeutic area head and vice president of global development at AmGen. Welcome, Dr. Kewalramani.

DR. KEWALRAMANI: Thank you. Good morning. I am a nephrologist at AmGen, and I'm very grateful for the opportunity to present to you today.

Let me start by addressing the tech assessment, which has major limitations that have led to conclusions that are in stark contrast to U.S. and European guidelines, textbooks, published reviews, and the clinical practice of transplant nephrology. While I don't have the time to go into specific limitations, let me say the following: There are scores of high quality journal articles that have not been included. Two, the patients waiting on the transplant list, transplant time and access to transplantation were outcomes that were simply not included. And three, even in the literature that was reviewed, there are significant limitations in interpretation and analysis.

Let me be clear that the data are there and the evidence is very clear in this regard. Sensitization has a negative impact on graft access and transplant survival. In point of fact, the entire U.S. allocation system for organs is predicated on this notion of the importance of

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sensitization, and points are allocated to patients with elevated PRA levels.

There are four points to convey but I will highlight just two here. First, as was discussed with this panel last March, and at the recent FDA advisory committee, dialysis patients and patients with kidney disease who are not on dialysis are different, and therefore, the benefits and risks of anemia management need to be considered separately in these two patient populations.

ESAs when used in accordance with the FDA label improve anemia, they decrease the transfusions, and in dialysis patients they have also been shown to improve exercise tolerance and physical function. Anemia in dialysis patients is severe, it is unrelenting and it is unlike anemia seen in other populations. The treatment of this disease is required and transfusions, because of their risks, are not a viable therapy.

The crux of the issue that we are discussing today has the data represented on this slide. What is the relationship between transfusion, PRA levels and outcomes? Here it is. Transfusions are related to increases in PRA

levels. The higher the PRA levels, the longer our patients stay on the wait list. And why is this important? It's important because the longer patients

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spend time on the wait list, the higher the likelihood of death without a transplant. Let me focus your attention on just the panel to the far right. This is a study of 116,000 patients who have received a transplant. The relationship between PRA levels and graft survival is clear. Sensitized patients on average have a three-year shorter graft survival than patients who are not sensitized. The data I presented on the previous slide and these data on this slide were not included in the tech assessment. Clinically, here is the issue that we face. What do we do with our patients with anemia on dialysis? The data from registrational trials as well as from USRDS, which represents near total surveillance of the entire U.S. dialysis population, have shown that ESA can effectively manage anemia, and ESA unambiguously decreased transfusions.

DR. GOODMAN: You may want to wrap up, Dr. Kewalramani.

DR. KEWALRAMANI: Thank you. With the introduction of ESAs, hemoglobins have gone up, transfusions have gone down, and concurrently, there has been an almost doubling in the proportion of patients on the wait list who are unsensitized. I urge the panel to probe deeply into the inadequacies of the technology

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assessment and to please preserve the benefit of ESAs and transfusion minimization so that our patients are not subjected to unnecessary development of antibodies. Thank you.

DR. GOODMAN: Thank you very much, Dr. Kewalramani, for your clear presentation. Next is Dr. William Harmon. He is the director of nephrology in the division of the Children's Hospital in Boston, and professor of pediatrics at Harvard Medical School, today representing the American Society of Nephrology. Welcome, Dr. Harmon.

DR. HARMON: Thank you very much, Mr. Chairman, members and guests. Unfortunately, the slides that I prepared have not been, are not going to be able to be presented here, so hopefully my presentation will be clear without them. As noted, I am representing the American Society of Nephrology, on whose public policy committee I've served for several years. You've heard speakers emphasize the fact that pretransplant blood transfusions may lead to sensitization and may affect the outcome of kidney transplantation. Blood transfusions are one source of sensitization in candidates awaiting kidney transplantation. Sensitization leads to decreased opportunity for transplantation in the

first place, and for those who have been sensitized and
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subsequently do receive a kidney transplant, sensitization is clearly an increased risk for graft survival. Sensitized candidates must wait longer for an appropriate donor. Extending the time on chronic dialysis substantially increases the risk of dying. Moreover, kidney graft survival is inversely proportionate to the time waiting on dialysis. Those who receive preemptive kidney transplants do the best, and those who have waited for many years do the worst. The likelihood of finding a crossmatch negative deceased donor kidney is very low, so highly sensitized candidates can rarely find an appropriate donor, and those who are actively awaiting kidney transplant have double the annual mortality rate than those who have already received a kidney transplant. The second consequence of being sensitized is the relationship to lower graft survival. Analysis of recent SRTR data that shows that for a PRA greater than 40 percent, the risk of graft loss at one to three years increases in an exponential fashion. To translate this, someone who is 80 percent sensitized has a 1.4-fold greater risk of graft loss compared to someone with a PRA of 40 percent. Analysis of data in the North American Pediatric Renal Transplant Cooperative study reaches a similar conclusion. Based on multivariate analysis of over 5,000
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children who received deceased donor kidney transplants in the past 20 years, those receiving greater than five blood transfusions prior to transplantation had a relative hazard of graft loss of 1.28, which is highly significant. Indeed, this risk factor trails only black race of the recipient and prior transplant in terms of its significance in graft loss. Let's briefly look at the question of donor-specific transfusions. Early in this history of kidney transplantation, those recipients who received blood transfusions prior to transplantation were observed to have better early graft success than those who never received a transfusion. This observation was taken to the next step in protocols that deliberately transfused blood from the prospective donor to the recipient prior to transplantation. Those who were not sensitized by these transfusions did do better than expected graft survival rates. However, up to 30 percent of the recipients of pretransplant donor-specific transfusions became sensitized to the blood donor, and thus were unable to receive a graft from that specific donor. Therefore, the beneficial effect of the donor-specific transfusions may have been through elimination of high risk donor-recipient pairs, or through the identification of highly immunoresponsive transplant candidates. Whether there was
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a positive tolerance effect induced by these transfusions was never identified. Importantly, this practice was abandoned after the introduction of modern immunosuppression, which has led to dramatic decreases in early acute rejection rates, and substantially better early graft survival rates.

Finally, it should be noted that the introduction of modern immunosuppressive agents, as well as adjunctive treatments, has led to a higher incidence of post-transplant anemia in kidney transplant recipients. This early anemia has been correlated with poor transplant outcomes in several studies.

From these data I would propose the following two conclusions: First, blood transfusions should be avoided prior to kidney transplantation to decrease the likelihood of sensitization and to decrease their detrimental effects on transplant outcome. Secondly, anemia is increasingly prevalent in the first several months following kidney transplantation, and may have deleterious effects on recovery. Insofar as is possible, it seems reasonable to avoid anemia prior to kidney transplantation.

On behalf of the American Society of Nephrology, I thank you very much.

DR. GOODMAN: Thank you very much, Dr. Harmon,

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for those clearly made points. I do note with regard to slides that CMS has a deadline for submission, and that may have been the case here.

Next is Kathleen LeBeau. Ms. LeBeau is with weKAN, and she is a program manager for Renal Support Network. Welcome, Ms. LeBeau.

MS. LEBEAU: Thank you. Good morning. I'm Kathy LeBeau, and I'm a home hemodialysis patient and awaiting transplant candidate, representing the Renal Support Network, a national patient-run organization who supported my travel here today.

We have been here before, and it's important to know that we were before the FDA CRDAC as well, so the million dollar question is, what do we renal patients really need when it comes to anemia management, and how would we accomplish this in a safe, cost effective and productive way to optimize our quality of life and health? It's a very big question.

I think one of MedCAC's panelists at this very meeting last year captured it best. Dr. Rajiv Agarwal, a voice of reason who clearly understands the patient perspective, characterized the problem of looking merely at the clinical profile of the patient as it exists in the computer with certain diagnostic lab values and the like, but failing to remember to ask the patients how they feel,

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how are they doing, is not taking very good care of the patients. And he made a perfect analogy of walking the

fine line to address safety, and the difference that judicious use of a medication can make in a person's life, the choice between risk and benefit. He offered the patient who feels well and is able to run on the golf course and play, and is living life to the fullest, even if he may be at risk of a stroke or other adverse event, would consider themselves as having a good quality of life, versus the person who may live for 10 or 20 years but just sitting in a chair, and for whom life simply seems longer, but certainly not better. Which do you really think your patients would want? Which would you choose for yourselves or your loved one?

When looking at these determinations, regulators are often hesitant to consider quality of life issues because they are difficult to quantify. Of course, the very point of any medical care is to improve the quality of the patient's life and health. I can tell you, patients measure quality of life every day in many ways. I'm a good example, having gone from being almost unable to participate in life four years ago when my disease was most symptomatic, to being a fairly energetic person today, with all the ramifications of CKD fairly well under control. Just because we don't have the ideal

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evidence-based tool to measure this quality of life is no reason to discount it.

We are very aware of the fact that ESA has known serious side effects when targeting, and I emphasize targeting and not achieving, hemoglobin levels at or above 13, and we take these side effects seriously. We support the need for using these agents responsibly in all patients to avoid serious side effects, and feel that the present hemoglobin level as verified at the FDA meeting in October of 10 to 12 can help meet that goal.

Further, we support ongoing education to ensure that both patients and clinicians are aware of how anemia should be treated in patients with CKD, and how best to maintain a healthy hemoglobin level. Because the problem of adverse events is not well understood, though, we seem to be willing to let the pendulum swing from one extreme to another. Since targeting high hemoglobin can result in adverse events, there are people that advocate for keeping the level much lower. There was and is considerable conversation of nine or lower, at the last MedCAC hearing and today.

I would just note that the proponents of this have never taken a hemoglobin of nine or lower out for a spin. Speaking from experience, I promise you, you would not like it. I would ask you, please, not to subject

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patients to something that you would not want to tolerate yourselves.

Moreover, a lower level of hemoglobin could necessitate the use of blood transfusions more often to

get a quick enough response to treatment to prevent further dropping of hemoglobin levels and the resultant complications. Although the technology assessment presented today seems to indicate through studies, though the evidence is ranked as low, that transfusion may not be implicated in future graft rejections. That's not the biggest issue of patient concern. Transfusions can cause patients not to be able to receive a transplant at all, due to high CPRA level.

DR. GOODMAN: You may want to wrap up, Ms. LeBeau.

MS. LEBEAU: Thank you. For this reason, I have known patients who have languished on the transplant list for years, waiting in vain, and have had friends who have died on these lists. Kidney allocation is a very difficult thing to do fairly, we do not wish to make it any more difficult for a potential recipient by shrinking their potential donor pool to nothing. Our needs are very simple. We want to feel well enough to do the everyday things that most people take for granted, made extraordinary by the fact that before ESAs they were

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impossible. Thank you.

DR. GOODMAN: Thank you very much, Ms. LeBeau, and particularly for your on-the-ground patient perspective, very insightful and very helpful. Thank you for being here again.

Next is Paul Conway. He's the vice president of American Association of Kidney Patients. He also chairs the American Association of Kidney Patients public policy committee. Welcome, Mr. Conway.

MR. CONWAY: Thank you very much, Chairman, and members of the committee, thank you for allowing me to speak today. I'm a 1997 kidney transplant recipient, and I've managed kidney disease and kidney failure for 30 years. Over the course of my career I've served my country and my state as an appointed official under in four Presidents, four cabinet secretaries, three governors, and a Marine Corps major general, including service as one of the youngest deputy secretaries for the Department of Health and Human Services for the State of Virginia. I presently serve as vice president of the American Association of Kidney Patients.

My appearance before you today is due in part to my strong faith and discipline, and multiple teams of highly skilled doctors, nurses, researchers, pharmaceutical companies, whose noble efforts to extend

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the lives and develop life-extending treatments has saved my life and the lives of tens of thousands of other patients. As an American, I'm proud of those who choose these professions and I respect their avocations to professional pursuits, and will be further grateful if we look at a nation whose free market philosophy views both

the protection and extension of life and advancements in medicine as the traditional hallmarks of a high quality medical system.

I'm fortunate that I received the gift of life through a kidney transplant. Many patients never have that opportunity because of disparities based on blood groups, ethical factors or race. However, one disparity totally preventable is the presence of panel reactive antibodies secondary to blood transfusion. Kidney patients lose blood from their gastrointestinal tracts. This was shown in predialysis and in dialysis patients in 1982 by a team of doctors including Dr. Fadem. At that time there was no drug to stimulate red blood cell production and patients often required blood transfusions. These were given routinely in predialysis units. In the 1990s the ESAs were deployed, and the requirement for transfusions fell dramatically. However, it is still common for kidney patients, even those waiting for a transplant, to receive blood transfusion.

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Transfusions are not harmless. They can spread viruses such as hepatitis C and B, but more relevant in the transplant patient, they cause an immunization type reaction and infuses a set of antibodies that will fight a new kidney transplant. This is known as panel reactive antibody, or PRA level. The patient with the high PRA will react immediately to the newly transplanted kidney. In other words, the higher the PRA level, the less likely one is to match with a donor.

This is true in the U.S. and in Europe. The 2010 USRDS annual data report showed that the three-year cumulative incidence of blood transfusions in patients on the transplant list with PRAs was over 80 percent, or those over 80 percent was around 40 percent, while those who had no antibodies was around 24 to 25 percent.

A study published in Ireland in 2003 demonstrated that 100 percent of the patients who were highly sensitized, had PRAs over 80 percent, had received blood transfusions. Public databases show that sensitized patients must wait at least one to three years longer on a list for a transplant. The transplanted kidney did not survive as long. These patients have more complications and they have a 19 percent higher risk of death. In all likelihood, patients who have high PRAs may never receive a kidney transplant, they spend a longer period of time on

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dialysis.

As an informed patient and an American taxpayer, it is important to me that our healthcare system continues to allow me the opportunity to choose optimal care in consultation with my doctor, particularly when that choice is cost effective. It is much less expensive to sustain a patient with a kidney transplant than dialysis. The data is compelling. Blood transfusion-sensitized patients

score high PRA levels and take them out of the loop for a successful transplant. It is therefore important that the American health system continue to deploy strategies that minimize transfusions. If I were one on dialysis who is waiting for a kidney transplant, or if I were a CKD patient who could preempt dialysis altogether by receiving a transplant, I would not want my hemoglobin to drop to a level that necessitated a transfusion.

DR. GOODMAN: You need to wrap up now, Mr. Conway.

MR. CONWAY: Yes, sir. Take it from one who has lived through some of the best and worst experiences. If you or a family member were ever confronted with kidney disease or kidney failure, I think you too would want the latitude to choose the best treatment option in consultation with your doctors. Thank you.

DR. GOODMAN: Thank you very much, Mr. Conway,

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very helpful comments with regard to choices of patients and consultation with physicians. Our last and actually 16th scheduled speaker is Shad Ireland, and he is from the Shad Ireland Foundation. Welcome, and I should say welcome back, Mr. Ireland.

MR. IRELAND: Thank you, and good afternoon, or good morning. For purpose of disclosure, my organization has received educational grants from AmGen, but in no way does that present any form of conflict of interest. I am here today to talk with you a little bit about my story. My organization has a position on this but I also as a patient have a position. I have been on dialysis for 29 years. I'm a professional athlete. I was the first dialysis patient in the world to compete in and complete an Iron Man, I've done multiple triathlons. For those of you who aren't familiar with Iron Man, it's a 2.4-mile swim followed by a 112-mile bike ride, and then a 26.2-mile jog.

I have received over a hundred blood transfusions. I am sensitized due to the blood transfusions that I've received. When I was first diagnosed, my mother was almost a perfect match, but due to the multiple blood transfusions that I received, she became, I was untransplantable and I no longer was a match. I had a hundred percent antibody level for seven

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years. My PRA came down slightly, and I was transplanted in 1990. The issues that I had following the transplant I believe were due to the sensitivity that I had from the multiple blood transfusions that I received.

If you look at the median wait time now, it's about five-and-a-half years for patients waiting for transplant. If blood transfusions are used more frequently, I believe that that number will significantly increase, resulting in more patients ending up like myself, untransplantable. I believe that the sensitivity

that I have directly correlates to the issues that I had with transplant. I received a second transplant in 2000 and had the same issues that I had with the transplant in 1990, and my PRA was about the same level when I received that transplant in 2000.
My organization, its position is that we need to leave the ESA decision with the patient and the physician, which will result in appropriate access to this lifesaving and life changing therapy known as transplantation. Transplant is not a viable option for me. My PRA is still above 80 percent, and due to that fact I've had to push the envelope with the level of therapy that I receive. The dialysis care that I receive is extraordinary, it allows me to do what I currently do for a living, and it allows me to strongly advocate for the

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patients in my community. Options are limited for patients that are sensitized, and I just want to make this point again. I am not transplantable. I will live on dialysis for the rest of my life. I would encourage the panel to -- excuse me. I would encourage the panel to consider this. We have the ability to ensure that this patient population has access to this therapy, and that they don't have to hurt themselves. Thank you.
DR. GOODMAN: Thank you very much, Mr. Ireland, and I must say congratulations. I think that companies like Nike and Adidas are upset that you're wearing out all their running shoes and swim suits and bicycles. Your fitness level is admirable, I could use it myself sometimes. Thank you very much once again.
Those are our 16 scheduled presenters. We have a public commenter in the number of one, I believe, Ms. Ellis, is that correct?
MS. ELLIS: Yes, that's correct.
DR. GOODMAN: So we'll take our public commenter now if he doesn't mind. That would be J. Michael Lazarus, who's a nephrologist, and associated with FMCMA. Dr. Lazarus, you've only got a minute.
DR. LAZARUS: Thank you very much. I am an employee of Fresenius Medical Care. I would like to address the second statement of the CMS summary.

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I have no data but I have experience. I practiced nephrology and took care of dialysis patients for 40 years, 20 before the advent of ESAs. In my practice in those early years, 60 to 70 percent of my patients were transfused, the average transfusion rate was two units per month. We did this not to achieve a target hemoglobin, not to prevent cardiovascular disease, but simply to try to get the patients to come back each and every time for a very difficult treatment.
I do not think you can compare recent-day acute studies of ICU patients without renal failure for short-term outcomes with this population. It is totally

different. I do not suspect that patients or physicians will follow the recommendations of CMS to allow hemoglobins of six to ten, doctors and patients simply will not do that. If CMS decides that they will not reimburse for either ESAs or hemoglobin at that level, I'm not sure that there will be an increase in cardiovascular events, but I can assure you that there will be a significant increase in the number of withdrawals from dialysis treatment. I urge you not to take us back to the dark days of hemoglobins of six to ten grams per deciliter. Thank you.

DR. GOODMAN: Thank you very much, Dr. Lazarus, for those comments. Well, we're getting close to where we

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see our lunch break, and we're probably going to take it, panel. We're behind in the sense that we did take, on purpose we took some time earlier today to get some questions from us to our initial speakers from CMS and the Connecticut EPC, so we're going to have to make up a little bit of that time this afternoon.

