about measures of inflammation, for example CRP. Is anybody looking at that as a possible marker for responsiveness?

DR. EISENBERG: We have an answer behind you. I think Dr. Klassen can answer that.

DR. KLASSEN: So, we have looked at measures of CRP in the available data sets and, as you would expect, increases in CRP are associated with both patients who have lower hemoglobin values and greater dose requirements. In terms of the specific incorporation-Bif your specific question was have we incorporated CRP levels in a definition of responsiveness, the short answer is that in order to do so many of the available data sets have CRPs who have CRP measured so we don't have a variety of data sets in all patients had CRP values and we have not been able to incorporate a specific CRP value that would, in fact, enhance the definition of hypo-responsiveness. We actually think it is a better measure to simply look at some combination of hemoglobin levels and dosing and that, in essence, represents responsiveness which

is impacted by a variety of different factors.

DR. PLATT: Dr. Black?

DR. BLACK: I wonder whether you have looked at something like blood viscosity or clotting time, or something more related to the thrombotic episodes that occur.

DR. EISENBERG: My area of research for about 20 years has been blood clotting so I have looked at this fairly hard. The answer is no, we haven't though, as you know, this is one of the challenges here. So, we have both the risk factors and underlying health status, as well as achieved hemoglobins that are high--even when you transfuse patients have been associated with clotting and other factors so that fits in. But, unfortunately, there just isn't definitive evidence because it hasn't been looked at.

DR. BLACK: I think as you know, higher hemoglobins are sometimes a risk factor--

DR. EISENBERG: Yes, absolutely for thrombosis--

DR. BLACK: B-and maybe relatively higher

hemoglobins for this population.

DR. EISENBERG: No, I agree. I think if you look at Normal Hematocrit, the dialysis population, that comes to mind. You know, there certainly are other studies that were done in the '90s. Back when I was in critical care, it was my primary occupation, looking at transfusion as a strategy in the critically ill patients turned out to be not a very good idea to get to normal hemoglobin. So, I think that is a very good point.

DR. PLATT: Thanks. Dr. Kramer, a question? No? Go ahead.

DR. NEATON: Just a question for Dr. Eisenberg I guess. As I understood it, in all your early trials for transfusion where you looked at functional status as well you used a target of 10.7 to 12.7.

DR. EISENBERG: So, the early epoetin alfa studies which actually were cited also by FDA which were the U.S. studies-Bslide up, please.

[Slide]

These would be the studies that we are

talking about. Yes, that would be the hemoglobin translated from hematocrit target at that time. Slide off, please. Now, we also cited the CSG study, which was a study that was performed by Johnson & Johnson where there were two targets. There was a 9.5 to 11.5 and 11.5 to 13. If we could go to the slide that we showed during the presentation on exercise from that study--

DR. NEATON: No, I think--

DR. EISENBERG: So, that one had the differential--

DR. NEATON: I am curious, in your outcome studies, why the highest target that was chosen in the control arm was 11.5. In your three outcome studies the highest target among those three studies was 11.5, and in none of the three studies is there any evidence of superiority of the higher target over the lower target. Yet, you are now claiming that the targets should be 10-12 and I am not--

DR. EISENBERG: I want to make sure I understand your question. I think what you are

referring to perhaps is in the CHOIR study.

DR. NEATON: Well, the CREATE study was 11.5--

DR. EISENBERG: Right.

DR. NEATON: The CHOIR was 11.3 and, as I understood the Normal Hematocrit, it was 10, plus/minus 1. So, the control arm that, you know the higher target didn't beat, none of them were as high as the upper target that you are proposing now and I am not sure I follow the logic.

DR. EISENBERG: Okay. Certainly the outcome studies need to be considered both from the perspective of dialysis studies and non-dialysis studies. So, in terms of the non-dialysis, the Normal Hematocrit study is the only outcome study in that population.

From the perspective of improvement in cardiovascular performance, I think what occurred at the time that study was done in dialysis patients is that there was a sense that higher was better. That turned out to be clearly wrong. But there was also at that point in time considerable

clinical experience among the dialysis community on the benefits of patients, from reducing transfusion perspective, in the 10-12 range. So, that has been where practice has remained in dialysis.

Now, in terms of CHOIR, again, I think the question there--and also we have actually asked the more robust question. I think the more robust question is what TREAT is addressing. Right? Which is let's get the answer against placebo of 13 versus the lowest. So, we believe we have asked that question and we anxiously await the results of that.