And what I would ask you all to do is, and I ask all of us, is to return from lunch prepared to ask specific questions that apply to our questions today. Be prepared to ask those of our presenters and then to carry on discussion among ourselves. What I'll ask is that when we reconvene from lunch, if our initial speakers, in particular Drs. Koller, White, Bowman, Carson and Cecka, arrange yourselves somewhere in the near radius of that microphone with these chairs up front.

MS. ELLIS: If you look to the front, the first two rows of chairs have been reserved for all the presenters today, so if you could after lunch please sit up front in one of those seats.

DR. GOODMAN: Thank you, and I guess we have quite a few of them. We have two rows, but I would ask in particular Drs. Koller, White, Bowman, Carson and Cecka to be closest to the aisle because we may be bothering you the most, although that's not necessarily the case, and then we'll have potential questions for our 16 presenters

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and others.

Panel, anything else you need to know before we break for lunch, other than the fact that yes, it has been an intense information data-driven morning, and we'll ask you to digest that along with your pizza and spaghetti at lunch. And with that, look at your watches now and add 60 minutes, that's when we'll start speaking again. Thank you very much. This has been a very helpful morning. See you in an hour.

(Luncheon recess.)

DR. GOODMAN: Thank you very much. I hope you enjoyed your lunch, and I hope this morning's discussion gave rich fodder for your midday meal there. We're going to move into our questions for presenters and then

discussion among the panel members here, so questions to presenters is first. But just to help structure this a little bit, I think it's pretty clear that we have a pretty complex set of interrelated issues here. It's also clear that the body of evidence is in certain obvious ways rather inconsistent and irregular. That does not mean that there aren't good studies there, apparently there are some good studies there. We had a technology assessment presented today very well that had some questions in it, key questions. Those key questions do not align precisely

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with our questions today, which is often the case, but it sometimes makes it a little bit difficult to track things, so I want to make sure we're able to do that. I think it was also clear that there was some polite disagreements regarding some of the findings of the TA and some of the observations made by CMS, and we're not only going to politely disagree, but try to work through some of those issues, so that by 4:30 we'll have a greater understanding. To help set the stage, and I'm going to turn to Dr. Satya-Murti in a moment, I just want to remind our panel that we need to get our questions answered today by 4:30, and just at a very high level, I just want to remind you about what these questions are. And I want to remind our presenters today that when we have some discussions in a very few moments, it's very important to try to focus your discussion and even occasional controversy along the lines of the questions that we need to answer. So as a reminder then, our first two questions are about PRA assays and their ability to predict renal transplant graft survival, so questions one and two are about PRA assays, all right? Questions three and four concern the role of therapeutic transfusions and their impact on renal transplant graft survival. So one and two are about the role of PRAs, three and four about

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therapeutic transfusion impact on renal transplant graft survival. Questions five and six concern use of ESAs, that is ESA use to maintain hemoglobin levels greater than ten, and that role in improving renal transplant graft survival. So it's basically three sets of two questions here, the first two about PRAs, the second two about therapeutic transfusion impact on transplant graft survival, and the last pair have to do with the use of ESAs and their impact on transplant graft survival. Questions seven and eight concern evidence gaps; I gather there may be a few. So that's the general, that's kind of a very high level picture of what we need to go after today, and I know that some of the issues raised this morning were

interesting and meritorious, but may not necessarily be pursuant to these questions, so let's keep that in mind. The next thing I want to do is ask Dr. Satya-Murti to, in the spirit of framing the big picture here, to address kind of a high level picture with regards to the relationship among some of these issues. I hope that that will help my understanding of this, as well as that of the panelists. And following that, I will probably ask someone

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from the team, I believe it was AmGen, to restate some of their concerns with the technology assessment. Those were clear points but since they weren't in a slide, I want to make sure we heard them. I also want to make sure that we hear what the Connecticut EPC folks have to say about the extent to which their TA did or did not address those issues, so I think that's something that will help all of us as we pursue this. Dr. Satya-Murti, would you take the next step, sir?

DR. SATYA-MURTI: Thanks, Dr. Goodman, for alerting and focusing our attention. From what we have been listening to this morning and reading, it seems to me that we have separate spheres or balls of evidence, discrete pieces, so my question is, are these discrete pieces connected, is there a median consequential result? We heard that anemia is not very helpful and that it has an adverse impact on general well-being, including production of fatigue. We also heard that transfusions have lost their effect over the years, they don't have the transfusion effect anymore, but when they are in fact transfused, they seem to have the long-term consequence of raising antibodies. Then we heard that antibodies are not all the same, there are antibodies, there are general PRAs and CPRAs, and very specific crossmatched antibodies. And

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then lastly, we also heard that ESAs are very helpful in treating anemia.

So in our minds, are we supposed to be bringing these discrete packets together to see a consequential connection? If ESAs are present, there is no need for transfusion, no PRAs, and therefore successful grafting. Is it always the case, or has the TA shown that there may be a connection and there may not be? Even within these individual balls of evidence, or spheres of evidence, it's not always beneficial, it could be neutral. So for us it's very difficult to see one leading to another, particularly that there is a forward irreversible negative effect of anemia and not having ESA, and then a forward beneficial effect of giving ESA, does it connect all of these together in a causative fashion? I'm not sure it does, but that I think is the focus of our tasks.

DR. GOODMAN: Thank you very much, Dr. Satya-Murti. What Dr. Satya-Murti just presented is a

very good way of saying that there's a lot of spotty evidence out there, that the body of evidence appears to be pretty inconsistent and irregular, although it may have a few gems of strength, but that body of evidence does not hold together along some kind of critical pathway that helps us answer these questions. Dr. Satya-Murti has alerted us to some gaps in this critical pathway that

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weren't quite apparent to us; is that correct?
DR. SATYA-MURTI: Yes, that is correct.
DR. GOODMAN: Panel, if you don't mind, I would like to proceed and ask someone from the AmGen team to kind of state their points again. I see nodding of heads. That might be a good step to get going. So if I may ask, whether it's Dr. Kewalramani or another person from the AmGen team, to come to the mike, if you're ready with this. And just to remind you, at the beginning of your presentation you said you had three or four major concerns with the TA, and they weren't on a slide per se, so it would be helpful to us if you restated those. And then I will remind you and the panel to think about the extent to which those concerns are relevant to any of the questions. I suspect that most of them are, but also keep that in mind so we don't go off on a tangent. One question for you, yes?
DR. HOLMBERG: I would also appreciate if you could reference the data. Specifically, you raised information concerning data with the transfusions directly related to the PRA.
DR. GOODMAN: That's very helpful. Yes, Dr. Kewalramani, that's kind of a tall order, but see what you can do.
DR. KEWALRAMANI: Let me try to address your

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question first, Dr. Goodman, about what those three points were, because they were not on a slide. We just received the tech assessment and the slides had gone in before the tech assessment was released, but let me try to just state those, and then I can try to answer additional questions. One, there are at least a dozen, two dozen studies that are large and of good quality that are not included in the tech assessment. Two, that the critical outcomes of time on wait list and access to organs were just not evaluated. And three, that in the studies that were cited in the literature, the analysis was incomplete. If you want me to give you an example of the last, because I think that might be vague, you could look at the data, for example, on transfusions and the impact on transplant outcomes, okay? And if we look at that broad category, we have in there DST studies and some random transfusion studies. My concern, my critical concern about the reason we may have ended in the conclusion that we did is that the DST studies are completely different. As CMS rightfully pointed out in

the question, donor-specific transfusions are completely different, they have no, none, nothing, no relevance to therapeutic transfusions for the purposes of anemia management. Donor-specific transfusion are largely done in the situation of a living donor and recipient, you have

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to have that match, and you get a transfusion from that donor to that recipient.

Now here's my critical concern. There are two sides to the DST analysis and the DST data are in there. One is what is the impact on graft, the graft outcomes, which were evaluated. But two, critically important and almost completely ignored, is the impact on sensitization. Up to 30 percent of patients who receive donor-specific transfusions develop donor-specific antibodies. Many people would consider this catastrophic. What it means is that if you identify your mother to provide a transplant to their child, you provide a DST and they develop donor-specific antibodies, your mother can no longer donate a kidney to you. That was just not analyzed, and we've only seen the analysis of DST on graft outcomes.

Just one more point on that and I can stop after that. When you think about the literature of transfusion and graft outcomes, the tech assessment rightfully pointed out that there are three critical periods to evaluate. Pre-1984. Why? Because that's when cyclosporin was approved. And around 1992, because that's when triple therapy started and this process came into being. But what I think, the further analysis that's required is you cannot combine these. I think Dr. Satya-Murti rightfully pointed out, if you look at current literature with

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current immunosuppressants, and there's a paper by Mackie that solely reviews this concept, it's pretty clear, there's no transfusion effect.

And I think we might be giving ourselves, our patients, physicians a very wrong impression that there might be a transfusion effect and that this might be a good thing to do. It is not a good thing to do. There is no evidence in modern medicine for this.

DR. GOODMAN: Okay. Thank you, Dr. Kewalramani. So at a high level, Dr. Kewalramani, the concerns stated have to do with missing studies, the issue of not having looked at time on wait list for organs, and what you characterize as incomplete analysis of the literature, right? What did I miss there?

DR. KEWALRAMANI: Access to organs.

DR. GOODMAN: Which is part of point two, or point three actually.

DR. KEWALRAMANI: I actually think it's related to two, but it's separate. So if you just look at time on wait list, you will never get this group, because these people die without getting the transplant, so it's related to two, but it's separate.

DR. GOODMAN: So that's a fourth?
DR. KEWALRAMANI: One could take it as a fourth.
DR. GOODMAN: We do take note that one of the
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issues that arose several times has to do with use of PRA not such as a clinical individual patient decision-making support tool, but kind of a broad population sort of tool with sometimes a higher threshold, so, which is used from an operational standpoint to make decisions about allocation, understood.
I'm next going to ask Dr. White and team to help let us know about the TA and how it does or does not address those issues. Any comments on what you just heard, panel, from Dr. Kewalramani? Yes?
DR. KLEIN: I have a question. Are there data that would enable you to quantitate the extent that you, to quantitate the extent of delay attributable to blood transfusions in pretransplant patients?
DR. KEWALRAMANI: I hate to say this, but yes and no. So by yes, what do I mean there? There are clear examples in the literature, and the DST literature cited by the TA is a good place to look at this, where in provision of transfusion you have eliminated the donor-recipient possibility because of donor-specific antibodies, which is something you can't cross.
The issue that you face when you think about PRAs is that there are only three known ways to get elevations in PRAs, pregnancy, previous transplant, and transfusion. So you can try to get to your question, you
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could look at only males, and you could look for the transfusion impact. And there are studies, the one I'd point you to is probably Hardy, that has looked at transfusion impact on PRA levels and subsequent graft survival. You do have to look carefully, there are some nuances to this, but it is not unclear.
DR. GOODMAN: Thank you. Mr. Samson is next, I believe.
MR. SAMSON: You mentioned that there are one or two dozen studies that weren't selected in the TA; do you have a list of those studies?
DR. KEWALRAMANI: I can provide those studies today. We just received the tech assessment I think yesterday or the day before, so we're going through it. Prior to receiving the tech assessment, we had as our own internal team of nephrologists, looked at all of the data, and so there is a briefing book that we put together and at least on one level of review we are comparing the data we were able to find with the data in the tech assessment, and on first review there are at least a dozen or two dozen that don't match.
We've also tried to do searches replicating search terms and such, and a preliminary inclusion of certain search terms, and to the best of my knowledge that

I can glean from what was done, were not included, and it
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changes the number of citations drastically. And so this is something that's going to take a couple of days, but at least for today I can tell you that there's a dozen or two dozen articles that seem quite relevant that are not included.
DR. GOODMAN: Thank you, Dr. Kewalramani. Just as someone who has done this, although not as often as the EPC folks at Connecticut, the EPC folks did document their inclusion and exclusion criteria, they gave us a diagram showing how things fell out, so they are at least quite specific in what they did in their methodology. And if your team, Dr. Kewalramani, at some point would like to replicate something like that that might produce different results, I would imagine CMS wouldn't mind seeing it. That may help to support your assertion or may not support it. Thank you.
Dr. Singh is next.
DR. SINGH: I mean, I think it's, at least to my ears, quite astonishing that we are hearing that there are dozens of studies that are not being included in the TA. As far as I can see from the methodology that was utilized to put the TA together, clearly there was a large body of studies they considered and then they narrowed it down through selection criteria, as you pointed out. So I want to ask Dr. Kewalramani more
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specifically, is there a study that she can cite today, now, since she made the statement today, now, and we have to consider this question now, not later, that is, you know, either a good quality study or a number of good quality studies that were left out, that would have to be included? Not I think there may be studies, but is there a study or are there studies with citations? Because we're not going to have the opportunity to come back and evaluate this, and the assertion is actually quite, seems to be quite firm, that this is an incomplete analysis.
DR. GOODMAN: Thank you, Dr. Singh.
Dr. Kewalramani, if you have something now, we would appreciate it. If you need a few more minutes, that would be okay too.
DR. KEWALRAMANI: Sure. Just as an example, Dr. Singh, there is, I'm sure you're familiar with the Opelz paper from 2005, that's the one with the 116,000 transplant recipients that actually had two important papers from it. Opelz looked at a European experience of about 116,000 transplant recipients and looked by PRA levels, the impact on graft survival. That was one. But the second very important element, and I didn't go through the details here today, was the experience in the same paper on HLA identical sibling transplants. As you know, HLA identical siblings are not
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necessarily identical twins, but they share the HLA match. Interestingly, you would expect that these patients should not be impacted by PRA levels because they share HLA, that's what the antibodies indicate. But the very interesting observation by Opelz is when you look ten years out, HLA identical siblings, in the same paper, are impacted by elevations in PRA levels. And that might be just one paper I happen to be very familiar with because of the nuance around, the very limited work around the HLA identical sibs, but it is in that same paper, the 116,000-patient experience is reported.

DR. SINGH: But what about the blood transfusion? I mean, is there a study demonstrating, because I think that's what's germane to this discussion, and I know that there may be hundreds of studies about the effect of panel reactivity on transplant outcomes, but using that criteria, is there anything in that analysis of your -- I mean, you made a very specific statement, that there were studies that should have been included in that analysis. So therefore, using their criteria for selecting these studies, did they perform an inadequate analysis that questions the validity of the analysis and impact their conclusion, using their criteria, not other criteria?

DR. GOODMAN: Okay.

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DR. KEWALRAMANI: You know, I suppose it's a fair question. I don't know how to answer that question but to say when you look at the body of evidence, and you can see in the briefing book that we provided, and you ask the question, are transfusions negatively impacting transplant outcomes, I don't see any other way that you can arrive at the answer except yes. And if you look at the data that one would sift through, there are some studies that don't appear. It's difficult to comment very specifically on why they don't appear, and I don't want to hypothesize without knowing, but one search criteria that may have altered this is whether or not PRAs or an equivalent, panel reactive antibodies are used in the search criteria or not.

DR. SINGH: You're quibbling with the search criteria, I'm asking a much more specific question. Using their search criteria, if you use their search criteria, did they leave out studies that should have been in that? Because arguably, their document would be less valid if they used search criteria and then omitted a dozen or two dozen studies from the analysis.

Now you may quibble with the search criteria, that's a different matter, you may question the design of their study. But using their design, was there a problem in terms of omission.

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DR. GOODMAN: I would appreciate a brief answer to that. It's kind of getting to where the flow of the

discussion here is quite clear, if you can provide as brief answer as possible.
DR. KEWALRAMANI: Sure. What I can say very clearly without any hesitation is that there are studies that are relevant to this discussion, which is complex, that have not been included.
DR. GOODMAN: Thank you very much. Dr. Singh, your point is very well taken. I might suggest to the AmGen team that in order to back up or try to verify the earlier assertion, it would be an excellent exercise to apply the TA's inclusion and exclusion criteria to the body of literature and see if that assertion still holds up. Dr. Singh, your point is well taken. Thank you, Dr. Kewalramani, for your on-the-point response. Dr. Holmberg, I believe.
DR. HOLMBERG: I appreciate Dr. Singh raising the question, because that's what I was trying to get to, was the specific data related to the transfusion and the PRA. Clearly, unless I'm wrong, what's the scope of importance as far as causing the PRA to be elevated? You know, you mentioned pregnancy, the pre-transplants, already been transplanted, and then also transfusion. If you had to look, are there data out there to say what is

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the significance? I guess what I've heard and the data that has been presented, it sounds like those individuals that have been transplanted several times have a much higher PRA than others, but can you give us sort of a priority of what is the significance there as far as causing an increase in PRA?
DR. GOODMAN: Dr. Holmberg, of whom are you asking that?
DR. HOLMBERG: Dr. Kewalramani.
DR. GOODMAN: Okay. Is this pursuant to the three or four main reasons given why there was a concern about the TA?
DR. HOLMBERG: Well, yes, because they claim those articles weren't included, those references were not included.
DR. GOODMAN: Okay, thank you. Dr. Kewalramani, would you briefly care to respond to that at this point?
DR. KEWALRAMANI: Just to make sure I answer the right question, the question is can one prioritize whether or not between transfusions, pregnancy and transplantation, where does this fall out? There is a review in the literature, I can get you the citation that's looked at this, and has pegged transfusions on that list of three as number two.
DR. GOODMAN: Okay, thank you. Let's move -- I

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don't see a question from the panel immediately at this point. I wanted to move next, unless somebody has -- Dr. Dmochowski, did you want to ask Dr. Cecka that?
DR. CECKA: I can answer the question at least

in part. 75 percent of patients who are on the list for retransplant are sensitized. About 25 to 30 percent of multiferous women are sensitized. Transfusions add to that a relatively small percentage, but it's focused on those groups, the multiferous or the ferous women, and the retransplanted patients, and there are four now, with other surgeries. So we see that you can be sensitized if you're a male who gets an ACL replacement. If you get surgery that involves infections and you're getting blood at the same time, that synergistically can cause sensitization, so that gives you sort of an idea of the hierarchy. Males are the least, untransfused males are the least sensitized, around two percent.

DR. GOODMAN: Does that help, Dr. Dmochowski?

DR. DMOCHOWSKI: Yes.

DR. GOODMAN: Dr. White, if you would, we just restated and clarified some of the concerns with regard to the technology assessment, and again, I'd remind you to address or critique those issues that pertain to our topics and questions for today.

DR. WHITE: Yeah. I guess the most important

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thing to keep in mind is that our technology assessment was meant to answer the key questions that we were given, not necessarily the key questions that you were given, so our literature search was devised to be able to answer these questions.

Time on dialysis was not an endpoint, time to transplant was not an endpoint that we evaluated. We didn't evaluate the impact of transfusion on PRA or the impact of PRA on outcomes as separate constructs. Rather, what we had in our search was a search looking at PRA in patients with transfusions and the impact on outcomes, so that's the data that we were presenting.

So, the other thing I want to say about potentially missing studies is that the studies that were quoted in the discussion, so here we're talking about Cecil 2009 and there's two of those. There's Opelz 2005, there's Opelz 2009, so of these four studies, they all come from a collaborative transplant study. We quoted Opelz 2007 because that was the one where patients were actually randomized to transfusion or no transfusion, and talked about outcome.

Let's talk about Cecil 2009 because it has exactly the same results, a republication of the results in Opelz 2005. What they found in that study of human immunology was that people with a PRA of zero versus a PRA

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of greater than ten percent, that if you had one at zero you had higher graft survival, 72.4 versus 63.3 percent, and that was a significant finding. If your PRA was greater than 50 percent it went down subsequently to 55.5 percent. However, they say we cannot discern that graft loss was a direct effect of non-HLA humeral sensitization,

or whether PRA serves merely as an indicator of heightened immunity against non-HLA antigens.
So for Opelz 2009, what they ended up showing was that a positive crossmatch was associated with significant decreases in graft survival in first kidney transplants from 1990 to 1999, but not from the year 2000 to 2007 time period. But it said in kidney retransplants, regardless of the transplant period, that positive crossmatches were associated with significant decreases in kidney and heart transplant survival, so that they're looking at two different types of survival, even though it looks like the data for kidney was in kidney transplants and there was no one who had a kidney and a heart transplant being included.
In the Cecil 2009 there's another publication from the same study, and they showed that patients who are positive for both Class I and Class II HLA antibodies had poorer two-year graft survivals versus people with no HLA antibodies. So if you had no HLA, then it was 87.5

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percent survival versus 76.5 percent survival, and that was significant. However, if you only had Class I, it was similar, 82.7 versus 87.5, not significantly different.
DR. GOODMAN: Dr. White, just to kind of cut to the chase here, the main point you're making by assessing these articles is what?
DR. WHITE: The main point is they do provide useful information if you're interested in the link between PRA and outcomes, but that their link is a bit more complicated than saying that data is irrefutable, and these studies would not have made it into our technology assessment because they would not have met our inclusion and exclusion criteria, and some of those studies would have had to have been down, even if they had made the criteria, because they are reproducing the same exact data set multiple times. You can't say that there's seven studies that show something, if six of the seven are the same exact study published seven times.
DR. GOODMAN: That point is well taken. Do you have further points to make with regard to the earlier claim?
DR. WHITE: No. I think the big difference is just a difference that may be important for you but can't be answered by our technology assessment, what is the impact of being sensitized and not getting a transplant on

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outcomes? That's not something that we were charged with assessing and not something that we did assess.
DR. GOODMAN: Thank you. Now, panel, just to remind all of us, I guess, is that the TA holds in common with our questions the concern for health outcomes, patient outcomes, whether it's the first two questions having to do with PRAs and transplant graft survival, or the middle two that have to do with transfusion and graft

survival, or the last set of two that have to do with ESAs and transplant graft survival, that is the outcome that CMS charged us with investigating. Indeed, we're not asked to look at time on dialysis or time on transplant, or some of the other interesting sorts of intermediate outcomes that might be of interest. Those intermediate outcomes may be of interest to the various stakeholders, they may have some indirect relevance here, but the focus on the TA that is shared with our questions is on renal transplant graft survival, and that may help to explain why some studies that may have otherwise been interesting may not have shown up in the TA.

DR. WHITE: The good thing about the TA program is that the TA is going to be available for public comment starting tomorrow, so if you think there are studies that we're missing or if you have other comments, it's available for public comments starting tomorrow.

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DR. GOODMAN: Okay. So Dr. White, you've got no further comments in response to the concerns stated earlier?

DR. WHITE: No.

DR. GOODMAN: Not at this point. I hope you will remain ready to continue to respond. Before we go any further, I see Dr. Kewalramani wants to say something, but any further points to be made at this time? Dr. Grammer, you did you have a point you wanted to make?

DR. GRAMMER: No.

DR. GOODMAN: Anybody at this point? Dr. Singh.

DR. SINGH: The studies that Dr. Kewalramani cited in her presentation, study 8701, which was a study of hemodialysis patients which was unpublished, would that unpublished study have made it into the TA?

DR. WHITE: No, because we have to be able to have an update to be able to assess it.

DR. SINGH: So the question I would ask is if there are unpublished data out there, which has been there for years since they were part of the registration program for ESAs, you know, ESAs were introduced in the '80s, why has those data, if it's so compelling, not been published.

DR. GOODMAN: Was that a question directed to anyone in particular, Dr. Singh, and if so, to whom?

DR. SINGH: Dr. Kewalramani.

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DR. GOODMAN: Welcome, Dr. Kewalramani.

DR. KEWALRAMANI: Thank you. I want to go back two questions to a question Dr. Singh asked. There's a graph he may want to look at, I think it addresses his question.

DR. GOODMAN: I'll make a deal with you. If you answer his question ultimately, I will let you go back to those two. Go right ahead.

DR. KEWALRAMANI: Okay. I'll try to do it in the order that I'm remembering things.

DR. SINGH: Why is 8701 not published yet when the data have been around 20-plus years?
DR. KEWALRAMANI: You're absolutely right. 8701 is one of the original pivotal registrational studies filed to the FDA for the approval of Epogen, and I think the reason it's actually not published is simply because it was the smaller of a group of studies that came out at the same time. So recognizing that that might have been a concern for one of our speakers, I brought for you the Phase Three larger study.
DR. GOODMAN: Dr. Kewalramani, for the record, just handed the Phase Three study to Dr. Singh.
DR. KEWALRAMANI: The 8701 study is a smaller study. This study, published in the New England Journal of Medicine in the late '80s is the larger of the series

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of studies that were done around the time of registration. Going back to the point that you had --
DR. GOODMAN: Dr. Kewalramani, sorry to interrupt, but the study that you just handed to us, does that represent a subset of the same, or yet a different set of patients?
DR. KEWALRAMANI: Sorry. So just not to confuse, this actually has nothing to do with the question about transfusions and transplantation, it has to do with transfusion reduction with ESA therapy. It's a different study than 8701, which was a smaller study that was just not published because it was the smaller of the experiences, this is the larger of the experiences, but it's not related to the transfusion transplant question.
DR. GOODMAN: I didn't think so, but thank you.
DR. KEWALRAMANI: Yes. I just want to make sure I go back to Dr. Singh's question. And Dr. Singh, the other question you asked, you may find the answer to that on page 74 of 290 in the AmGen briefing book, Appendix A. This relates to number of transfusions by PRA levels on graft survival.
And then the last point I just wanted to make is I very much appreciate the additional clarification about the tech assessment, what goes in is what you get out, and I think that the one thing I would urge CMS to do is to

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maybe continue to work with this group to ensure that the foundational principle that we're talking about is sensitization. That's what we're talking about. Transfusions have their untoward effects on transplants because of sensitization, that's what it is, and I think we need to make sure patients, we make sure that transplant outcomes include three things, and you can't do it otherwise. One, graft survival. Two, time on the wait list. And three, whether you ever get a graft or not. They go together, we can't separate these, and the tech assessment sounds like they would be able to do this if they had the questions that are sort of addressed for them

in that way.
DR. SINGH: Did we get a briefing book on AmGen? I don't think we did.
DR. GOODMAN: Was that included in the big mail-out we got, Maria Ellis? You may want to check.
DR. STEINBROOK: A point of clarification. Are we referring to the comments from AmGen which were in the public comments which we got, or something else?
DR. GOODMAN: Let's take one question at a time. Was the AmGen submission included in our big thing? I know that the presentation was, that we saw today.
MS. ELLIS: All comments that were submitted were given to the panel members, including the thick one.

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DR. GOODMAN: The Power Point is included in the bound volume as well. Thank you, Dr. Kewalramani.
DR. KEWALRAMANI: Okay.
DR. GOODMAN: Okay. I guess Dr. Stroncek, yes, sir.
DR. STRONCEK: This may not be the right time to ask this, but getting to question five and six, and then a comment that Dr. Kewalramani just made, she commented that ESAs improve renal graft survival, or at least that's what she implied, but I haven't seen any data on that. I see that erythropoietin decreases transfusions, and we've seen things about erythropoietin and heart disease, but I'm not aware of a study that directly shows in a controlled study or prospective study that EPO improves transplant survival. Am I missing something?
DR. GOODMAN: You may not be missing something, that has been observed by others. We will get to questions five and six. I will just posit that that's not an insignificant point that you're raising. And Ms. Ellis does remind me that the aforementioned submission by AmGen is included in one of our very thick phone book-like volumes, along with the Power Point slides that we saw earlier.
MS. ELLIS: It's in the one that's labeled January 19, 2011 public comment, so it's in there.

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DR. GOODMAN: And it's a narrative sort of thing as opposed to a Power Point thing. Okay. I want to continue, before proceeding on this vein of potential concerns with the TA, several of which have been mentioned earlier when discussing those, and I think Dr. Mintzer has a point. Dr. Mintzer, on these?
DR. MINTZER: Not specifically on the TA.
DR. GOODMAN: Oh, okay. Anything else about, concerns about the TA, studies, time on wait list, et cetera, including access, incomplete analysis of the literature? Dr. Kewalramani made some assertions, we had discussion, Dr. White made some responses, we had some further discussion. Anything else on that? Okay. I just want to, if Dr. Koller wouldn't mind, and

I did want to ask about this, some assertions were made about the potential weaknesses in the CMS presentation, and I wanted to give you the opportunity at this point if you want to do it now, if you wanted to respond to and make some clarifications along these lines. Would you like another few minutes for us to come back to you?
DR. KOLLER: You know, I don't actually -- If someone has a point, I can respond to it.
DR. GOODMAN: So Dr. Koller is saying that if someone has a particular question for her, she will be glad to respond, and she's ready to do that if necessary.

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What I would like to do now, if it's okay with the panel, I know we've got a set of tough questions to start looking at, we've got to answer them by 4:30. I would like to start question one and have a discussion about that. So we're still free to discuss among ourselves, publicly ask questions of our presenters, but I want to start getting focused in on these questions. Did Dr. Paul have a question?
DR. PAUL: That's all right. I was just thinking about your comment to Dr. Koller. I would like to ask Dr. Koller about the German study that she quoted. What was the cohort of patients in that German study referred to, and was it acute bleeding or chronic bleeding?
DR. KOLLER: As I indicated, this was actually, it's basically the equivalent of a Cochrane review, and we made these citations because the original article was published in German. It has been accepted by the European Alliance and it reflects a meta-analysis of transfusions that were performed typically in a hospital setting. We used this data to basically say what do we know about physiologic requirements for transfusion and for anemia management, and if we don't know, do we know if people have to have immediate management if their hemoglobin is at this level or at this level, and this is the most

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recent and comprehensive meta-analysis, and that's why we presented it. We can provide you with the rest of the data. The material that we provided you with was basically a summary statement from the European Alliance.
DR. PAUL: So just for clarification, it was acute bleeding in a hospital setting?
DR. KOLLER: It was primarily directed at use of transfusions in an acute care setting, it wasn't necessarily for bleeding per se. It reflects a variety of studies and as I was trying to indicate, we have a certain amount of data that we know about, but althouhh we have much data, we have areas in which we do not know much about. I triec to lay out what was known and there is quite a bit of material that is not actually known about requirements for anemia management, what are the physiologic requirements, et cetera, in a chronic care setting. We outlined what we

do know, and therefore, we can help identify what the gaps are.
We end up then getting into issues if we do not in fact know what levels at which anemia needs to be managed in the chronic setting, when do we transfuse, where do we set our treatment threshold? What we do know from the acute care setting is that those patients who have issues with cardiac decompensation, that those people need somewhat different management than do other kinds of
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patients.
DR. GOODMAN: Sorry to interject, but Dr. Paul, did that answer your question? Good. Thank you, Dr. Koller.
Dr. Carson, do keep in mind that we'll call you to the microphone, because our court reporter can't account for your comments away from the mike. Before I move on, did I see Dr. Leffell's hand up earlier? Dr. Leffell, did you have a point you wanted to make? If you do, do come to the mike, and I'm sorry I missed you earlier. If we're past the point, then you need not do this.
DR. LEFFELL: I just wanted to raise one quick point about the study data. It is true that there is a large body of data. The specific study in 2009 is a subset of patients where the antibodies were determined by more sensitive techniques, showing that even low levels of antibodies can have adverse impacts.
DR. GOODMAN: So it was a subset of patients.
DR. LEFFELL: Yes.
DR. GOODMAN: Thank you very much, Dr. Leffell, sorry I missed you earlier. Dr. Mintzer was next, yes, sir, and into the microphone.
DR. MINTZER: I know our chairman wants us to keep on point and I don't mean to get off point, but this
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is a critical question for me, and I would ask this question of Dr. Becker or Dr. Chertow, one of the practicing nephrologists. If we're interested in the utilization of erythropoietin with patients with renal failure, let's say we had incontrovertible evidence that erythropoietin did not affect renal allograft survival, let's say we just knew that, and the only way I think we would know that is with a randomized prospective trial, which we don't have. But let's say that there was clear evidence that there was no benefit. Would that change the utilization of erythropoietin in our predialysis and dialysis patients one iota? Because I think that's relevant to what we're looking at here today, is this specific subset of patients who are potentially transplant candidates, but before we get to that question, I want to know if we really knew that it didn't make a difference, whether it would affect the utilization in renal failure patients in general.

DR. GOODMAN: This is Dr. Becker at the microphone.
DR. BECKER: So then, that is an excellent question. The nephrology community has focused aggressively over the last decade on using Level I evidence to inform its therapeutic decisions. This patient population that we are discussing, as you have

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heard, has several features that, I might dispute the idea we can have the critical path. These are event diagrams and not a linear effect of events and care delivery. So whether or not we would remove erythropoietin or ESAs from our therapeutic armamentarium for those patients if there was incontrovertible evidence it did not improve allograft outcomes alone is a question that we have to ask additional questions about. Are there data that it's beneficial to the dialysis population in some way differently, i.e., we talked about PRA? Are there ways that it will help in maintaining the hemoglobin to a certain level that seems to offset negative outcomes? That would be an important consideration, and that type of evidence continues to inform our decision-making there. So I don't believe that the incontrovertible finding, if it were ever to be determined that ESA use does not affect graft outcomes, would necessarily change immediately practice with dialysis patients without a recap or look at that evidence in that group of patients.
DR. GOODMAN: Thank you, Dr. Becker. Dr. Mintzer, did you get the answer to your question, and if so, what do you conclude about it?
DR. MINTZER: I'm not sure I got it completely. My perception is that for most practicing hematologists and erythropoietin patients for now many years is

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principally it's a quality of life endpoint for most patients, to avoid the negative effects of transfusions. And so at least my perception would be if it had no impact on allograft, we should tear up the guidelines and shoot for 10 to 12, and it's not clear to me if a darned thing would change in the utilization of the EPO, and that's what I want to hear from the nephrologists that are treating this population.
DR. GOODMAN: That's a point well made. I trust that you think that that's relevant to our questions, and it might be relevant to questions five and six, I believe. Did you want to continue to pursue that point now, Dr. Mintzer?
DR. MINTZER: Did he have another viewpoint?
DR. GOODMAN: Dr. Chertow, would you address that point?
DR. CHERTOW: Thank you. I will answer your question briskly with a no, I know of no evidence that ESA therapy directly influences allograft function, but it's impossible to disentangle the effects of ESA on

transfusion and the sensitization issue, so there is no direct evidence. The answer to your question is no, but the issues are dramatically relevant because of the entanglement of transfusion and sensitization.

DR. GOODMAN: Thank you, Dr. Chertow. I need to

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add here that this observation is not confined to our particular set of topics today. This is yet another instance where we're looking at some kind of intermediate outcome or measure pursuant to some outcome we care about, which in this case is transplant graft survival, and in this particular case at a very high level, there's some clinical or medical thing going on, and there's a policy thing going on with regard to sensitization so far as PRA might be used to make a decision of where one sits on a transplant list. So your point is very well taken and I'm glad you raised it with regard to where there is evidence or not about the direct relationship between ESAs and transplant graft survival, and I appreciate the responses that we just heard.

It looks like, this is Dr. Von Hartitzsch. Do you have a good answer for us?

DR. VON HARTITZSCH: This is an abstract from the renal meeting at Denver. It's from a group of transplant surgeons in France, and they did a controlled trial of high hemoglobins post-transplant versus the normal range, and the people in the high treatment group have a stable renal function. People in the lower group, 10 to 12, they progress to loss of graft.

DR. GOODMAN: Thank you, Doctor. You can just leave that with me, if you like, or leave it with Ms.

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Ellis, and we look forward to the time that that abstract undergoes peer review and is or is not accepted for publication in that peer reviewed journal. Dr. Mintzer, I hope that was helpful.

What we would like to do now, panel, is as follows. We've got our eight questions to deal with here and as I suggested earlier, they come in pairs. So if there's no objection, what we would like to do at this point is discuss the first two, which concern the availability of the evidence and what you think the evidence says regarding the relationship between PRA assays and transplant graft survival. So that's the issue on the table now, we can have some discussion from presenters, and we may in fact vote on it. I just want to point out again, and I'm sorry for all the bureaucratic talk here, but if you look on your question sheet under number two there's a set of discussion questions, A, B and C, and I think rather than waiting until after we vote on question two, let's have those discussions prior to the vote.

So I would like to pursue now, if there's no objections, discussion of questions one and two, they're

actually linked, if you don't mind, and we'll start with Dr. Satya-Murti.

DR. SATYA-MURTI: As someone outside of the

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specialty, what I really want to ask our presenters and panelists, particularly Dr. Cecka is, we really should not be looking at PRA and CPRA in the same league. CPRAs are your newer assessment tools and they are going to modify many of the results of graft survival because they're a lot more specific. And is the point of discussing PRA moot anymore, or should it also include CPRA, if they are qualitatively so different?

DR. CECKA: The measures are not so different. In fact, as I pointed out, the original panel reactive antibody was a way of assessing what frequency of donors would be excluded for a patient. You measure against a random panel of donors that represent potential donors and you estimate how many of those are going to be incompatible with that patient, that is the PRA. The fact that that PRA can be measured in different ways affects small differences in the percent of PRA, and the evolution of these tests as we appreciated the complexity of the HLA system, panels were selected to represent all of the HLA antigens, some of which are common, some of which are rare. In order to accommodate the rare antigens, the more common antigens had to be deemphasized, so the PRA became a slightly unbalanced system, but still basically gave you the estimate of how many, what percent of donors would be incompatible.