DR. NEATON: I applaud the trials that you are doing, and I am just trying to understand now kind of the target that you are proposing for the interim before those trials are complete.

DR. EISENBERG: Sure. I think that the basis for the recommendation of 10-12 is based on two key issues. The first and most important is that is where transfusion reduction has been demonstrated both in the pivotal trial and, if you look at the observational data, we can take out

issues of outcome or any other component, and you see that, as Dr. Klassen showed you, hemoglobins dropped below 11 and transfusions increased dramatically. So, I think there is good data that in clinical practice unless, of course, one were to find that that was a gad idea from an outcome perspective, that targeting between 10-12 reduces transfusions. So, that is the basis--

DR. NEATON: But there is no randomized evidence of 12 versus 10 or 11.

DR. EISENBERG: We have presented all the outcome data that is currently available.

DR. TEERLINK: Yes, some quick questions in regards to patient-related outcomes. Looking backward, I would actually be interested in hearing Dr. Trentacosti's approach, what her interpretation is of the Sickness Impact Profile and the symptoms that were related from the kidney questionnaire, as well as the exercise performance in terms of the past evaluation of the patient-reported outcomes. Are you still here?

DR. TRENTACOSTI: Yes, I am over here. The

kidney disease questionnaire was developed to measure health-related quality of life in patients undergoing dialysis and, as such, as not developed for evaluating anemia and some of the questions pertain to are you frustrated by your dialysis treatments? Well, that is not going to address anemia symptoms.

The physical symptom component of the kidney disease questionnaire actually gave patients a list of 26 symptomsB-infection, hypertension, nausea, vomitingB-and they picked which symptoms they felt pertained to them, and they followed those symptoms in the trial so it really did not evaluate physical function.

The Sickness Impact Questionnaire is a generic questionnaire that was developed to measure the impact of sickness for a general population. It was used in EP-84006. The inclusion criteria for that study was that patients had to be able to perform the six-minute walk test, but some of the questions in the Sickness Impact Questionnaire were generic and said things like can you move? Can you

get out of bed? Do you need help with ambulation? So, again, it was a generic instrument used for the wrong population.

DR. TEERLINK: And the exercise?

DR. TRENTACOSTI: That study also used the exercise stress test and the six-minute walk test. The initial data in the study report said that the six-minute test did not show statistical significance but the sponsor has subsequently sent in additional data sets and we haven't reviewed that yet.

DR. TEERLINK: It was the intention-to-treat analysis I believe. Then, looking forward, Dr. Pfeffer, I have a question in terms of the TREAT study. In terms of the symptoms and the quality of life assessments in that study, are they going to give us more information on kind of an official approach to patient-related outcomes?

DR. PFEFFER: Well, we fully agree with what Dr. Trentacosti just said, that the patient perspective is an important component of the

overall global assessment of therapy and that is built into our study. I am not an expert in this area, as you probably know, but we do have colleagues that are and we are doing the EQ5D, the F-Fatigue and the SF-36 at multiple visits. Also, in line with some of the other questions about inflammation, we are going to have a very rich database on biomarkers for the academic people to pursue to address some of Dr. Unger's questions.

DR. TEERLINK: And you have just addressed some of my other questions.

DR. PLATT: Very good. Dr. Kaskel?

DR. KASKEL: Yes, along the same lines for the biomarkers, we have to deal with acidosis, folic acid status, obviously iron, carnitine. I am assuming those will all be included in this database?

DR. PFEFFER: What is definitely included is permission from our patients to obtain blood and urine. We didn't think we were smart enough in 2004 to know all the markers we were going to measure in 2009. So, there will be some

competition as to what is the best use of these precious samples. Some of the ones you mentioned I am sure will be on the top of our list, and I am sure there are some that we would all like that aren't on anybody's list and we will wait until 2009 to start looking at those.

DR. PLATT: Dr. Hunsicker-Boh, excuse me, Dr. Lincoff didn't make the list.

DR. LINCOFF: I would like to get into a little bit more of the assertion that the alarming consequences of not having a hemoglobin target in terms of increasing transfusion rates that Dr. Nissenson and Dr. Klassen have pointed to.