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So the idea of PRA and CPRA are the same. It's just small technical differences, and the precision of the CPRA is much better. The sensitivity of the tests that are used mainly for the studies of survival, because you have to have a certain amount of follow-up time, tend to be the less sensitive tests, so you're underestimating sensitization in those settings.

DR. GOODMAN: Thank you, Dr. Cecka. Just a reminder to all. What we really want to pursue now as to PRA assays' ability to predict renal transplant graft survival, we care first about the adequacy of the evidence and then we're going to want to know how confident we are that they actually do predict renal transplant graft survival, okay? So let's try to keep on those issues with this discussion. I believe Dr. Klein was next. Dr. Klein?

DR. KLEIN: Yes. I guess it's for Dr. Cecka, perhaps Dr. Becker or Dr. Leffell. When you look at these panel reactive antibodies, you present it as essentially a percentage score and that's an estimate of the percentage of compatible donors. But then you're also typing, because you're providing a specific antibody profile which you're then using in a virtual crossmatch, is that correct? And that's current practice, is to do a virtual

crossmatch and then you'll go and do a regular crossmatch?

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Okay.

I guess what I'm trying to understand when we have question one, and it says how confident are you that there's adequate evidence to determine whether or not current PRA assays predict graft survival, to me that suggests, it's dependent upon how the test is used, and if you're using it as a screen in order to predict crossmatch, and we believe that crossmatch matters, then I would logically infer that there's at least some evidence without a direct study, and so I would like your comment on that, because I'm trying to analytically understand.

DR. GOODMAN: This is Dr. Cecka at the mike.

DR. CECKA: Well, I think that your question goes to an essential bit of missing data. In the time when the transfusion effect was identified, and even up until recently, we focused on the patients who got transplants. The problem is that a lot of the patients who get sensitized do not get transplants. And now when you look at patient survival on the wait list, you see that it's much lower, and that has been presented in several of the comments this morning, than it is if you get a transplant. So if you had taken a much more global view of the patient population and looked at survival according to sensitization, you would get a different result, and this is what I brought up in explaining the

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transfusion thing, is that what you really did was you didn't transplant patients that had a high risk of graft rejection if they were transfusion respondent because they made these antibodies and were excluded. If you didn't transfuse them, there was a percentage of them who would respond to the transplant instead of to the transfusion and would fail.

DR. KLEIN: So in the patients in whom you're using this as a screen for whom you could find a match, it should be predictive of graft survival. Is there any data to show that?

DR. CECKA: Yes. I would say that survival rates of sensitized patients are increasing since the introduction of these solid phase tests that give us a much more precise measure of the low level antibodies, and they're very specific. So if you're able to avoid these antibodies you get a much better outcome, but you're also excluding more patients from the option.

DR. KLEIN: Thank you. Very helpful.

DR. GOODMAN: Dr. Singh is next. Thank you for your question, Dr. Klein.

DR. SINGH: I would like to just invite Dr. Harmon to answer a question pertaining to this question one. If one took, let's say an unsensitized patient, a male patient not sensitized, and administered a

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blood transfusion, I wanted to ask you your thoughts, synthesizing the data that's been presented as well as your own experience, what are the chances that this sensitized patient, what degree of panel reactivity would this patient develop on average, or would you expect this patient to develop?

And then secondly, in the modern era where we not only have the availability of three different immunosuppressive agents, but also strategies to try to deal with sensitization, what clinical impact would this panel reactivity, in your view, have on graft survival?

DR. HARMON: Thank you very much for that question. The first question I think is best answered with the old studies of donor-specific transfusions in which you took patients and specifically transfused them with blood from the particular donor, and 30 percent of them became sensitized to that donor, and most importantly, didn't get a transplant from that donor, so you can't talk about their transplant outcome, they just didn't get a transplant. So the chance of three transfusions sensitizing somebody, if you look at it in a global sense, is about 30 percent.

What is true is that all the patients are different, so there are patients in whom you can give ten transfusions and they never become sensitized, and that

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may be the transfusion effect, that it identifies those people who have low level immune response who eventually get transplanted because they're not sensitized, and therefore they do better. So there's no specific answer, if I transfused you today, what you would do, because it depends on your immune response to it.

The second question was?

DR. SINGH: The second question is, in the modern era of immunosuppressive regimens coupled with the strategies such as rituximab and plasmapheresis and other things, how impactful is this on graft survival, because that's a question. Supposing, I think the issue in question one is, how would it predict renal transplant graft survival, so what's the impact of this, clinical impact? If you are sensitized and you get an organ and you're able to do something about it, can you continue to survive?

DR. HARMON: If you're sensitized to the particular donor, and we see this when we do these desensitization protocols now that you saw mentioned there. These are typically living donors, because you can't try to desensitize somebody and then wait for them to get a kidney on the waiting list, because they'd lose their benefit on the waiting list of being sensitized as soon as you desensitize them. So if you take a patient

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and you desensitize them to a specific living donor, their likelihood of acute rejection is double or triple what it

is in an unsensitized patient, and their graft survival is less.
So we can successfully transplant them. If our only goal is to transplant them, there should be a terrific opportunity, using pheresis and rituximab and IVIG, and all the things we do to desensitize them. But if our goal is to have five-year graft survival, it's not as good. Some still do well, but most of them have more trouble if they're desensitized.
DR. SINGH: So among patients who develop panel reactivity, graft survival is impacted, even in the modern era?
DR. HARMON: Yes, absolutely.
DR. GOODMAN: Thank you, Dr. Singh. Is that Dr. Stroncek at the very end?
DR. STRONCEK: My understanding of the panel reactive antigens is there's two issues. One is based on 50 percent reactive, the choice is to get a transplant that doesn't express the antigen those antibodies react to. And then my interpretation of the data is when you give an organ from an antigen negative person, the transplant survival may be as good, but the data suggests it's slightly reduced for, I'm not sure what reason, is it

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just empiric data?
And then the other issue, though, is definitely if a person has 80 percent PRA, or a hundred percent, and you can't find an organ that doesn't, obviously then you can't find an organ that doesn't express that antigen, then, you know, you're transplanting across this crossmatch positive barrier, and then you have to desensitize the patient, and the outcomes are much worse.
DR. GOODMAN: That's very helpful. Other questions on the PRA transplant survival relationship? Dr. Samson is next.
MR. SAMSON: I would like to direct this to Dr. White at the EPC. According to the TA, the grade of evidence is low or insufficient for basically all of the conclusions, and that was basically pooling all of the studies across different levels of risk of bias. And I was just curious. If you simply segregate the studies that were of higher quality, the controlled trials and the observational studies that were done well, is there some pattern of results that leaps out at you?
DR. WHITE: Yeah. There were five good quality trials. Let me tell you what the largest two had, we pulled them out and looked at them over lunch. One is the Opelz 1997 study, it was a randomized controlled clinical trial, 423 patients, so that's the largest clinical trial

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data set that we have. People were randomized to three transfusions or no transfusions, and in that study graft survival over five years was better in the patients who received transfusions, 79 percent versus 70 percent, the P

value was .025. They then did multivariate analysis and found that getting a transplant was an independent predictor of graft survival.

The second study was a study by Alexander, and this study was specific to donor-specific transfusions and this had 212 people in it, so that was the second largest. No difference in graft survival for up to two years, 91.8 percent versus 92.0 percent, the P being not significant. The other trials, there was one with 110 people, one with 106, and one with 30, and we haven't been able to go back and pull out the information in sufficient detail to be able to tell you exactly what they showed. Our general assessment is that these good quality trials are not showing anything outside of what the individual trials have shown of lesser quality. There were some clinical trials in answering Question 2.B, and those trials had fair quality, they were fair quality, they were not randomized trials. One was -- actually, there was one controlled clinical trial when you look at rejection only. That same trial also had data for graft survival, and the results of the Al Grexton study, which

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was a controlled clinical trial, but not randomized. The incidence of rejection episodes was not significantly increased in the PRA greater than ten group in comparison with the PRA less than ten group. Al Grexton in 1987 looking at graft survival, graft survival was significantly better for PRA less than ten at one year, and then there was nothing for patient survival, so all the others were randomized observational studies. But in multivariate analyses, there was a trial in the New England Journal of Medicine --

DR. GOODMAN: Dr. White, I have to interrupt you. Just randomized observational trials?

DR. WHITE: No. The one in the New England Journal was also a controlled clinical trial, and they looked at an extensive number of variables, generally well done, looking at multivariate analyses, and what they found was that if your PRA was greater than 10 percent, that there was no significant impact on patient death, but there was a significant increase in graft loss. If your highest PRA -- and that's current PRA. If your highest PRA was greater than 50 percent, then they showed nonsignificant effects, so both trending toward an increased risk if you had a higher PRA, it was 1.15 and 1.45, so those were not significant.

DR. GOODMAN: So what's the wrap on that?

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DR. WHITE: The wrap is that good quality trials seem to be in line with trials of lesser quality in terms of what they were showing, but there were three smaller controlled clinical trials for which I don't have specific information on what they were showing.

DR. GOODMAN: Thank you. Dr. Klein. I

apologize. Dr. Holmberg, and then Dr. Klein.
DR. HOLMBERG: This is a question for Dr. Cecka. I'm trying to get my hands around the CPRA, and if I understand the calculated correctly, it's basically the identification of the antigen and then the determination of the frequency of the antigen in the population; is that correct?
DR. CECKA: Yes, that's correct.
DR. HOLMBERG: Then my next question is, why did UNOS move to the calculated in 2009, and has the calculated PRA been validated?
DR. CECKA: The reason for the change was that in the allocation algorithm, you see that's the point of having a high PRA, 80 percent or above, that gives you a slight advantage over other patients who are otherwise similar to you on the waiting list because of the fact that you're going to have a lot of incompatible donors. Now the change was to add accountability. In order to calculate a PRA, you have to tell UNOS what HLA antigens

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you will not accept in a donor, so you are preemptively declining offers from donors who have an A2, for example, if the patient has an antibody against A2, you will not be offered the kidneys from that patient.
So in the old days you could say you had a PRA of 80 percent but you could still do a final crossmatch, because you would get an offer from all the donors. So you might have exaggerated the PRA and gave the transplanted patients without regard to that percentage of PRA. So now it's absolutely accountable; you're actually preemptively declining offers from those donors that have the antigens that constitute that calculated PRA.
And the calculation, as I showed you, was based on the frequency of the antigen, so A2 is most common, 50 percent of people have that, and they go down to .001 percent of the population, so each antigen that you add in there adds something to this calculated PRA.
DR. GOODMAN: Thank you. Dr. Holmberg, what do you take from that?
DR. HOLMBERG: Well, I take that, you know, it's less than a perfect system, and it's one way to make sure that the players are playing correctly.
DR. GOODMAN: Thank you, Dr. Cecka. Dr. Harmon, did you have a comment on this question? And Dr. Leffell, if you do, you will be next, if you don't mind.

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DR. HARMON: I didn't tell you that I sat on the board for three terms at UNOS and was aware of the reasons for these changes. A significant part of the reason has nothing to do with graft outcome, it has to do with the efficiency of allocating the organs. So that with many potential recipients there, if you have to do the crossmatches, the final determination is the crossmatch, on 20 different people, and you find out that 19 have a

positive crossmatch, you've spent a long time with the organ removed from the recipient, from the donor before you transplant it. So the point is to predetermine which people are going to have a positive crossmatch, and therefore you can allocate the organs more quickly. And nowadays, we can allocate the organs even before the grafts have been removed from the donors.

DR. GOODMAN: Thank you, Dr. Harmon, that was especially helpful. Dr. Leffell.

DR. LEFFELL: I wanted to address your second question, and that was in terms of whether or not the CPRA was validated. CPRA is based on a published algorithm that's based on basic fundamental principles of population genetics. CPRA is in fact much more accurate than PRA. We can account for antibodies to both types of HLA antigens, whereas the traditional PRA had to be either Class I or Class II. And it's consistent across the

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country, which was the other reason for using the same frequency for crossmatching, so everybody has the same definition of sensitization.

DR. GOODMAN: Dr. Leffell, if you wouldn't mind sitting next to Dr. Koller, because we're going to call on you in a moment for the next question.

We want to keep moving ahead here, and I want to ask Drs. Leffell, Chertow and Harmon to help us answer the following questions. I'm happy with our discussion questions, I really appreciate the previous answers. On discussion question 2.A, which is, how do PRA assays relate to more specific tests for HLA sensitivity, and whether titer levels predict specific organ HLA sensitivity? What I really want to know is how does PRA stack up against some of these other tests for sensitivity? I know, Dr. White, your slides 38 to 40 addressed this. So I want to know about how PRA stacks up vis-a-vis these other tests.

The second one has to do with various proprietary PRA assays. Are these clinically interchangeable or are they different, okay? Those are the proprietary PRAs.

And then the third one has to do with whether current PRA assays provide the same clinical information as the old assays? And I think this was addressed before,

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with the issue of historical data on PRA performance and how it applies to currently available assays.

So these are these three discussion questions, how do PRAs stack up with regard to these more specific tests for HLA sensitivity, are various proprietary assays clinically interchangeable, yes-no, and do the current PRA assays provide the same clinical information as was the case, does that information, historical information apply to currently available assays, in other words, is the assay still up to date? So Dr. Leffell, if you want to

start, and then followed by Dr. Chertow and Dr. Harmon, and Dr. White, unless anybody else has what they believe to be better answers. Dr. Leffell.

DR. LEFFELL: The current CPRA, I just said, is more accurate than the older PRA, so in that sense they are not comparable, the CPRA is more accurate. Determination of PRA is dependent upon the type of assay used and the panel that's used. In the old days we used cell panels, today we're using purified HLA antigens, but the different panels made by different manufacturers do differ somewhat. However, when you define an antibody and list that as an unacceptable antigen and then calculate its CPRA, you're on a consistent basis.

So the third comment I would address is current assays, and the use of CPRAs give a better true estimation

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of sensitization. PRA, the older PRA detected certain levels of sensitization, but I believe Dr. Cecka pointed out, it overestimates sensitization, because our current assays are much more highly sensitive.

DR. GOODMAN: Current assays are more sensitive, highly more sensitive. Thank you, that's very helpful. I wanted to hear as well from Drs. Chertow, Harmon and White on these issues, and I don't mean to exclude anyone, I just want to get concise answers to these questions. Dr. Chertow.

DR. CHERTOW: I wonder whether you might have wished for Dr. Becker to speak rather than myself.

DR. GOODMAN: We'll get to him, but I thought you might have a clinical perspective.

DR. CHERTOW: My clinical practice is the care of patients with chronic kidney disease, I spend much less of my time caring for transplant recipients. My understanding of the sensitivity of the CPRA as opposed to the traditional PRA is as Dr. Leffell stated.

DR. GOODMAN: Thank you, Dr. Chertow. I thought you might have a clinical perspective. Dr. Harmon.

DR. HARMON: I have a slightly different perspective. The newest tests are much more accurate and define specific antigens to which the patients are sensitized, and therefore give us the opportunity to avoid

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those donors. That's the critical issue.

DR. GOODMAN: That's very helpful. Dr. White, and then Dr. Becker, if you've got a good answer for those questions, we'll appreciate it.

DR. WHITE: I would agree that, with what people were saying up to this point. I don't have anything additional to add. I can reiterate what we talked about before, CDC seemed to have somewhat less correlation, ELISA versus ELISA seemed to have reasonable correlation, from what I have been able to see, correlation coefficients like 0.72 to 0.83. The only thing we found that was a little bit different was that one analysis

looked at patients specifically with graft failure and showed that the correlations that they have with each other is less, but still significantly correlated, than it was in patients when you just limit it to all comers, so it might not be as good correlation.
DR. GOODMAN: Good. Dr. Becker, anything to add?
DR. BECKER: I will add to Dr. Harmon's comment, it also makes it more difficult for us to find a donor, not just avoid donors, and that has therapeutic implications in the new sensitization protocols, which traditionally we would not have done so.
DR. GOODMAN: Thank you. Dr. Paul is next.

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DR. PAUL: I just wonder if those four gentlemen, or three gentlemen and one lady could expound upon the question asked in the third item, do current PRA assays provide the same clinical information as older assays? I deduce from the answers to the questions that the answer to that is no, but please elaborate. And secondly, what can we say about the historical data on the performance of the PRA assays as they apply to currently available assays? So could you expand on your answers with regard to those?
DR. GOODMAN: We don't need answers from all. If you've got an answer, we'd like to hear it. If you don't have an answer, you need not approach the microphone. I see Dr. Leffell rising out of her chair.
DR. LEFFELL: I think you have to remember that the historic data were determined with less sensitive tests, so therefore those studies that showed an adverse impact on graft survival were even more meaningful, because these were high levels of antibodies. So I think you can look at PRA and CPRA both as measures of sensitization. CPRA is more sensitive in defining more antibodies and in finding lower levels of antibodies. Current data suggests that even low levels of HLA-specific antibodies can be detrimental, and sensitization in general is a reflection of poor outcome that may be

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augmented or synergistically impacted by non-HLA-specific antibodies, including some autoantibodies that very highly sensitized patients are prone to make. Did that address your question?
DR. GOODMAN: Thank you, Dr. Leffell. Anyone else on those questions? Dr. Steinbrook.
DR. STEINBROOK: I want to ask a question of clarification, which is, in question one it refers to current PRA assays and predicting renal transplant graft survival. I may be confused and somebody can straighten me out, but it seems to me that the PRA source of assays are not really used at this point in terms of individual patients, and I'm wondering if what is meant by current PRA assays in terms of individual patients is the CPRA.

Can somebody clarify that for me?
DR. GOODMAN: Dr. Cecka, will you be able to answer that?
DR. CECKA: Yes, I think that's correct. In the old assays you couldn't identify specific HLA antigens for patients if they had not too many antibodies. I passed over a slide to show that, but once a patient made several antibodies, it becomes difficult to find all of them that they make, so you couldn't do those kinds of tests in the old days for the individual patient. Today you can, and it is very individual. What the PRA was used for in

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analyses of survival was to identify a population of patients who were sensitized. Now, that sensitization is on two levels, because as I think was mentioned earlier this morning in the TA analysis, you have to have T-cell stimulation in the immune system to get antibody, so if you had a T-cell and D-cell immunity, only the D-cell produces the antibody, but that means there's also underlying T-cell immunity.
Now in the old days before immunosuppression, those patients often failed because they had rejection that couldn't be managed with products available at the time. After the introduction of cyclosporin, many of those patients were manageable and survived.
DR. GOODMAN: Okay. I think Dr. Stroncek is next, and then Dr. Klein.
DR. STRONCEK: I have a question related to question 2.B about are the various PRA assays clinically interchangeable. Now the HLA antibody detection tests that labs are using, I agree, the new ones are very sensitive. But it's my understanding that they're so sensitive there may be a problem between laboratories on where the cutoff is for weak antibodies, and this has been a topic for the histocompatibility community deciding what to use for a cutoff, and then even comparability with some of the results of the assays between laboratories. I'm

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not saying that, my understanding is that the assays are really very good assays and they're better assays than they were in the past, but there still are some issues on comparability between laboratories.
DR. GOODMAN: So, that answer then is what, Dr. Stroncek?
DR. STRONCEK: Well, let's let them comment.
DR. GOODMAN: Okay. Dr. Cecka, you're up.
DR. CECKA: So, all 125 laboratories in the United States have to do proficiency testing, and in the old days with the assays that we had available, there was a lot of variability among labs. In fact, we rarely achieved consensus on what PRA meant, because people used different panels, they were using different techniques, and they were getting different answers.
Today there is almost a hundred percent

concordance among laboratories, at least for strong antibodies, the ones that would be identified by, for example these old tests, the cytotoxicity-based tests, everyone agrees on those antibodies. There are also very weak antibodies that people don't agree on, and these are still questionable. So if anything, the PRAs today may be somewhat broader than previously, because some labs don't include those weak antibodies.

DR. GOODMAN: Thank you, Dr. Cecka. Dr. Klein.

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DR. KLEIN: Yes. Just to follow up on this, so normally, so by increasing the, by changing the methodology and increasing the breadth, you're improving the lower level of detection and you're increasing the range of antibodies we can detect so you're analytically more sensitive. It's normal when you analyze a diagnostic test, you look at sensitivity and specificity through a receiver-operator curve. So, I guess what I would ask you folks is, if you have a sense of, to follow up on this question, for the loss in specificity based on clinical outcomes, for example, detection of clinically either, antibodies of either known or minor relevance, to what extent have the improved sensitivity of these tests decreased specificity, and are there data on this?

DR. GOODMAN: It looks like Dr. Leffell is coming up.

DR. LEFFELL: There are data, and one reason I rose to answer this question is there's been a recent paper, of whom the first author is Mike Cecka, showing the first data from the implementation of the CPRA showing in fact the transplantation of highly sensitized patients has been increased and the rate of false positive or, excuse me, specifically organ refusal due to positive crossmatches has decreased significantly. This is saying that we're doing a better job of defining HLA antibodies

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and that by this process we're able to transplant sensitized patients. And you're looking puzzled, so --

DR. KLEIN: I guess I'm wondering about the base of data. You're detecting some low level -- actually, in your own paper you mentioned this, and you're detecting low level antibodies that may or may not have clinical relevance, and I'm wondering how much investigation has been done into the relative significance. I mean, blood transfusions, for example, we know that there are low level antibodies that aren't clinically important, and of course there are some that can kill you. So this is really the question, is how well this has been investigated and if we can get a sense for whether there needs to be greater sensitization.

DR. LEFFELL: I think there certainly needs to be more investigation in this currently controversial topic, different centers have different cutoffs. At Hopkins we tend to have a very high cutoff because we have

a very active desensitization program, and so we will transplant at levels that other centers wouldn't. But again, I think the printed use of this is certainly working. As Dr. Cecka pointed out, we agree on very strong antibodies and avoid those.
DR. GOODMAN: Thank you, Dr. Leffell. Dr. Kewalramani, on this point?

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DR. KEWALRAMANI: Sometimes it helps to be able to bridge the immunology and transplant nephrology into the others to try to bring this point home. In trying to read and understand and put all of this literature together just to address your point very directly and follow on what was said, PRAs generally speaking are in the same ball park of what they're trying to tell us. They're trying to tell us that they're alloantibodies. CPRA is a more sensitive way to do this, and it increases organ efficiency. We don't have the same kind of data with CPRA that we do with the older PRA because it's just plain newer.
But what you would take away from this is because it's more sensitive, what one would find is that if you are transplanting and we fast forward to five years or ten years, the prediction would be that this sensitive assay would tell us even the low level antibodies would perhaps prevent it, but we don't have that just yet. But if you want to start just putting a few dots together, if you go back to the Opelz paper, and transplantation across HLA identical siblings, you can get a sense, because HLA antibodies should not even make a difference, but they do.
DR. KLEIN: So it's primarily pathophysiologic.
DR. GOODMAN: Thank you. Dr. Becker, and then Dr. Koller.

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DR. BECKER: One addition to that is a follow-up point which we haven't discussed, is actually in this context. Let's look at the patient populations transplanted between 2005 and 2009 when we had traditional PRAs before implementation more universally of CPRA. In center-specific studies the rates of antibody-related rejection tended to go up, and in center-specific studies when in particular there was now review of a donor-specific antibody or identification of it, or a review of the CPRA in some centers, there was now evidence that there was direct immunologic activity against the organ. That's a post hoc way of trying to demonstrate, I think, a little bit of what your question was going towards.
DR. GOODMAN: Thank you. Dr. Koller.
DR. KOLLER: I just wanted to address the question you had about clinical outcomes. The way the United States collects data is through the UNOS system, and that data is ultimately put into the USRDS data system. And if you actually go and look at how the data

are entered, you have to fill out a form before the transplant and then after the transplant, and in the forms prior to the transplant, the old forms which were before CPRA basically had a line for PRA, and it was sort of a drop-down menu, but it doesn't really say what assay did
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you use, these kind of important criteria that you want to actually have to make future assessments about particular assays and to make correlations.
And in addition, there is no information, or there is very little information on transfusions. The transfusion data is not collected in the initial transplant application form, it's only present in the transplant recipient form, and it's a line, and the line says did you receive, did the patient receive transfusion, that's it. There's no other material that go along with that.
DR. GOODMAN: So Dr. Koller, I think you're making a very good point. Could you just state, and this is important, what is your main point?
DR. KOLLER: What I'm trying to say is that when you're looking at how the various assays, old PRA, new variations on that, calculated PRA, how they relate to outcomes is not really going to be captured by our large system, and maybe with the calculated PRA it will be better with time, but this is relatively new, but you're not going to be able to make a correlation with something that's clinically important to us, which is to know what is the role of transfusions in sensitization, and in terms of ultimate outcomes, because those data are not collected in the system that we currently have.
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DR. GOODMAN: Very good points. Dr. Koller makes the very strong point that we're looking for something for which there are few data, at least systematic collection of data.
I want to proceed as follows. I'm conscious of the time, and I want to get some distilled opinions from the following four people in the following order. I want your input on the first two questions and I'm specifically going to call in the following order on Drs. Harmon, Cecka, Leffell and White, and I want to ask each of you essentially what our questions are, and I would like to get a distilled perspective on this. So Dr. Harmon, if you can be pretty brave and concise, our first question has to do with the adequacy of evidence, not what the evidence says, the adequacy of evidence of the relationship between PRA assays and how well they predict renal transplant graft survival in individuals. So PRA assays predictive of renal transplant graft survival in individuals, is there a strong body of evidence?
DR. HARMON: It's weak.
DR. GOODMAN: It's weak. If you look at that weak body of evidence, what would you say about the

ability of current PRA assays to in fact predict renal transplant graft survival in individuals, based on that weak body of evidence?

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DR. HARMON: I can tell you what we do.
DR. GOODMAN: Tell me what you think, if it has to be based on what you do, that's fine, but I would like a more global perspective if you could offer it.
DR. HARMON: Well, I'm involved with several NIH multicenter trials and we are trying to minimize immunosuppression and trying to identify low risk patients. Anyone who is more than five percent sensitized by the new assay is not considered a low risk patient.
DR. GOODMAN: Okay. It's not directly considered, but how predictive is it?
DR. HARMON: Well, that's the best we can do. We don't have a linear relationship that we can use. What we're predicting is that the patients who are more highly sensitized will do worse.
DR. GOODMAN: That's how you're interpreting that data?
DR. HARMON: Yes.
DR. GOODMAN: Dr. Cecka, same two questions, sir. How good is that body of evidence, and then what does that evidence say?
DR. CECKA: Well, I think that the question about the PRA, which is an estimate of frequency of donors that would be incompatible is weak, because we're not looking specifically at the donor. If you're looking

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specifically at the donor, there is very good evidence, 50 percent of patients with low levels of donor-specific antibodies develop transplant coagulopathy within the first three years and fail within the next five years, 50 percent, so it's very clear that the donor-specific antibody is what we care about.
The PRA is for allocation, that tells you how many donors are not going to be compatible, it's whether the patient has antibody against the donor that gets transplanted into.
DR. GOODMAN: And that is predictive.
DR. CECKA: That is absolutely very predictive, and is very patient-sensitive.
DR. GOODMAN: Thank you. Dr. Leffell, the same two questions, if you would.
DR. LEFFELL: If you look at the historic data based on the traditional PRA and ask the question, is that related to outcome, I think I would have to agree that the data on the whole are weak. The critical point is, as Dr. Cecka said, is there donor-specific antibody.
However, if you consider PRA simply as a measure, an indication of sensitization, and you consider the body of data, I think it's much more compelling, because there is increasing evidence that sensitization carries with it not

only HLA-specific antibodies, but other antibodies that
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may contribute to the chronic hemo nephropathy and even more acute or accelerated hemo rejection.
DR. GOODMAN: So the body of evidence you characterize as weak.
DR. LEFFELL: Based on the traditional PRA. But if you consider sensitization and its impacts on graft outcomes, then I think there is compelling data using both the old and current data.
DR. GOODMAN: Is that the old and current tests, the PRA assay?
DR. LEFFELL: The old data based on CDC and other methods, and then the current data, which is solid phase immunoassays.
DR. GOODMAN: Based on the PRA.
DR. LEFFELL: PRA or CPRA, as a measure of sensitization.
DR. GOODMAN: Thank you. Dr. White, you didn't look at exactly this question, but you looked most comprehensively at the literature. Those two questions, please.
DR. WHITE: For the first one, the strength of the body of evidence is weak. The second one seems more tangential to what we were doing, so I don't think that I can give you from a systematic review of the literature what our feelings are to the relation of elevated PRAs to
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outcome. But with the data that we do have, transfusion patients, their PRAs and outcomes, the data there would also be weak, but there's a body of evidence that we did not review.
DR. GOODMAN: Okay, thank you. We want to wrap these questions one and two up fairly quickly, we're going to go to the vote soon, so if you want to stoke up the gizmos that take our votes, I know that takes a couple of minutes, so you might want to do that now.
Dr. Satya-Murti.
DR. SATYA-MURTI: If this last question goes by you then, makes a split between the conventional and the new CPRA, if that were the question, if such divisions were acceptable, and I'm a reductionist, so I don't want to split the questions. So our question one and two should really address what is known with the PRA and not the CPRA. The prior question brought out the fact that the evidence strength category is not the same for the two of them, so we're only addressing the PRAs.
DR. GOODMAN: Dr. Steinbrook, then Dr. Klein, and then Dr. Holmberg, brief comments all.
DR. STEINBROOK: This is exactly responsive to that point. The question is how to interpret current PRA assays for the purpose of the vote. My view would be that current PRA assay equals CPRA, but I don't know whether
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that level of guidance is already provided.
DR. GOODMAN: I think that's a fair assumption. Does anybody quibble with that? That's the current version of the test. I believe Dr. Klein was next.
DR. KLEIN: I would make the comment that if you're talking about individual patients, I mean, you guys determine how we're supposed to determine this question. To me it says individual patients is a virtual crossmatch, so I would kind of like to understand what you're looking for out of us.
DR. GOODMAN: I'm interested in how the test is currently used. Dr. Leffell.
DR. LEFFELL: I think you're confusing, Dr. Klein, virtual crossmatch with CPRA. CPRA is a measure of the breadth of sensitization, the percentage of donors that would be incompatible.
DR. KLEIN: I understand that you're using, as Dr. Cecka pointed out, there's one purpose and that's allocation, and there's another purpose, and that is the screening test or crossmatch in order to more efficiently allocate organs. What I don't understand from my point of view to answer this question is whether or not I'm looking at the body of data for a PRA or a CPRA in terms of predictive outcomes, or whether I'm looking at an individual patient and the use in that specific patient as

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a predictor of crossmatching reactivity. That's kind of how I'm thinking.
DR. GOODMAN: This is in application two, the individual patients. We got that part.
DR. LEFFELL: The second part of your question, the current use of CPRA would exclude a patient from being considered with a donor, so on an individual level it's exclusive, but on a population level it speaks to the breadth of sensitization.
DR. KLEIN: Our question says individual.
DR. GOODMAN: That's our question. Dr. Cecka.
DR. CECKA: Maybe the answer is that these are all crossmatches, CPRA, everything is a crossmatch, they're surrogate crossmatches, you're using another population to identify whether somebody will not be transplanted with that donor or they will be. If the crossmatch is positive, you do not do that transplant. That's why it's hard to make the kind of assessment that I think you're trying to make, because you're looking for people who don't have antibodies against the donor.
DR. KLEIN: Right. But if you look at the totality of patients, and look at patients and I see that somebody has a certain antibody to a certain donor, the likelihood of rejection in that donor is probably extremely high, and so to me it's predictive in an

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individual patient, and that's kind of why I'm trying to frame the question.

DR. CECKA: Right. So it's because a patient who is sensitized, who has a PRA or a CPRA has demonstrated immune responsiveness. Someone who does not have a PRA, does not have antibodies, has not demonstrated immune response.
DR. GOODMAN: Okay. So Dr. Klein --
DR. KLEIN: And a proportion of patients will also reject.
DR. GOODMAN: Dr. Klein, in view of the response to your question, do you want to shed any further light on how we might interpret question two? What's your short answer?
DR. KLEIN: The way I interpret it is looking at individual patients, do you have exclusion, which probably has very high reliability, and then you have potential matching, which probably has lower reliability.
DR. GOODMAN: Dr. Mintzer, will you concur with that?
DR. MINTZER: Yes.
DR. GOODMAN: Dr. Dmochowski, views on that, does that sound about right to you?
DR. DMOCHOWSKI: Yes.
DR. GOODMAN: All right. I think we need to

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move to voting here on these first two questions. I understand that there's a little bit of ambiguity as there is always for some questions. The saving grace there, though, is that every word we said today is in the record, and CMS can go back and parse that for further elucidation.
So Ms. Ellis has I believe handed out little voting machines. Ms. Ellis, what great instructions do you have about using these things?
MS. ELLIS: As stated this morning, there will be two separate scores, there will be the overall score, which means all of the panel, and then there will be the scores of just the voting members. Nonvoting panel members, your vote will be recorded via, on our website, so you don't have a recording device, but voting panel members, you do. We are scoring one through five, you can push the button as many times as you like, but your last vote will count.
Also, in your folder there is a pre-score sheet for all voting members, or not just the members, but voting and nonvoting members. So please make sure that you write your name at the bottom of the pre-score sheet and record your score on that sheet also.
And seeing as though it's being broadcast via Webinar, we also need you to state your score for those

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who are on the Webinar. Does anybody have any questions for me?
DR. GOODMAN: Okay. So, the last time you vote is the one that counts. Once all the votes are posted,

once they're all posted, I'll go down the row and ask you what your vote was. But that means, the reason we're going to do it that way is that we don't want your vote to be influenced by what some colleague might have said, and all votes are going to be in the can by the time we find out who voted how; is that correct?
MS. ELLIS: That's correct.
DR. GOODMAN: And you see that we have nine voting members. Do know, however, that eventually on the CMS website, all the votes will be totaled with averages for voting and nonvoting, so you will see two sets of votes. Is that Dr. Stroncek with a question, or -- okay. I think we can proceed here.
The first question -- remember, these questions come in pairs. The first part is not what the evidence says but how adequate the body of evidence is, and then the second question is if it's sufficiently adequate, what does it say. All right.
So the first question to be voted, on a range of one, no confidence, and five, high confidence, is as follows: How confident are you that there is adequate

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evidence to determine whether or not current PRA assays predict renal transplant graft survival for individual patients as opposed to populations? So this is the confidence you have in the body of the evidence, the adequacy of the evidence regarding whether the current PRA assays predict renal transplant graft survival, that's the outcome, for individual patients, and we're interpreting that to include the CPRA as the panelists might infer.
(The panel voted and votes were recorded by staff.)
DR. GOODMAN: I think we have everyone, Ms. Ellis; is that correct?
MS. ELLIS: Yes. And if you can state your name and your vote, that will be greatly appreciated for the Webinar and the transcriptionist.
DR. GOODMAN: So starting with Dr. Satya-Murti, I won't call out all the names as we go down, but would you state your name and your vote.
DR. SATYA-MURTI: Satya-Murti, three.
MS. CABRAL-DANIELS: Cabral-Daniels, three.
DR. DMOCHOWSKI: Dmochowski, three.
DR. GRAMMER: Leslie Grammer, two.
DR. KLEIN: Roger Klein, three.
DR. MINTZER: Dave Mintzer, three.
MR. SAMSON: David Samson, two.