In slide CC43 of Dr. Klassen's presentation there was association between transfusion rates and hemoglobins below 11. Yet, this seems to me to be confounded also by the issue of hypo-responders and I am not clear why. Perhaps someone could expand on why an approach that is currently labeled, that is, to use the lowest dose necessary to prevent transfusions, is so unfeasible or would seem to be so unfeasible. What are the

triggers for transfusions in these patients? In fact, in the ongoing TREAT trial it looks like the control arm is a rescue of less than 9 that would seem to be a more conservative approach that doesn't target a particular range.

DR. NISSENSON: I think the issue is really one of clinical practicality for nephrologists, and the current trigger for transfusion is entirely patient symptoms, and these patients are terribly ill, as I tried to illustrate, and if we don't have a target range for hemoglobin to shoot for which seems to be reasonably safe and to minimize the symptoms, then we are going to have to treat entirely based on symptoms and the vast majority of patients already have symptoms. So, if that is the trigger we are going to, for the good of the patients, have to start transfusing them more frequently because we don't have any other guide for how to get their hemoglobin a little bit higher and mitigate the symptoms.

DR. LINCOFF: Another question relates to the analysis that Dr. Zhang showed on slide 38 and

39. This is obviously, I think, the key finding or the key question of the analysis, is there a relationship with mortality and dose? But it looks to me like these aren't significant differences. In the IPW on slide 38 even the highest tertile that had the elevated risk ratio looked like it crossed the line of unity and there are no confidence intervals on slide 39. So, my question from this analysis of a simulation of a randomized trial is, is there significant influence of dose on mortality? DR. PLATT: Dr. Zhang, do you want to respond to that?

DR. ZHANG: So the question on 38, I think there are significant differences between the results based on IPW and the results based on standard adjustment. Just like I cited in the presentation, results based on IPW show that moderate EPO doses are significantly associated with lower mortality risk compared to the higher and low EPO doses. In contrast, standard adjustments show consistently higher, increased risk associated with a higher EPO dose. So,

basically to answer your question, I think the results based on IPW and the standard adjustment are quite different.

Regarding slide number 39, the thing is that with a big sample size, and if we are doing confidence intervals with, you know, more than 200 in samples, it is very time consuming. But definitely, when we have the confidence intervals we will send it over to FDA.

DR. PLATT: Dr. Hunsicker?

DR. HUNSICKER: My two questions are for Dr. Unger. The first is related actually to what Dr. Lincoff asked before, and I am going to quote briefly from the briefing document I got and it has to do with what target would be an indication for transfusion. Additionally, clinical data were not available to justify any specific hemoglobin or hematocrit levels that directly correlated with, quote, a reduction in the need for red blood cell transfusion, unquote, the main treatment effect. Hence, the March, 2007 label revision allowed prescribers to use their clinical judgment in

determining the lowest level sufficient to avoid the need for red blood cell transfusion.

I am a practicing nephrologist. I am aware of the fact that the measure of hemoglobin at any one time is going to be predictive of the need for some sort of intervention down the line because people vary. If you are trying to stay above a level at which transfusions are needed, you are probably going to have to maintain on ongoing level that is higher than the level at which transfusions are needed, if you follow what I am saying, because it will go down.

So, my question then gets back to the data that were presented by Dr. Klassen showing the relationship between prevalent hemoglobin level and the need for transfusion. Would you be willing to extrapolate from that a guidance as to the level needed to avoid transfusion that was in the neighborhood of 10 or 11?

DR. UNGER: I mean, the transfusion—B threshold is really, pause, —you are talking about clinical practice.

DR. HUNSICKER: Indeed, and, unfortunately, we have no information about what hemoglobin level is associated with a good biological effect. That just doesn't exist. We don't have it. So, what we have to do is to go on the practice. The practice shows that people whose hemoglobin drops below 11 or 10, depending upon which number you want to take, the incidence of transfusion is higher. Trying to stick with transfusion, my question is would this be sufficient to lead the FDA to suggest that these levels seem to be levels at which the need for transfusion is avoided?

DR. RIEVES: Dr. Hunsicker, we actually discussed that in our initial presentation, the considerations of identifying a target hemoglobin level and, again, to make sure we all understand, the current label, based upon the revision from March, does not identify a target. It defaults to, as you say, the subjectivity information which, candidly, could probably be inferred and that is what we are hoping to achieve today. And, yes, as I pointed out earlier this morning, the

consideration is tied in not only to safety but also efficacy. So, the considerations relating to transfusion, the transfusion triggers, if you will, would be a reasonable consideration in there.