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DR. SINGH: Ajay Singh, four.
DR. STEINBROOK: Robert Steinbrook, three.
DR. PAUL: Les Paul, three.
DR. HOLMBERG: Jerry Holmberg, one.
DR. STRONCEK: Dave Stroncek, three.
DR. GOODMAN: Thank you. So we've got the

votes, it looks to me as though the mean exceeds 2.5.
MS. ELLIS: Correct.
DR. GOODMAN: Therefore, we can proceed to question two. Now that you've made an observation about the confidence you have in the adequacy of the evidence, two asks about what it's telling us. So, how confident are you that current PRA assays predict renal transplant graft survival for individual patients? This is how well it actually does the prediction as opposed to how good the evidence is. On a scale of one to five, where one is low confidence, five is high confidence, would you please enter your votes.
(The panel voted and votes were recorded by staff.)
MS. ELLIS: We're waiting on one voting member.
DR. GOODMAN: Does anyone think they have not entered their vote yet? Why don't you enter your same votes again, please?
(The panel voted and votes were recorded by

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staff.)
DR. GOODMAN: Okay. Dr. Stroncek, we'll start with you, if you'll state your vote.
DR. STRONCEK: David Stroncek, two.
DR. HOLMBERG: Jerry Holmberg, three.
DR. PAUL: Les Paul, four.
DR. STEINBROOK: Robert Steinbrook, four.
DR. SINGH: Ajay Singh, four.
MR. SAMSON: David Samson, two.
DR. MINTZER: Dave Mintzer, three.
DR. KLEIN: Roger Klein, three.
DR. GRAMMER: Leslie Grammer, four.
DR. DMOCHOWSKI: Dmochowski, four.
MS. CABRAL-DANIELS: Cabral-Daniels, three.
DR. SATYA-MURTI: Satya-Murti, three.
DR. GOODMAN: Thank you very much. All recorded?
MS. ELLIS: Yes.
DR. GOODMAN: Very good. We're now going to proceed to questions three and four. I don't know that this is possible, but it would sure be good to do this without that overhead noise. Can we be switching off and on with that while we have our discussion, or would that blow up your system?
SPEAKER: It will take two minutes to actually

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start up again.
DR. GOODMAN: I don't mind, we'll give you a two-minute warning, so if you wouldn't mind shutting down the noise, that would help us. I'll give you a two-minute warning.
(Discussion off the record.)
DR. GOODMAN: Let's take ten minutes, not 11, let's take ten minutes so they can change their batteries

and do other biological functions. Let's do it.
(Recess.)
DR. GOODMAN: We're going to take questions three and four together as we just did with one and two, and again, the first version talks about adequacy of evidence, the second version, which is number four, talks about if that evidence is any good, what does it say. Don't be thrown off by the preamble to number three which talks about donor-specific transfusion, that's just making a distinction between donors and what we care about here, which are the therapeutic transfusions. And here the therapeutic transfusions refer to those that are performed for anemia blood loss management, okay, that's what therapeutic transfusion means in this context. And so the two questions we're going to deal with here are going to be how confident are we that there's adequate evidence whether or not therapeutic

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transfusions, i.e., for anemia blood loss management, decrease renal transplant graft survival, and we will be asking for a rating from one to five. If the answer to that is more than two-and-a-half, then we'll actually ask you how confident you are that therapeutic transfusions do indeed decrease renal transplant graft survival. Note with regard to discussion under number four, and we will do this now as opposed to after the question, some of the things that are of interest are whether the decrease is involved in the role of sensitization as opposed to underlying comorbid conditions that affect the renal transplant graft survival. With regard to the adequacy of the evidence, they're concerned about the relationship, if any, between the number of units transfused, and remember that we had some discussion there, and renal transplant graft survival, so it's not just yes-no, but also how much, i.e., is there a threshold number. And then finally, if there's anything that's relevant here about the relative role of transfusion and pregnancy, prior renal transplant, and other factors that may affect sensitization. So those are some of the discussion issues that would pertain to questions three and four.
So, panel, at this point, do you have any top of the mind issues or questions with regard to the matter of

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the relationship between therapeutic transfusions and renal transplant graft survival? Dr. Singh will start it off.
DR. SINGH: Well, I think my perspective here is that the key word is confident, and here confidence really pertains to our review of the TA. In other words, if we believe that the TA was done rigorously and key studies were not left out using their criteria, then the TA would suggest that the evidence, or the level of evidence is relatively weak and the level of confidence consequently

would be relatively low, that's my understanding of it. So I just want to be sure that there isn't anything that we need to know about with respect to evidence that should question that assertion or that assumption. And as far as I can understand it, we haven't been presented with any studies up until now that question that assertion that was made in the TA.

DR. GOODMAN: Thank you. And you were very persistent in your pursuance of that very issue with Dr. Kewalramani, who was quite gracious in forming her response, which we also appreciate. So, any further discussion on this aspect of the adequacy of the evidence? My recollection from Dr. White's presentation was that I saw slide after slide after slide that characterized the evidence as low or insufficient on this issue. And I also

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recall seeing that, when it came to the magnitude of effect something between neutral and beneficial, but rarely statistically significant, so that's an overall recollection.

Dr. Kewalramani.

DR. KEWALRAMANI: Thank you. I just want to make a couple of points as we think about this question. I tried to make this point earlier but it's a little bit complex, although very important, so I'm going to try again by just sort of simplifying the concept.

DR. GOODMAN: We'll do our best. Thank you, Dr. Kewalramani.

DR. KEWALRAMANI: I'm trying to negotiate between the intricacies of microbiology and then the sort of practical medicine that we have to deal with here. Here's one thing to just think about as you review this evidence. When you think about the evidence that has to do with transfusions on graft survival, just know that this is inherently biased. It doesn't matter if it's a randomized control trial or a big observational study or small one for the following reason, and let's just break it down into one person.

If you have one individual and you gave them 37 transfusions and nothing happened, there are people like that, nothing happened, they would go on to get

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transplanted. And you were asked the question, does transfusion have anything to do with graft outcomes, and probably your answer is going to be no, because that person went on to get transfused, because that's the kind of person that Dr. Cecka and some of the other immunologists were talking about, there's some people who don't develop these kinds of antibodies. So by looking at the group who are transplanted, you are self-selecting a group of people who are not going to have the biggest transfusion effect.

And I'm a mere nephrologist, but I invite some of the immunologists, or if the panelists can, if you want

to ask me some questions, I just want to make sure that you see that denominator issue here.
DR. GOODMAN: So Dr. Kewalramani, the implication of your assertion regarding inherent bias means what for how we might consider these questions?
DR. KEWALRAMANI: The key to this conundrum is sensitization, that's the key, and there are links or parts of the Venn diagram that go in various directions after that, so the key here is sensitization. And so the question that we're really asking ourselves goes honestly back to the first question. If you give somebody something, transfusions, pregnancy or transplantation, a previous transplant that fails, they develop antibodies.

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Is that a good thing or a bad thing, and does that impact transplantation? That's really what you're asking, and you ask it in a few different ways, but when you ask it like this, we inherently pick people who were able to get transplanted.
DR. GOODMAN: So, what does that say then? We need to get this point. What does that say about the adequacy of the evidence for this question? Are you saying that that body of evidence is limited, constrained, biased, or what are you saying?
DR. KEWALRAMANI: The way to ask this question, I think, is do transfusions impact transplant outcomes broadly speaking? That's what we're all interested in. Do our patients with kidney disease get the transplants, do they get them in the quickest time, do they get grafts that last long. If you use the right denominator then you're looking at the right question, but I think the true question is do transfusions impact transplant outcomes, and those outcomes are broader than just those who got transplanted. In a roundabout way you could think of this as an ITT versus protocol analysis, you're only looking at the responders.
DR. GOODMAN: Thank you very much for that view. So a lot of people get transfused, not all of whom end up getting transplanted. So if we're just looking at those

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who end up having a transplant, we're not getting the full picture, I believe that's the point you made.
Dr. Holmberg is next.
DR. HOLMBERG: Well, even in phrasing the question that way, what evidence has been presented today to say there was any change? I still think that the body of evidence is strongly weak.
DR. GOODMAN: Dr. Stroncek.
DR. STRONCEK: I guess I look at this question differently than Dr. Kewalramani. It's not an issue of whether or not transfusions increase PRAs, it's that transfusions affect graft survival. It's well known that transfusions not only can cause alloimmunization and antibody production, but they do have an effect on

cellular immunity, and cellular immunity and humeral immunity are both involved with graft survival. So I think we have to look at the big picture, we can't just use alloimmunization or production of antibody as a surrogate.
DR. GOODMAN: Good point, Dr. Stroncek, thank you. Further points on this. Dr. Singh, did I see your hand?
DR. SINGH: I mean, I just want to reemphasize what Dr. Holmberg made, the point he made. Our mission here, I sound almost like the CMS administrator, is to

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look at and answer the question that was put in front of us, and the question that was put in front of us is our level of confidence about the evidence that's been presented to us. I don't know what my level of confidence would be about evidence that hasn't been presented to us. And so all I can do is look at this and say the evidence as provided to us is, supported by the TA, suggests that we should have a low level of confidence based on what was presented to us. That's all we can deal with. It may well be that Dr. Kewalramani is correct. I just don't know that.
DR. GOODMAN: Okay, good point. Further questions about the adequacy of the evidence, any questions that the panel has? Dr. Paul.
DR. PAUL: So just to follow that point, though, hypothetically, is it even possible to generate that evidence to prove the point that Dr. Kewalramani is making? Is it possible to, or would it violate equipoise to do a study like that? It's a hypothetical question because we don't have the evidence presented to us, but I would be interested in that.
DR. GOODMAN: I'll just add a corollary to that. There's also a cost, and I don't mean economic, of not having that evidence. The absence of not having that evidence doesn't exactly help us treat patients, and so

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there may be downsides of not pursuing the question. Yes, sir, Dr. Harmon.
DR. HARMON: I think you're right, though, that you can't answer that question the way it's phrased because there's a huge variable that isn't accounted for in the question, which is the changing of immunosuppression over time. So you've heard data that is retrospective registry data, bu that's in many ways the best data that we have in transplantation. You heard data from Opelz that there were many transfusions that were correlated with improved outcome of transplant, this is before 1982. And you heard data from me that after that, the 5,000 children in the registry, random transfusions were associated with worse outcomes, and a difference of that more than just the children and adults was immunosuppression changed, and we've seen that this has

happened between '82 and '94. So you can't answer this question in a vacuum, you have to say in this type of immunosuppression, would you go ahead and do these transfusions, and most people won't.
DR. GOODMAN: Most people won't, but does that necessarily mean that you can't design a fair trial?
DR. HARMON: It remains to be seen.
DR. GOODMAN: Remains to be seen.
Dr. Satya-Murti.

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DR. SATYA-MURTI: I will skip my comment.
DR. GOODMAN: Dr. Grammer.
DR. GRAMMER: Then should we perhaps only consider, since we're I guess interested in now, data that would be more like immunosuppressive regimens available to us now?
DR. GOODMAN: I think the most helpful way to look at this is in the current world. CMS has to make decisions in the real world now and henceforth, so I do not want to put this back as a historical question. Other points or questions to be made on this matter of transfusions and transplant graft survival? Other points? Dr. Kewalramani, briefly, please.
DR. KEWALRAMANI: In the interest of helping this question, I think when I looked at it, and one of the struggles I had, and I would ask Dr. White this question, when the tech assessment there were three kinds of data that are pulled in here, DST, donor-specific transfusions, very specific living donors getting inoculated with blood. Two, small amounts of random transfusions for the purpose of inoculation. And three, a separate category which is what I think this question is particularly asking, therapeutic transfusions. You take people who have true anemia, and you treat them as Dr. Lazarus described when we didn't have ESAs, with two transfusions per month. So

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I'm wondering if we actually saw any evidence today, and I'm wondering if Dr. White could comment on the true question of therapeutic transfusions.
DR. GOODMAN: We're going to get to Dr. White in a moment. Thank you for that. Any other questions now from the panel or anyone from whom you would like to hear? Okay. I'm going to recast this earlier question, as we did before. Is Dr. Becker still here, or Dr. Chertow still here?
DR. CHERTOW: Yes, sir.
DR. GOODMAN: I would like to hear, if you wouldn't mind, from Drs. Chertow, Harmon, Carson and White on these two questions. All right? And as we did before, Dr. Harmon set a very good example the last time as I recall. I want just a summary view, if you wouldn't mind, on the adequacy of the evidence about the relationship between therapeutic transfusions and renal transplant graft survival. So rethink about the adequacy of the

strength of the overall evidence, and let's start with that.
DR. CHERTOW: I believe it's weak.
DR. GOODMAN: You believe it's weak. Within that weak body of evidence, or from that weak body of evidence, how confident, or what can you say about the relationship between the therapeutic transfusions and the
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graft survival itself? The body of evidence sounds weak. What can you say about the relationship there, what does it tell you?
DR. CHERTOW: Given its weakness and the bias based on the denominator issues, I'd say there's very little if anything that can be said about the therapeutic either benefit or harm.
DR. GOODMAN: That's very helpful, thank you. Dr. Harmon, could you opine on both of those?
DR. HARMON: I think the evidence is quite weak. If pushed to come up with any answer, I would say that it's -- on the basis that transfusions are not beneficial and probably detrimental.
DR. GOODMAN: Thank you. Dr. Carson, I'd ask you to opine on those issues as well.
DR. CARSON: This is not my area of expertise, so I'm just a consumer of the same information you guys have all had.
DR. GOODMAN: We'd still like to hear from you.
DR. CARSON: Okay. What I heard was that the evidence is weak. I think the absence of the proper denomination makes it impossible to determine whether this is beneficial or not. What I also didn't hear was, what I would have done is to randomize evidence, and I don't see a lot of that, and it is not a common denominator, so I
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think we have very little information.
DR. GOODMAN: Dr. White.
DR. WHITE: One thing that we did, we looked at DST trials separately, and this is something that we just did sitting over there, so it's not in the DST book, but looking at Question 1.A, pulling out the data specifically for DST.
DR. GOODMAN: First of all, your Question 1.A isn't the same as ours.
DR. WHITE: Okay. Our Question 1.A was transfusions versus no transfusions, and it could have included whole blood, packed red cells, DST, and so one of the things was, you know, what would have happened in that DST subgroup, because people are thinking that DST might be beneficial, and if you pull it out, the overall effect isn't beneficial.
DR. GOODMAN: For transfusions that are therapeutic.
DR. WHITE: That's right. So, there were 11 trials that looked at DST and graft survival significance.

Six of the 11 showed a significant improvement, five of the 11 showed no significant effects, so it doesn't change our overall conclusion for the strength of the evidence either for DST versus no transfusion alone, or for the absence of DST versus no transfusion alone. And so, I

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agree that the data that we're looking at here is weak data.

DR. GOODMAN: It's weak, and please say once again, the relationship there comes down to what, the transfusion?

DR. WHITE: What I'm saying is that when you look at DST, the conclusions don't change versus therapeutic transfusions.

DR. GOODMAN: So if you kick out DSTs, what do you have left, that's what I want to know.

DR. WHITE: I don't know. It looks like for graft survival there were originally 55 studies for one-year graft survival, and when you look at DST you would be taking out 11 of those trials, so you would end up with 45 trials. The original analysis with everything included, 53 percent significant increase in survival, 47 percent no significant effect on survival. When you look at DST alone, it's six out of 11 studies showing a significant approval, five out of 11 showing no significant effect, so the conclusion is exactly the same, DST alone versus when everything is taken together, and then I need to hypothesize and say if they took it out, the ones that would be remaining would be unchanged.

DR. GOODMAN: It still doesn't make a difference, okay.

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Now just briefly, Dr. Leffell and Dr. Cecka, if you could come up and make an observation, or if you'd care to add to it. Dr. Leffell, yes, briefly.

DR. LEFFELL: I would have to agree that the body of the evidence is weak, specifically on the impact of therapeutic blood transfusions.

DR. GOODMAN: It's weak, and then what does the weak evidence suggest, if at all?

DR. LEFFELL: I think -- I'm sorry. I don't think that the data support a beneficial effect of transfusions.

DR. GOODMAN: Thank you. Dr. Cecka, did you want to add to that briefly, those two items?

DR. CECKA: I would just reiterate that, the evidence is weak, and certainly in the current era the benefit is not there.

DR. GOODMAN: Is not there, thank you.

Dr. Holmberg.

DR. HOLMBERG: Could you also ask Dr. Goodnough what he thinks of these two questions?

DR. GOODMAN: That's not a bad idea. Dr. Goodnough.

DR. GOODNOUGH: I wanted to reiterate my strong concern that one of the problems with this is that it seems to have some kind of a neutral or beneficial effect

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on transfusions related to graft outcomes, and there's a substantial Type II error effect. We're not counting the patients who were censored, who were sensitized by transfusions and never came to transplant. And as was previously mentioned, under any intention to treat real life analysis, if you did it that way and counted the people who never came to transplant because of adverse effects from the transfusion, I'm concerned that we would be missing a substantial deleterious effect from the transfusions.

DR. GOODMAN: Understood. Thank you, Dr. Goodnough, the point is well taken now and before, and Dr. Holmberg, thank you for the suggestion.

I want to proceed very soon to a vote on these two questions. Does anybody on the panel have any further questions for any of our speakers and/or discussion among ourselves with regard to the adequacy of the evidence on this matter and then what it says? Dr. Klein, and then Dr. Satya-Murti.

DR. KLEIN: I have a question for Dr. White. In analyzing these studies that compared transfusion with outcome, I think about that, and to me that's somewhat unsatisfying our crude way to look at it because you're not looking at intervening variables, including a surrogate marker which we have, which would be

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desensitization, and behavior, which is allocation of organs based upon the results of the sensitization. Can you say a few words about whether or not these studies in fact considered those parameters, commented on them, or if you have any other thoughts on that.

DR. WHITE: In some studies but not others, they stated that there were some patients who were sensitized who ended up not going into transfusions. The studies that did not say that, it doesn't mean that that's not what they've done. So in a lot of studies, they started at the time of transplantation, so it's really difficult to really get a good handle on that data. The studies were more clear about what happened from the time of transplantation on, and that's the data that we were looking at.

DR. GOODMAN: Thank you. Dr. Satya-Murti.

DR. SATYA-MURTI: Several comments. At this point in MedCAC we often do run into our need to vote on an issue where there is absent evidence. So we can only vote, as Cliff said, on what is available. So what evidence is not collected, or absent, then becomes a gap, which also is the last discussion item. So if we can just vote on what we have and identify the gaps, that would actually serve the purpose.

DR. GOODMAN: We will vote and we will have a
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chance to identify the gaps. Dr. Singh, last comment.
DR. SINGH: I think since these are, our remarks are being recorded, I think it would be important, at least from my standpoint, to emphasize that the major problems of limitations of systematic review, and for us to, and for CMS actually to carefully weigh, not overinterpreting results of the systematic review, however well it's done, and I have no reason to say it hasn't been done well, but it has these issues.
The second point is, I think that we are voting really on our level of confidence about the evidence, and we're not really voting about what necessarily we think, to Dr. Goodnough's point as to whether we're missing a probable -- and what we all agree on is that we need further evidence, we need more evidence in order to gain some assessment of whether there is a positive effect of blood transfusions, and we just don't know that, and I think we should keep an open mind. I for one believe that there is, but I don't know that the evidence is sufficiently strong for us to have a definite way of voting on it.
DR. GOODMAN: Thank you, Dr. Singh. And there's always, we vote with what we've got before us, we try to address the questions from CMS, and as noted, the fortunate aspect of these meetings is that all of the
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beautiful narrative that is going through your lips and those of others is duly recorded, and so that will be informative to CMS. Dr. Paul.
DR. PAUL: Yeah, I'm sorry. On this point that Dr. Satya-Murti just made, I just want to point out that there is considerable risk in voting on the evidence that we have with regard to the interpretation that CMS will make with that vote. If we list the gaps under the gap section, that's fine, but this is such a substantial flaw in the evidence that I just want to make sure that the way CMS interprets this particular vote adequately considers that particular flaw in the evidence.
DR. GOODMAN: Your point is very well taken, Dr. Paul, and I believe that that was raised once this morning, twice this afternoon, and we'll have a chance to raise it once again. CMS is quite, does heed these things, and I see Dr. Jacques has appeared very close to the microphone, and it looks like he wants to comment on that. Dr. Louis Jacques, who runs the Coverage and Analysis Group.
DR. JACQUES: I'm Louis Jacques, director of CAG. We're quite aware of that, and when we are looking at in terms of what you make from MedCAC, we're well aware, whether it's this particular committee or any other committee, that the verbiage is often sometimes more
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informative than simply a narrow look at the vote itself, which is why there are actually quite a few members of my staff, we haven't identified ourselves, but we have been generally in the room just so we can pick up the richness of the dialogue, which in many cases is more informative than the votes themselves.

DR. GOODMAN: Thank you very much, Dr. Jacques. Your point is well made, Dr. Paul.

Seeing no other questions, let's proceed to the vote. We're going to vote on questions three and four in sequence, if everyone's got their handy-dandy vote-maker there. So remember, the first question is about the adequacy of the evidence, and the second one is if it's sufficiently adequate, what does the evidence say?

So question three, then, is as follows: How confident are you that there is adequate evidence of whether or not therapeutic transfusions, not the DST, but therapeutic transfusions decrease renal transplant graft survival, how confident are you about the adequacy of the body of evidence? One is low confidence, five is high confidence, and I will ask you to enter your votes.

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

DR. GOODMAN: Ms. Ellis, I see nine votes and as Ms. Ellis pointed out, you will only see nine votes on the

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board. However, all votes, including the nonvoting members, are going to appear as part of the record, and you can find them not long from now on the CMS MedCAC website. Ms. Ellis, I see a mean vote of 1.5556, which is precision, I don't know that any test is that precise, but in any case, that does not appear to me to reach the threshold of 2.5.

MS. ELLIS: That's correct.

DR. GOODMAN: So, before we go to the discussion about that, I'm reminded that we need to announce our votes for the benefit of Webinar, starting with Dr. Satya-Murti.

DR. SATYA-MURTI: Satya-Murti, two.

MS. CABRAL-DANIELS: Cabral-Daniels, one.

DR. DMOCHOWSKI: Dmochowski, two.

DR. GRAMMER: Leslie Grammer, two.

DR. KLEIN: Roger Klein, two.

DR. MINTZER: Mintzer, two.

MR. SAMSON: Samson, one.

DR. SINGH: Ajay Singh, one.

DR. STEINBROOK: Steinbrook, one.

DR. PAUL: Les Paul, two.

DR. HOLMBERG: Jerry Holmberg, one.

DR. STRONCEK: Dave Stroncek, two.

DR. GOODMAN: Thank you very much. I know that

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Dr. Dmochowski has got to run. Dr. Dmochowski, I know that actually speaking of risk, you're actually at risk of

missing your plane, we very much appreciate you putting these questions. I will add just for the record that you will see that Dr. Dmochowski is handing his scoring sheet for all the questions to Ms. Ellis, and so when we get to voting on questions five and six, Ms. Ellis as a proxy for Dr. Dmochowski will be answering his votes just as he has given them to her. I presume they're legible to you, Ms. Ellis.

MS. ELLIS: Yes.

DR. GOODMAN: So she'll be entering them as a proxy for Dr. Dmochowski.

Before we proceed, panel, to five and six, since we're not answering question four, I'll take any brief comments you might have about how you feel about not being able to be in a position to answer question four, any message here. Dr. Steinbrook.

DR. STEINBROOK: Well, I think without getting into the details of how one would design a study, I think it's possible to get better evidence to address these questions. And whether it could be randomized with transfusion risks with defined criteria for patients who are transfused out, the ESA agent used, et cetera, et cetera, to account for people who never get a

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transplant. There are ways to get at this, and a different question might do it, or they might design it.

DR. GOODMAN: I'm glad you're making that point. We're not giving up on the evidence here, and there may be some concerns about what might be an appropriate trial design or study design, but we're not giving up on the possibility of getting better evidence, we were just dissatisfied with the body as it is now.

Dr. Holmberg, and then Dr. Klein.

DR. HOLMBERG: I think that we're missing quite a bit of evidence, and one of the things that has been mentioned over and over again is the denominator, and also the situation at UNOS where they do not capture how many transfusions have been. Within the nation here we are trying to move towards a biovigilance program, and what I mean by biovigilance is blood, organs and tissues, and one of our hopes is that as we develop this, that UNOS will come along with us so that we can be able to capture some of this information more appropriately.

DR. GOODMAN: Great. Excellent time with the body that is administering, helping to coordinate transplants, so that's a very important point, something to raise with them. Was it Dr. Klein next? No, Ms. Cabral-Daniels.

MS. CABRAL-DANIELS: I would like to just say

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that I'm pleased to know that people are interested in having more robust evidence, but I think when we do that, that when the design of future research is being contemplated, that industry and government come together

and agree to what that design should be so that we don't go into parallel tracks.
And second of all, no matter what we do with future studies, if we have patients who don't even understand whether or not they received a transfusion, that's troublesome, because that represents a patient safety issue, and so I think we should also consider the role of involving patients going forward with future studies. Thanks.
DR. GOODMAN: Thank you, a point very well made, Ms. Cabral-Daniels. I believe you haven't been to these meetings before. I will share with you now as well as some other folks that haven't attended, one of the purposes for holding these meetings pursues the point you made earlier with regard to industry, government and other stakeholders being in the same room when we're trying to go over and appraise the strengths and weaknesses of evidence, and we look at those that might design studies, might take this in mind when they do try to come up with stronger evidence, so your point is very well taken at this time.

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Any other comments about the pair of questions three and four before we proceed to five and six? Okay.
So just for the record, because question three didn't achieve a threshold of 2.5, we are dispensing with question four.
We'll now move to the pair of questions five and six, and as you recall, these had to do with the relationship between ESA use for anemia blood loss management and the extent to which that might improve renal transplant graft survival, and I'll just remind you, just to read it again, we're going to ask you how confident you are that there's adequate evidence to determine whether or not ESA use for anemia blood loss management improves renal transplant graft survival. If the voting on that achieves a threshold of 2.5 on a one to five scale, we will go on to ask how confident you are that there's adequate evidence to conclude that ESA use to maintain hemoglobin levels of ten or greater is required to improve renal transplant graft survival.
Oh, by the way, with the hemoglobin levels, we're not talking about other sorts of gradations or intervals there, this particular question addresses ten or greater. Okay.
With that, panel, if you have particular questions to ask of our speakers, or would like to raise

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points among ourselves in discussion, let's proceed, starting with Dr. Satya-Murti, followed by Mr. Samson, followed by Dr. Paul.
DR. SATYA-MURTI: This to me is the meat of this entire MedCAC. We have evidence that improving anemia would improve graft survival. We have evidence that ESA

would improve anemia. But the connection there is a fairly good leap, and we don't have prospective studies to show that. All we rely on is two discrete pieces of evidence and then link them together, and say ergo, there should be an improvement. So, I don't know if the other panelists and presenters agree with me, but this to me is the largest hiatus so far.

DR. GOODMAN: Thank you. That's certainly a good point. Mr. Samson, and then Dr. Paul.

MR. SAMSON: All right. I made this observation probably earlier, that there was no direct evidence presented this morning bearing on this question, and that was by no fault of the U.Conn EPC, they just were not given the question to address. But I didn't hear any other presenters touch directly on this question. I did speak with Michael, and he identified a single study which did have some direct evidence, it was a retrospective observational study that was rated poor in quality, that did find a relationship that in a multivariate analysis,

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they found that pretransplant non-use of EPO was significantly associated with graft failure.

I know there was also a speaker who said there was an abstract from a conference, but what we don't have is a systematic search for studies that talk to this question. And just to summarize, the paper that Michael White showed me, you know, that's just sort of a random event to find that. We really don't know what the other evidence might be.

DR. GOODMAN: Let's just make sure we're clear on this. Are you saying that there is no evidence on this save for the one study cited, or we didn't look for it?

MR. SAMSON: We didn't look for it, so we don't know if there's additional evidence beyond that single study, because we did not have a search specifically tailored to look for it.

DR. GOODMAN: The TA did not.

MR. SAMSON: Right.

DR. GOODMAN: Okay. An important point. Dr. Paul, and then Dr. Singh.

DR. PAUL: Earlier Dr. Chertow made a comment and he used the word entanglement between ESAs and sensitization and graft survival, and I wonder if he could elaborate on that, because we didn't get a chance to really discuss, or vote I should say, on an item that we

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omitted, but it's directly relevant to this question of entanglement. So if it's sort of common practice among the nephrology community and the manufacturing community, for example, that we consider this issue of entanglement, I'd like to better understand what evidence is used to make those conclusions, in the absence of evidence of direct relationship.

DR. GOODMAN: Dr. Paul, that's a very important

question, and Dr. Chertow may be able to answer. Interesting question, Dr. Chertow, and you could probably write a dissertation on it, but we'd appreciate a one-minute answer.

DR. CHERTOW: No dissertations. It's simply impossible to identify a complete independence between the use of ESAs, the use of transfusions and sensitization because the patients who are transfused are more likely to be sensitized. The patients who are on dialysis who are waiting for a kidney transplant are almost all on ESAs, and any difference between the provision of ESA or non-provision of ESA in that population would be heavily confounded. So, there are so many layers of confounding, I just don't think that we can determine an independent association between ESA and graft survival independent of the association between transfusion and graft survival, and I don't think that we can disentangle transfusion and

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sensitization in the association between those two factors and graft survival.

DR. GOODMAN: Thank you, Dr. Chertow. Dr. Paul, I know that among the entangling factors is that policy, clinical management of these patients and policy evolved in the absence of some evidence which we wish we had a few decades ago, it wasn't generated at the time that we needed it. And so we're suffering from that absence of earlier evidence, so that failure to generate evidence is affecting us now, and it's built into policy, so this does also go to Dr. Chertow's point. Dr. Singh.

DR. SINGH: I just want to clarify something that Dr. Satya-Murti alluded to. As far as I'm aware, and you can correct me if I'm wrong, there is no evidence that correction of anemia in transplant patients or patients prior to transplant results in improvement of graft survival. In other words, you stated that improving anemia might improve graft survival, but there is really no evidence of that. What there seems to be evidence for as far as I can see is that higher hemoglobins in the post-transplant period are associated with better graft survival, but higher hemoglobin doesn't necessarily mean that improving the hemoglobins is associated with better outcomes. So it is important to note that the question here is talking about an intervention, not hemoglobin

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per se, number one.

And then the second point I want to just make is that we should be careful, that this question is really, I think alluding to the use of ESAs in preventing blood transfusions that in a linear fashion may subsequently improve graft survival, and what the evidence or what our confidence is about the evidence with respect to that question, and I think the other panelists support the limitations of the evidence in that regard.

DR. GOODMAN: Dr. Satya-Murti, did you have a

comment on that?
DR. SATYA-MURTI: Your point is well taken, that what you said further adds to my diffidence as it were, that there is an ongoing study, a prospective study done that shows a connection, that there is therefore that cause and effect. So I thought the anemia would impact survival, but if you feel there is no data even for that, then it further affects my thought process that the connection is just not there with the data we listened to today.
DR. GOODMAN: Thank you, Dr. Satya-Murti. Dr. Klein.
DR. KLEIN: It seems to me that, I think it was Dr. Carson who presented some preoperative data on hemoglobin levels and postoperative survival, was it you?

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So that there was, as I recall, there was a connection between preoperative hemoglobin levels and overall survival at least, particularly in patients with coronary artery disease. And so I guess I would think that there may be some possibility of extrapolation in that context. Perhaps you could comment on that. I realize they weren't renal patients that you were discussing.
DR. GOODMAN: Dr. Carson.
DR. CARSON: Yeah. I don't think it helps in this situation.
DR. KLEIN: Okay.
DR. CARSON: So in that study, it was a study of patients who declined blood for religious reasons and we looked at hemoglobin with allograft relationships, and when you're very low they don't do very well, okay? But the question here is graft survival and, you know, I don't think it has anything to do with --
DR. KLEIN: I agree with you in terms of graft survival. I was just wondering how many studies actually had these endpoints for graft survival and so that --
DR. CARSON: And let's go to the next thing. So then, the next question is if you show this association between anemia and mortalities, the second question then is, does giving blood transfusions, which is the question that's partially answered, but does giving ESAs reduce

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those events, and we have to test that. Because all I can show you is this association between anemia and outcome, it doesn't mean giving blood improves outcome, and in fact our trial data doesn't seem to suggest that.
DR. KLEIN: Right, but in terms of operative settings, I mean, they don't go into operating settings with hemoglobins of six. I mean, I don't think most surgeons would take them.
DR. CARSON: Only if the patient declines blood.
DR. KLEIN: Right.
DR. GOODMAN: Dr. Mintzer.
DR. MINTZER: Just to clear up this question,

are we considering renal transplant graft survival to include whether you get a graft or not? I mean, successfully transplanted patients are less likely to be transfused, less likely to have HLA antibodies, and they're more likely to get a graft. So are we just looking at patients that have been transplanted and whether that transplant survives, or are we also looking at whether the patient gets a transplant or not?

DR. GOODMAN: The way I read the question it sounds like somebody has gotten the transplant, and then we're asking whether or not the graft is surviving.

DR. MINTZER: So we're interested in successful transplant outcomes that could include both potential

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benefits?

DR. GOODMAN: Well, I think you can comment on that, but when it comes time for voting, I think we should take the question pretty literally. You know, speaking of entanglement, I don't know that anyone's mentioned this today, but simply the fact that we don't have enough kidneys to go around complicates this issue a lot. If anyone who needed a kidney could get one, I think the body of evidence would look a lot better. That's not an issue that we're addressing today, but that's the sad state of affairs on this matter.

Other questions from the panel on five or six at this point? Dr. Steinbrook.

DR. STEINBROOK: Since we feel, or at least some of us feel that we haven't had evidence directly about this, I think it's fair to ask whether anybody wants to bring something to our attention.

DR. GOODMAN: That's a fair question. Does anybody have any evidence to bring to our attention on this question about this relationship?

Dr. Von Hartitzsch, if it's not about evidence, keep it short, okay? Come to the microphone. We really want to hear about evidence, but if it's something else, please keep it brief.

DR. VON HARTITZSCH: I've taken care of a lot of

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transplant patients for many years, and I have a group of people who have a normal hemoglobin, who have normal creatinines with cyclosporin. And on the other side, I have people that have low hemoglobins and progression at the ground. And I also was asked to see people who had coronary arteriograms and then developed post-contrast nephropathy. And they were young people, they had clean coronaries, but they were very anemic. So what I'm saying is, does anemia make you more susceptible to effects that don't normally affect people with an ordinary hemoglobin. So I'm saying that I think maybe anemia may make you more susceptible to graft, shortening of graft survival. Normally most people who have had transplants lose their kidneys around ten years, but I have had some, a lot that

have gone 20 years with a normal hemoglobin.
DR. GOODMAN: Thank you, Dr. Von Hartitzsch.
Dr. Steinbrook, if one might observe, the best answer you got to your question about this is that the evidence sounded like a small set of cases so far.
DR. STEINBROOK: There's one more.
DR. GOODMAN: Let's go to Dr. Chertow, then Dr. Kewalramani, and then Dr. Koller. Dr. Chertow.
DR. CHERTOW: I will be brief. I know circumstantially this can be often confounded by changes in immunosuppression. I think it's worth making the point

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that over the 20 or so years that ESAs have been available, and that the relative usage of ESAs in contrast to blood transfusion for the therapeutic treatment of anemia in patients with ESRD, patients on dialysis, and that over that same time frame, patient and graft survival have improved considerably. Again, that's difficult to attribute to use of ESAs. Since many other things were changing at the same time, if ESAs were associated with an adverse effect on graft survival, it would be hard to reconcile that with the observed observational data.
DR. GOODMAN: Thank you very much, Dr. Chertow, so interesting, but admittedly confounding. Yes, Dr. Kewalramani briefly, and then Dr. Koller briefly.
DR. KEWALRAMANI: I think others have appropriately pointed out that we have not done a study of ESAs for the explicit purpose of graft survival. Why haven't we done that? We haven't done that because we don't like to transfuse our patients. There are a host of risks associated with transfusion, we have an effective therapy, and we don't give them transfusions. That doesn't mean that there's no evidence. So for example, if I look and say what is the current evidence, what is the state of the evidence that complete mismatched kidneys have poor outcomes, I might conclude that the evidence is poor because we don't do that

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anymore, but my confidence is pretty darned high that that's a bad idea because of what you know and the relationships.
Let's just break this apart. What are we really talking about here, what do ESAs do? ESAs decrease transfusion, that's unambiguous. They decrease transfusions in a chronic management of our dialysis patients. Again, there's only three ways to develop panel reactive antibodies due to sensitization, pregnancy, previous transplant and transfusions. So the evidence that we have, including the evidence that's confounded that Glenn has mentioned, that's the evidence from USRDS, there is equivalent evidence from UNOS, there's similar evidence from the collaborative transplant study. They're there.
Over a period of time as we have gotten better

regarding management of anemia, decreasing transfusions, sensitization has improved. We have more unsensitized patients on the wait list now than ever before. That evidence can't be discarded. And again, there's a difference between, I think as the questions point out, level of evidence and confidence when you pull all of these things together. I would just ask for any of the transplant physicians in the room, immunologists, anybody who cares for transplant patients, would you give your

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patients transfusions, do you want in your center a patient who is sensitized or unsensitized.

DR. GOODMAN: Thank you, Dr. Kewalramani. I would just remind you, and all, that we're looking at evidence, preferably that which has been peer reviewed and entered in the literature. Your questions may be interesting for discussion, but are not evidence-based questions, but we appreciate your sentiment. Dr. Koller.

DR. KOLLER: This is to address the question from one of the panelists as to do we actually have, did anyone actually look for information to answer questions five and six, and internally we did look, and we basically did not find any studies that would be informative. The data that we suggested today, basically all the transfusion data from the registration studies was shown to you today, the entire data set that is publicly available. And as was noted, we have no information on the criteria for which transfusions were performed and other aspects in terms of for what reasons they were performed, what the hemoglobin levels were, the number of units per person and PRA levels, we have no data, and the data, the entire data set that might be relevant, we presented in our presentation. Thank you.

DR. GOODMAN: Thank you, Dr. Koller. Other points or questions from the panel on the matter of ESA

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use vis-a-vis renal graft survival? Dr. Steinbrook, I think we polled the room as thoroughly as we could in response to your question. Were you overwhelmed by the evidence on this?

DR. STEINBROOK: I'm not sure I need to respond to that. It doesn't look like there's a lot out there to be uncovered, and again, what's important is evidence directly responding to the question as written, not trying to look at the question in broader ways.

DR. GOODMAN: Understood, and thank you for that. We are looking at a specific question as presented to us by CMS with regard to voting but we are not limited insofar as comments, as you obviously are making and which you have made, which is also very helpful. Dr. Paul, did you have your hand up? Okay.

Just another reminder with regard to this sort of causality here. It may be true that ESA use has decreased transfusions but it's not necessarily from the

physiological or biological effect that a decision was made to use ESAs sometimes instead of transfusion. That does not necessarily mean that there's a causal relationship between ESA use and graft outcomes, so there's data about what's going on out there, and that's not necessarily evidence about causality. I hope that point isn't lost on the panel.