Part of our challenge though is that in most of the studies, in fact all of the studies, we have no data on transfusion triggers, if you will. But that could be part of the considerations from this committee and that is actually what we are hoping to hear.

DR. HUNSICKER: Okay. The second question is more directly related to Dr. Unger. At the very end of his presentation, I can't quote you exactly because it went by very quickly but you said that the best current evidence suggested that the optimal hemoglobin was in the range of, as I recall, 10-11. What is the nature of that evidence? Is that evidence that is admissible or useful for FDA purposes or is it not?

DR. UNGER: That is slide 53, if you want to put it up.

[Slide]

I mean, that is the information that we have from the randomized, controlled trials. I mean the target of 10, plus/minus 1 comes from the Normal Hematocrit study and 11.3 comes from CHOIR, and that is the RCT data that we have. So, that is what that is meant to mean.

DR. PLATT: Dr. Good, do you have a question? So, we will go through these two questions and then we will do lunch.

DR. GOOD: My question would be for Dr. Singh. In trying to weigh the risks and benefits of the ESAs, I think we have to put a lot of thought into patients' quality of life. I have a hard time working through the evidence reported on industry-sponsored trials that are open-label and evidence gathered by research assistants that, you know, are probably very eager to gather this from patients, and I was very intrigued that the CHOIR study found no difference in patient-reported quality of life. So, I was wondering why you think that is. Is there an attenuation of patient-reported quality of life once the

hematocrit reaches a certain level, you know, once you get above a hematocrit of 11 or 12? Or, why did you find no difference in quality of life when others have reported significant improvements in quality of life despite having similar levels of hematocrits that you found, similar to your trial?

DR. SINGH: Thank you. Just to be accurate, the quality of life improved in both arms. So, for the lower hemoglobin arm and for the higher hemoglobin arm there was an improvement in quality of life. The key finding in CHOIR was that there was no statistically significant difference for any of the quality of life instruments or the domains within those quality of life instruments, any difference between the two arms.

That would suggest, at least interpreting just the CHOIR data and, as has already been discussed, there are some limitations of open-label studies, and so on and so forth, but with respect to quality of life that would suggest that there is no quality of life benefit in raising the hemoglobin from the target level of 11.3 to 13.5

g/dL. I can't speculate about lower levels. That has been discussed already. There are a number of studies, the limitations of which have been alluded to, that suggest an improvement from very low hemoglobin levels to higher hemoglobin levels but, again, the limitations of those have been discussed. But for CHOIR there was no difference between the two groups.

Now, in the studies that have been published, the other randomized, controlled studies, the quality of life reporting was selective for certain domains and for certain quality of life instruments, and the improvements appeared to be different for different domains. So, for example, in one study there was an improvement in the vitality score. In another study there was an improvement in physical functioning, you know, between the hemoglobin arms. So, that is another factor that is contributing to the noise in this, not only that the studies were open-label, and that the instruments used may or may not have been validated, but also that the

reporting of the quality of life data was very selective for different domains. For CHOIR we have data for all the domains and for three different instruments, and there was improvement in both arms but no difference between the two arms.

DR. PLATT: Thank you, and last, Dr. Day?

DR. DAY: This is a question for Dr. Nissenson and it concerns benefits claims. In your presentationB-I know you had to get a lot in, in a brief amount of time, but you did mention benefits in evoked potential studies. Now, these would speak to some kind of cognitive benefit and I was wondering were the data that you were referring to have to do with the behavioral components, say, accuracy in reaction time, or in electrophysiology itself, so the event-related potential, its magnitude or its time course? That speaks to what cognitive function do you think this is enhanced?

DR. NISSENSON: Well, the studies that we conducted-Bwe actually did two sets of studies, first the study comparing lower hemoglobins, below 10 to a hematocrit of about 35 percent, so a

hemoglobin close to 12. And, we did a whole panel of patient-reported outcomes, general cognitive tests and, to cut this a little bit short, the greatest change we saw on neurocognitive functioning was with trail making tests, with the two trail making tests. Then we did the evoked potential EEGs in the initial studies, a little less sophisticated than the later studies. We used a P300 and showing the efficiency of cognitive functioning based on the P300. We subsequently did a study comparing a hemoglobin of 10 to a hematocrit at the time of 45. Again, these were not safety studies. These were just brain function studies. We raised hemoglobin for two weeks, maintained it for two weeks, did the same studies, more sophisticated P300 tests and those are the ones that improved compared about 10 to about 14 or so.