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Any further questions or points to be made before we launch into these questions? And please fire up the voting system. So what we're going to do is, let's set up the question here. Again, this is a pair. The first part is about adequacy of evidence and the second one's going to be, if we get a threshold of 2.5 on adequacy of what you think the relationship is. So I'll start with the question. The question before the panel at this point is, how confident are you that there is adequate evidence to determine whether or not ESA use for amenia blood loss management improves renal transplant graft survival? One is low, five is high, and Ms. Ellis will tell us when it's ready for your vote.

MS. ELLIS: Go ahead.

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

DR. GOODMAN: Ms. Ellis, you have entered Dr. Dmochowski's vote?

MS. ELLIS: Yes.

DR. GOODMAN: Thank you all for voting. Let's do the countdown here. Dr. Satya-Murti, name and vote.

DR. SATYA-MURTI: Satya-Murti, one.

MS. CABRAL-DANIELS: Cabral-Daniels, one.

DR. GRAMMER: Leslie Grammer, one.

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DR. KLEIN: Roger Klein, two.

DR. MINTZER: Mintzer, three.

MR. SAMSON: David Samson, one.

DR. SINGH: Ajay Singh, one.

DR. STEINBROOK: Steinbrook, one.

DR. PAUL: Paul, two.

DR. HOLMBERG: Jerry Holmberg, one.

DR. STRONCEK: James Stroncek, one.

MS. ELLIS: And for Dr. Roger Dmochowski, he voted one.

DR. GOODMAN: Thank you. The mean vote is one and a third, which does not hit the threshold of 2.5, and therefore we won't pursue voting on question six. But before we proceed to question seven -- and by the way, can you turn off the voting machines?

MS. ELLIS: Yes, we're done.

DR. GOODMAN: At least as far as the voting questions. Before we proceed, since we're not going to answer question six by voting, I will start with Dr. Steinbrook and perhaps others. What else did you want to

say here about evidence for this relationship between ESA use and transplant graft survival? Dr. Steinbrook.
DR. STEINBROOK: I wanted to make a specific comment which had to do with what CMS has told us several times, most recently in this current discussion, about the
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registration studies. Apparently some of the data in the registration studies is unpublished and I think it would be helpful, since these registration studies were done a while ago, if this information were in the public domain, maybe it helps, maybe it doesn't. Perhaps if there's somebody from the companies that did the studies, they may want to address that. But it seems to me that either through the FDA or other mechanisms, whether published or otherwise, that this information should be looked at. If it helps, great; if it doesn't, it doesn't. I'm not sure it does anybody any good ten years later sitting in a file drawer somewhere.
DR. GOODMAN: Are there any speakers today that may be able to address Dr. Steinbrook's point now, or we will just take the point home with us. Dr. Kewalramani.
DR. KEWALRAMANI: I'm happy to address the point. I think that if there's interest in the community, and maybe more importantly the editorial boards of journals that published the data from a long time ago that are far smaller numbers than what we have today, that would be great. The data are available in terms of what went into the approval of the products and is listed in the USPI. But it is a fair point, and I think that the big difficulty will be finding an editor who is willing to publish data that's quite old at this point.
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DR. GOODMAN: Thank you, Doctor.
Dr. Steinbrook.
DR. STEINBROOK: A follow-up in one sentence. The point about publication is well taken. Frankly, I think if this data were available in a form for a review, meta-analysis, et cetera, it would be good enough at this point, as opposed to a standalone publication, which is a different issue.
DR. GOODMAN: Dr. Steinbrook wants it out there. Yes, Dr. Holmberg.
DR. HOLMBERG: I thought we heard from Dr. White that a lot of the data that are out there are not available for meta-analysis.
DR. GOODMAN: Dr. White.
DR. WHITE: They're available. You just can't meta-analyze it because of the extreme amounts of statistical and clinical heterogeneity among the studies, and then some of the inherent limitations within the study set. They wouldn't be, it wouldn't be informative to try to wrap these studies together and come up with a pooled effect with a 95 percent confidence interval.
DR. GOODMAN: Thanks, Dr. Holmberg and Dr.

White. Just for clarification, because sometimes these terms are somewhat misused. When we say meta-analysis, we literally refer to a statistical technique that pools the
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data or the summary data, the results, and in order to be able to do that, we need to have the data pass certain tests of homogeneity. And as we heard today, they're highly heterogeneous, so Dr. White and others could not perform a true meta-analysis. That does not mean that they can't conduct a systematic review that characterizes the body of evidence in other ways.
Dr. Singh, and then Dr. Klein.
DR. SINGH: I think addressing the specific issue of gaps in knowledge, I think some of this has already been alluded to, but I think to the list of UNOS and potentially other federal agencies that collect information on transfusions, we should also add to that the transplant community with respect to clinical trials. I mean, there have been a number of clinical trials sponsored by the NIH as well as by industry in the transplant population that are not collecting information with respect to transfusion. And even with respect to hemoglobin, there was a recent trial that was done in the transplant population that didn't even measure hemoglobin in patients.
So I think that the first level is we need to collect observational data that can inform what's going on out there, and I think one of the members of the panel made that point precisely. I think the second issue,
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then, is whether we can do randomized control trials, and I think that's much more difficult because of the ethical concerns. Even though we may think the evidence is not adequate in terms of influencing public policy, it's entirely possible that in an IRB, or for that matter a DSRB, might view it unethical to randomize patients to transfusion, given the limited data we have out there.
So I think we need to be a little humble in not demanding things that are going to be difficult for us to attain, especially with RCTs, but I don't think that's an excuse for not getting information from observational data sets.
DR. GOODMAN: Thank you, Dr. Singh, and since Dr. Singh broached it, although I couched it as discussion about the question six that we didn't answer, let's just open it up for the next at least ten minutes on significant evidence gaps, and Dr. Singh started that. And so in the questions that we were given, the areas of evidence gap interest were as follows, but we're not necessarily limited to those. The ones that were discussed in our questions had to do with clinical criteria, including hemoglobin level, or patients who might receive transfusions for chronic anemia. Other significant gaps might exist regarding any relationship

about the number of units transfused, the screening of PRA
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assays and the more specific HLA assays, immune suppressive regimen, timing of rejection to determine the various factors in transplant graft survival, and so forth. You need not limit your comments to those factors. What we're most interested in now are your views about evidence gaps that you would like to bring to the attention of all stakeholders, CMS included, patients, provider physicians and so forth, to help us get, provide better answers to these related questions, so we're talking about evidence gaps now. Ms. Cabral-Daniels.
MS. CABRAL-DANIELS: With regard to evidence gaps, it seems to me that probably the best data out there would be from CMS itself in terms of the reimbursement data, and maybe CMS could play more of a proactive role in helping researchers have access to the data people are collecting and that would be helpful to future research.
DR. GOODMAN: Good point, Ms. Cabral-Daniels. By the way, a lot is happening at CMS in the last year, and it is being a little more open with its massive bodies of data, and we hope that will help. Point well made. Yes, other, Dr. Grammer?
DR. GRAMMER: This is a point that several other people have made but I'll just say it, and that is that I think that one of the big questions of, is the contribution of transfusions and sensitization to people
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who don't even make it to the transplant list or are so highly sensitized that they just keep on the list forever and ever and ever. And asking the question, what does transfusions do to those -- the outcome of do you even get a graft, not, you know, once you get a graft, what's the survival. I think that's an important question to think about.
DR. GOODMAN: Great point, Dr. Grammer. She's right, and we did remember to emphasize that today. Dr. Satya-Murti.
DR. SATYA-MURTI: I know prospective trials with and without ESAs would be hard, I agree with Dr. Singh and others. I'm just wondering if there is any information available either from the past, historical data or prospectively, with the correlation between level of hemoglobin and survival if we have controlled for other variables as to the reason for transplant and age of transplant. If such were available, might we be demonstrating lower levels of hemoglobin at the time of transplant, might correlate in some fashion with short-term survival.
DR. GOODMAN: That's a good question, Dr. Satya-Murti. Do you want to pose it to anyone in particular?
DR. SATYA-MURTI: I was hoping, to anyone.
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DR. GOODMAN: Dr. Carson.
DR. CARSON: I mean, it's a trial that can be done, but the way you would have to do this is take your population of potentially eligible patients and then randomize them to either, to a target hemoglobin level through ESAs. So you might shoot for a higher target hemoglobin, a lower target hemoglobin, and see if it affects long-term management.
DR. SATYA-MURTI: I know it can be done, but I'm wondering with the current data available, those in the eight-gram range, given other variables or control, they survive six months less, or 16 months less than those who have, regardless of the treatment given, who had 12 grams of hemoglobin.
DR. SINGH: Can I -- I mean, people do go on to transplantation with hemoglobins of eight by and large, you know, dialysis patients, so I think that's the problem with that type of study. If you look at papers that have addressed the level of hemoglobin in the post transplant period early on, the lower the hemoglobin, say for six months, nine months, a year, the worse the outcome. I think those observational studies have been done. The problem is, as Dr. Chertow pointed out, these are confounded, and as there are layers of confounding, it makes the conclusions from that much less

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powerful than a randomized control study might.
DR. GOODMAN: Thank you, Dr. Singh. That was Dr. Singh, for the record. Back to Dr. Carson.
DR. CARSON: So if the post-transplant, you look at patients with lower hemoglobins and higher hemoglobins, why? In people with lower hemoglobins, their renal function probably isn't recovering the same, they require more immunosuppressive drugs, and all these things are going to affect their prognosis, and you really don't, you can't figure it out that way.
DR. GOODMAN: Thank you. Dr. Goodnough, would you approach the mike?
DR. GOODNOUGH: Echoing what Jeff just said, you can't prove causality, but there is a strong and emerging literature on surgical patients, non-transplant surgery, but surgical patients, and Medicare database patients being published in 1999 showing a strong correlation with adverse post-op morbidity and mortality with anemia, and I think the threshold was less than ten. And that was also echoed in a VA study also of several hundred thousand patients. So I think the emerging literature does show that surgery in general, non-cardiac and cardiac surgical patients, it's bad to go into surgery with anemia, so it's not directly to the point of transplant surgery, but general surgery.

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DR. GOODMAN: Thank you, Dr. Goodnough. Other points to be made about the important evidence gaps that

we would like to bring to the attention of stakeholders, any others that haven't been mentioned so far? We noted several important ones just now, and throughout the day others have been raised. Others at this point? Okay. Dr. Chertow, do you want to approach the mike?
DR. CHERTOW: Just a brief point. We heard from Dr. Koller and I believe as well from Dr. Singh, the issue about options for sensitized patients, that there are now desensitization protocols. These are really in their infancy, even at some of the great experienced centers like ours and Johns Hopkins. And subjecting Medicare beneficiaries who are already on triple immunosuppression to intravenous hemoglobulin, we're tossing out a lot of harmful antibodies, and possible pheresis, which are some of the interventions, need to be understood better. To say that there are options for sensitized patients, these desensitization protocols, is true, but we really are not certain as to all the implications that are there or their effect on outcomes.
DR. GOODMAN: That's a very good point. Thank you for making it, Dr. Chertow. Any other comments on the matter of evidence gaps? Dr. Koller.
DR. KOLLER: Yes. This in response to a
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question by Dr. Steinbrook and by Dr. Singh. They had questions about the availability of some of the original studies. In your packet you noted that what was provided to you were basically the views from the FDA for the various ESA products. There was material available for pegylated erythropoietin and for darbepoetin. Unfortunately there are no FDA reviews that are available for erythropoietin, and all of these documents are normally FOIA documents that should be available shortly after the time that an approval is made, and that is a gap in the data.
DR. GOODMAN: Thank you, Dr. Koller. This is just another reminder of how much data there aren't, how many data there aren't, pardon my Latin. Dr. Singh, did you have a comment?
DR. SINGH: I'm surprised that the data is not available from the registration process for erythropoietin. We have both the manufacturers and the FDA, and I would think that if there's information there that is germane to answer these important questions, it should be made available. I just don't understand that, it puzzles me.
DR. GOODMAN: I don't understand it either. There's an encouraging point to be made, first that you're raising it today. Second that it's true, especially
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lately, that FDA and CMS are talking to each other much more often, and a lot of that's becoming productive, and I think that the federal government, including the regulatory side and the payment side, are recognizing that

their respective evidence requirements don't always line up very well. And to the extent that they can talk together about the kinds of evidence that will be useful for both regulatory and payment purposes, that might send some signals to the market for generating better evidence. Dr. Singh.

DR. SINGH: But talking between them is one thing. We're talking to the American people about putting them into the public domain. I would think that the FDA evidence should be in the public domain, it's 20 years old, and if there are unpublished trials, they should be on their website for darbepoetin. I don't understand it.

DR. GOODMAN: It sounds like a great idea to me, Dr. Singh. Okay.

FACA rules have us ending this at 4:30, no later, so here's what we're going to do. We're going to start with Dr. Stroncek at the other end of the room, and I would ask each panelist to say in a bullet, and no more than a sentence, the single most important suggestion you'd make to CMS or the stakeholders about improving the body of evidence to improve decision-making with regard to

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this particular clinical area, what would it be. So a bullet point or sentence, starting at the far end, and then we'll close. Dr. Stroncek.

DR. STRONCEK: I would like to see a randomized trial, maybe with two levels of erythropoietin given to pretransplant patients, with documentation of the number of transfusions pre-PRA levels at the beginning of the study, and then going into transplant and documenting transplant. There may not be enough difference in transfusions between the two groups to show an effect, but it would be a start.

DR. GOODMAN: And that was one sentence. Thank you. Dr. Holmberg.

DR. HOLMBERG: I would like to see CMS and HRSA work together to influence the OPTN, which is UNOS, in collecting observational data, and be able to not only track the outcome, but also adverse events.

DR. GOODMAN: Excellent. So already Dr. Stroncek and Dr. Holmberg made superb suggestions about where we go next. Dr. Paul.

DR. PAUL: I just echo that. I would just say much more robust prospective observational registry designs to collect all this data going forward, with substantially more data analysis.

DR. GOODMAN: Thank you, Dr. Paul.

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DR. STEINBROOK: I really agree with what's already been said, and again, with the data that already exists, get it out there publicly.

DR. GOODMAN: That was Dr. Steinbrook, thank you. Dr. Singh.

DR. SINGH: I think the evidence to support a

benefit of blood transfusions is not there, and I think that the evidence for potential harm is also not there, although we could get information, and I would encourage CMS to collect more information with respect to that. They have the ability to get that in their databases.

DR. GOODMAN: Thank you, Dr. Singh. Dr. Mintzer.

DR. MINTZER: I think the last thing we need is more EPO studies. This is the most studied drug over the past 20 years, and I think that's how we got into this whole quagmire. I think that the issue, again as I mentioned earlier, is I think the majority of nephrologists prescribe erythropoietin so the patient can last the next month, not so he can receive a transplant in a year. That's nice if it will help him get a transplant, maybe it does, maybe it doesn't, but I don't see how the input today is necessarily going to change the utilization of this drug within current FDA guidelines.

DR. GOODMAN: Thank you, Dr. Mintzer. Dr.

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Klein.

DR. KLEIN: Given the heterogeneity of the evidence with which we are confronted, I think it would be useful to set up some working groups to try to establish standardized parameters to measure in both prospective trials, but also in observational studies, in order to be able to compare and collate data for different studies. And I think getting a group of experts together to try to do that would potentially be a useful idea going forward in trying to sort through this morass of data.

DR. GOODMAN: Thank you, Dr. Klein. Dr. Grammer.

DR. GRAMMER: This is along the same lines. Well designed registry prospective studies I think would be very useful.

DR. GOODMAN: Thank you, Dr. Grammer. Ms. Cabral-Daniels.

MS. CABRAL-DANIELS: Also, to share the data, for CMS and FDA to share the data with each other, but more importantly with the patient, to come up with some type of form where the patient also is well informed of issues regarding, relative issues here.

DR. GOODMAN: Thank you, Ms. Cabral-Daniels. Dr. Satya-Murti.

DR. SATYA-MURTI: In addition to prospective

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studies, I think there is a wealth of unmined administrative data that could be used to identify those who are long survivors from Medicare administrative data, and to see what at best correlates with their longevity of graft survival.

DR. GOODMAN: Thank you, Dr. Satya-Murti. A few final comments from this chair. The big picture point. ESRD patients, as we

heard today, comprise a little more than half a million of the 43 million Medicare beneficiaries, but those 527,000 ESRD patients account for 46 percent of all Medicare expenditures, so there is a disproportionate impact of the health status and care of these patients on the overall program, one important reason why it was discussed today, and we owe these people a lot more than what we produced for them in the way of evidence.

The body of evidence here is messy, it's heterogeneous, it's nowhere near as useful as we hoped it would be. The excellent TA put together by the Connecticut EPC came up with 172 studies that met their inclusion criteria, which, by the way, was not the most restrictive inclusion criteria. Fully 83 percent of those studies were retrospective population studies. This isn't exactly grade one evidence. Now, yes, there were a lot of studies out there on ESAs, the point was made earlier, but

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those lots of studies on ESAs are not necessarily the ones that we're looking for. So you could back up a truckload of evidence at the CMS loading dock, and that body of evidence may not answer the kinds of questions that patients and doctors need, in addition to policy-makers, to answer their questions and make their decisions about policies.

Yes, among other things, a comprehensive prospective registry, maybe even starting with CKD patients, will be very useful for answering these questions. Remember, sometimes we hesitate to look at stronger studies, including RCTs, but do recall that when we don't pursue those studies there are costs, and I don't mean necessarily economic, there are losses in safety and compromised effectiveness, so we do try to tease out those stronger studies when we can't.

We heard from our patient representatives today about the absence of attention to daily living, patient quality of life. So we have a lot of data on intermediate measures and so forth, but precious little on quality of life, and I think the body of evidence does not address that sufficiently.

Finally, this whole set of questions would be much different and our deliberations would have been far different were there enough kidneys to go around, and the

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absence of kidneys for transplant in this country is a very serious concern.

With that, before I turn it over to Dr. Rollins, on behalf of our panel, I want to thank certainly our TA presentation from the University of Connecticut-Hartford EPC, our invited speakers, all of whom were absolutely superb, and we very much appreciate the time that you put in to preparing for this meeting, it was excellent. We thank our 16 scheduled speakers who provided excellent insight. We thank our one unscheduled public commenter,

and we especially thank CMS CAG staff, always doing a superb job. Back to you, Dr. Rollins.

DR. ROLLINS: CMS would like to thank the members of the MedCAC committee, especially the chairperson as well as the vice chairperson, as well as the guest speakers. Have a safe journey.

(Whereupon, the meeting adjourned at 4:27 p.m.)