DR. DAY: So, the claim would then be about attention of the cognitive function--

DR. NISSENSON: Yes, and the thing that I wanted to emphasize, and again I am not presenting

this as some final, proven randomized, controlled trial fabulous scientific data, but what impresses me is that what patients say correlates exactly with the neurocognitive tests that are done, the same domains, which correlate with the neurophysiological improvements that we see. So, I think none of them is the most rigorous but the weight of all together I think is pretty impressive.

DR. DAY: So, you do plan to go forward with more neurocognitive testing?

DR. NISSENSON: I think those are very valuable studies and, hopefully, we will get to do more of those.

DR. DAY: Thank you.

DR. PLATT: It is time for lunch, folks. We are a few minutes late. Let me take a sense of the group. Is there anyone who would have a problem starting up at 1:00, which is the scheduled time? Not hearing that, I will say we will start at exactly 1:00. Thank you.

DR. PHAN: And please refrain from

discussions. Enjoy your lunch.

[Whereupon, at 12:04 p.m., the proceedings were recessed for lunch, to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

Open Public Hearing

DR. PLATT: Thank you for coming back on time. The next hour is allocated to the open public hearing part of this meeting. We have eight speakers who are registered and we will be very pleased to hear your comments. Dr. Phan, will you tell us how much time does each speaker have and what the rules of engagement are, please?

DR. PHAN: Each has seven minutes, except for the group who has ten minutes. There will be a timer at the podium and it will turn yellow at one minute and at zero seconds the mike is going to cut off. So, use your times wisely.

DR. PLATT: Say that again, how much time for each speaker?

DR. PHAN: Seven minutes, with two groups of ten minutes.

DR. PLATT: Good. So, could we have speaker number one, please?

MS. WAGER: Members of the committee, thank you for inviting me before you today--

DR. PHAN: Could you hold on one second?

MS. WAGER: Sure.

DR. PHAN: I need to read an OPH statement real quick. Will you read it?

DR. PLATT: Okay, I haven't rehearsed this. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of

your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Thank you. I am sorry that we interrupted you.

MS. WAGER: That is okay. I do not have any financial relationships. Members of the committee, thank you for inviting me before you today to testify. My name is Roberta Wager and I am the president of the American Association of Kidney Patients. AAKP is the only national non-profit organization founded by kidney patients for kidney patients.

Our organization is dedicated to serving the needs, interests and welfare of all kidney patients and their families, and this is the reason I am here before you today. As a two-time kidney transplant recipient and a practicing nephrology nurse, I am well aware of the human and financial cost of care. We, at AAKP, were able to testify

before the Ways and Means Committee two months ago and I am pleased to share our views with the panel today.

Our nation has the unique opportunity to provide better outcomes for kidney patients, and this can lead to substantial cost savings because, as we know, better outcomes translate into less reliance on drugs, dialysis and hospitalization currently covered by Medicare.

Let me begin by stressing how important it is to get the dosing of ESAs right for kidney patients. AAKP supports achieving a hemoglobin level of 11-12 g/dL. We view current CMS monitoring policy as somewhat out of sync with where the FDA is and where the mainstream medical community is. Although each case is different and there will always be outliers, from a patient perspective there is very little medical reason for a patient to remain at levels above 13 g/dL, especially in light of the current literature citing safety issues.

AAKP strongly adheres to the principle

that a physician and patient must be permitted to decide a care plan best suited for that patient. Separate Medicare reimbursement for ESAs potentially detracts from the doctor-patient decision-making relationship. So, we support bundling Medicare reimbursement for ESAs into the overall Medicare reimbursement rate. We believe that bundling the payment would not only result in cost savings but also would result in more appropriate dosing of ESAs and draw more attention to the comprehensive nature of kidney care.

Let me emphasize that under-dosing of ESAs is a danger too. Again, let me stress that ESAs should be given to reach a hemoglobin level of 11-12. We are concerned about any lower initiation point. Many kidney patients, as do I, remember the difficult times before ESAs were available, suffering the debilitating fatigue associated with anemia. I started hemodialysis in September of 1982 and I can personally tell you ESAs do make a difference in avoidance of blood transfusions, etc. However, most of all, ESAs have improved a

patient's quality of life. Without ESAs I would not have been able to continue to work full-time as a dialysis nurse while waiting for my second transplant. It does make a difference.

What we need is an FDA and Medicare policy that strives for a Goldilocks solution on ESAs, not too much, not too little but just right. So, we believe Congress, CMS and FDA should, one, establish guidelines regarding the proper dosage of ESAs and, two, link reimbursement to meeting those guidelines.

Let me first just say a few words about potential sub-q administration. We surveyed 3,600 patients about sub-q administration of EPO and we found that patients were willing to do sub-q. A majority of them told us they wouldn't mind getting EPO as a shot and even give themselves a shot. Most of these patients are already self-administering shots because of their diabetes.

AAKP applauds the FDA leadership on this issue that is so important to us as kidney patients. We offer ourselves as a resource to you

as your committee works on these issues. Thank you, and I look forward to responding to the questions.

DR. PLATT: Thank you very much. Speaker number two, please.

DR. HIMMELFARB: Good afternoon. My name is Jonathan Himmelfarb and I am chair of the Public Policy Board for the American Society of Nephrology. The American Society of Nephrology is a professional society with over 10,000 members, virtually all practicing nephrologists and most kidney disease researchers in the United States are members of the ASN.

I would like to take a few minutes to elaborate on some of the concerns that have been raised about potential unintended consequences should there be a change in labeling of ESAs such that the threshold for transfusion was exceeded. I would like to mention that kidney transplantation for patients with chronic kidney who have progressive chronic kidney disease and progress to ESRD, kidney transplantation is the preferred ESRD

treatment option.

This landmark study, published in the *New England Journal*, used USRDS data and compared patients that were on the waiting list receiving dialysis for kidney transplant to patients that were also on dialysis that received a deceased donor kidney transplant. This data relatively unequivocally shows that while there are early risk in the perioperative period associated with transplantation, those risks cross very early post kidney transplantation. By several hundred days post kidney transplant there is a net benefit to transplant versus dialysis, and that is maintained and enhanced long term. So, there is very little doubt that for eligible patients with end-stage renal disease receiving renal replacement therapy kidney transplant is the preferred option.

Transplantation in this country hasn't been mentioned much today, but it is clearly a success. This is SRTR, Scientific Renal Transplant Registry data, showing that more than 100,000 patients are now living with a kidney transplant in

the United States. On Friday, the 2007 USRDS annual data report went on line which showed that almost 150,000 patients are now being treated with a kidney transplant, and it is between 29-30 percent of the treated ESRD population at this time. Nonetheless, the kidney transplant waiting list continue to grow. It has crossed 60,000 and represents between 19-20 percent of patients that are currently receiving dialysis therapy.

So, if we combine those patients that are being treated with a kidney transplant and those patients that are waiting for a kidney transplant, they constitute very close to 50 percent of the prevalent treated ESRD population at this time.

Now, this is for historical perspective but I think it is meaningful. This is a paper that was published in JAMA in 1981 from a prominent transplant center reflecting their experience in the New York, New Jersey area. These investigators noted that despite the increasing prevalence of ESRD patients the number of transplants was declining, and this was due to progressively

increasing rates of allosensitization, such that 92 percent of patients who were coming forward for consideration of kidney transplant were highly sensitized and, thus, unable to receive a kidney transplant. So, this reflects data from the pre-ESA era in terms that clearly showed that frequent blood transfusion was a major risk factor for inability to receive a kidney transplant.

These are more recent data. These are from the SRTR 2006 annual data report. They indicate that this problem is not going away. The point I want to make is on the fifth or sixth line that even in the most recent era approximately 33-35 percent of patients remain sensitized while awaiting kidney transplant. So, this problem of sensitization has not gone away in the post-ESA era.

This is not just a problem of prevalent patients that are highly sensitized not being transplanted and on the waiting list because, if we look at new registrations, we find that a significant percentage of patients that are newly

registered for kidney transplant remain sensitized. We also see, if we look at median time to transplant, that there is an inverse relationship between time to transplant and the degree of sensitization that is very robust.

And, I would point out the third row up from the bottom where you see asterisks in the median time to transplant in highly sensitized patients. This goes back to 1996. The point is that one cannot calculate a median time to transplant in highly sensitized potential recipients because the truth is most highly sensitized potential recipients die on dialysis awaiting a kidney transplant.

Now, if a highly sensitized patient eventually does get a kidney transplant, it is worth noting that that excess waiting time is also a risk factor for adverse outcomes after transplantation. This paper reported the results of a paired donor kidney analysis also using USRDS data. This is a rigorous analysis where when a pair of deceased donor kidneys are allocated, if

one was allocated to somebody with short waiting time and one to somebody with long waiting time outcomes were compared. This adjusts for any potential confounding related to the donor, and we see that patients that have been waiting for a long time are more sensitized and have worse outcomes.

Now, has this problem gone away? No, this is recent data showing that transfusion-associated sensitization continues even in the era of leukoreduction of blood so for all-comersB-this is a study from Canada recently published, a third of patients who receive blood become sensitized for high risk groups that have had a previous pregnancy or transplant over 50 percent.

In summary, there is a high prevalence of anti-HLA antibodies after blood transfusion which can be virtually an insurmountable barrier to kidney transplant. It is associated with longer waiting times, increased rejection, decreased allograft survival, and sensitized patients continue to constitute a high proportion of patients on the transplant list.

So, any policy changes that are considered in terms of the use of ESAs need to carefully account for transfusion-associated risk in the transplantable population.

I would like to turn the presentation over to Dr. Szczech, who is chair of the ASN's dialysis advisory group and a member of the public policy board, as well as a CHOIR investigator, who is going to present data on new analyses, post hoc analyses of CHOIR data.

DR. SZCZECH: Thank you, Jonathan. In the interest of time, I can leave the methods, unfortunately, to questions if you have any.

My financial relationships, I have received grant support from Ortho Biotech. I am on speakers bureaus for both OBI and Amgen and the ASN is paying my expenses.

So, we have been interested in exactly what happened in CHOIR, to be very honest with you, for a number of months and we have done a number of analyses, including time-variate and two landmark analyses looking at four-month and nine-month

landmarks. Unfortunately, I don't think the pointer will reach so I am just going to describe these curves.

The two bottom curves, the solid line curves, demonstrate those people in group A, the higher group, and group B that achieved target. Those people that did not achieve target in group A and group B are above. So, clearly, if you did not achieve your target you did worse. Again, here you can see the two lower curves are those that got low dose of epoetin alfa. The two higher curves are those two groups in A and B that got the higher dose of epoetin alfa. Again, low dose curves, regardless of your goal, were superimposed; high dose, regardless of your goal, were superimposed.

So, what happened? Any analysis of trying to understand the relationship between dose and the potential influence of confounding depends on your assumption that randomization equally distributed those things that mark confounding between the two groups. What I don't show you here is that hemoglobin at baseline was similar for both groups.

Hemoglobin at three weeks was similar for both groups. I remind you, if you don't know, that CHOIR used 10,000 units sub-q every week for the first three weeks in both arms so the doses were the same. So, the fact that they had the same hemoglobin at three weeks indicates roughly that they had the same response. Albumin and ferritin were both equal between the two groups.

What you can see is that in that group A and group B an equal number of people did not achieve 11 and an equal number of people got greater than 11. So, this is yet another suggestion that randomization equally distributed on those things that are confounding in terms of dose were between both groups.

What happened in CHOIR is simply stated on this slide. The groups that did not achieve 11 have very small numbers of patients. I wish I could point for you. In group A there were 16 people; in group B there were 12 people. So, I don't really have any faith that those two point estimates are different in terms of the proportion

of people that reached the final endpoint.

What you can see is that those people who got to greater than 11 and those people who got between 11-13 and then reached their goal in group A had differential outcomes. And, it is that middle group, the people that could not get to 13 but did get to 11 in group A that really drove the analysis. What is different between those people that got to greater than 11 in both A and B? It is dose.

Looking at the multivariate models in the four-month landmark we used a subset of patients because, of course, they had to live to the four-month mark. You can see that target was the same in the intention-to-treat analysis. When you add in achieved hemoglobin target becomes very significant, not presented here, and achieved becomes significant in a positive way. When you add in epoetin dose the maximum dose...

DR. PLATT: I am very sorry, the time has elapsed. We will have to move on. Speaker number three, please.

DR. PORT: Thank you, Mr. Chairman, members of the committee. Dr. Wolfe and I are happy to present new research findings this afternoon. We are both from a non-profit institution called Arbor Research Collaborative for Health, in Ann Arbor. Our work presented today will be based on CMS-funded work.

As a declaration of potential conflict, let me indicate that other research at Ann Arbor Research is funded by Amgen and Kirin, that is, the dialysis outcomes and practice pattern study, we will not report on those findings today.

We report today on CMS-based analyses to deal with the hemoglobin goal in ESA treated patients in essentially all U.S. dialysis facilities. To introduce Dr. Wolfe, I would like to emphasize that there are observational study designs that provide different levels of evidence. What you have heard this morning, all the presentations this morning based on observational studies are based on patient-level analyses which are often confounded and biased even when using

advanced statistical techniques.

The second level of observational studies leading to evidence is facility-based analyses where, for example, the levels of anemia control and facility level outcomes are correlated. This is like a random treatment assignment where patients happen to be assigned to facility practices, treatment practices of anemia and then we rate the treatment of the facility with the outcomes at the facility level-Ba different level of evidence, and I hope you will have an open mind to look at the different levels that come from patient level versus facility level analysis.

The third level is even more important. It is when you can show that a facility-based analysis of changes in practice over time correlate with changes in facility outcomes. Dr. Wolfe will focus only on facility-based analysis this afternoon.

DR. WOLFE: Thank you very much. Next slide, please. I am going to skip a few slides. Rather than talk about the logic behind the

statistical methods, let me show you the results. These are data from the Medicare database from 1999 and, rather than classify patients according to hemoglobin levels, we have classified facilities. We classified over 2,800 facilities according to the fraction of patients in that facility who achieved hemoglobins or who have hemoglobins of 11 or greater.

On the right-hand side we have the group of facilities, 570 facilities, where over 87 percent of the patients had hemoglobins greater than 11. In the left-hand bar we have those facilities, 572 of them, where less than 65 percent of patients achieved hemoglobin over 11, and in the middle two bars we have the middle two quartiles of facilities, about 570 facilities in each group. What we are doing here is classifying facilities because if patients are essentially going to facilities that are close to them they are ending up randomized at different facility practices, and these different groups of facilities do represent very different practices with regard to anemia

control. Those on the right-hand side have a large fraction of patients achieving the goal. Those on the left-hand side have a lower fraction.

Let's see, based upon the vertical axis here, the corresponding differences in mortality related to these differences in practice patterns at the facility level. Notice, we are not analyzing patients who achieved 11 or greater; we are analyzing facilities who achieved a larger fraction of 11 or greater. Just as in a randomized, controlled clinical trial, we analyze groups of patients in treatment groups rather than groups of patients defined by their achieved outcome.

The vertical scale shows the relative mortality for these groups. On the left-hand side you can see that the facilities with the lowest level of amenia management had a relative risk of 1.1. That corresponds to 10 percent extra deaths, 1 in 10 more deaths. On the right-hand side we have relative mortality of 0.96, four percent fewer deaths. The difference between those two is about

14 percent.

If you happen to have been a patient who, luckily, was assigned to a facility achieving a high level of anemia management you would be at a facility where there were one in seven fewer deaths than if you happened to be an unlucky patient assigned to the left-hand quartile of facilities.

Now, what can explain these results? This is an observational study. Dr. Port suggested this may be different from the other observational studies that you have seen. I believe it is. Think about what could have led to these differences in practice patterns and the corresponding differences in mortality. Is it because facilities at the left just have sicker patients and, therefore, find it harder to get their hemoglobins up, and have higher mortality, and the ones on the right just happen to have healthier patients? Perhaps so.

But there is also an experiment that took place since 1999. Many of these facilities changed their practices. What happened to the patients at

those facilities when the practices changed? Did the patients carry their sickness with them as they moved from the practices on the left-hand bar to the right-hand bar? And, did the mortality go up among facilities in the right-hand bar? If it is due to sick patients, that is what you would expect to see. As facilities change their practice it won't change the mortality. Alternatively, if we see a change in mortality, that would suggest it might be because of the change in practice. This is actually one of the assumptions underlying this method of analysis which is called instrumental variables. It is well accepted and understood in the statistical literature. To infer causality from this relationship that you see right in front of you, it requires that the only relationship between mortality and the facility be expressed through the fraction of patients achieving the hemoglobin goal of 11 or greater.

The next slide shows what happened by 2002. The number of facilities in each of these same categories is shown in the pastel blue bars,

right there. You can see, instead of a quarter of the facilities having the worse anemia management we now are down to 83. Nearly 500 facilities have moved out of that category. In the right-hand side we have nearly three times as many facilities as we used to. These facilities, when they changed their practices between 1999 and 2002, saw a corresponding reduction in mortality down to what we would have expected based upon that first slide. The mortality in the right-hand slide is about the same as we saw in 1999. The patients weren't sick to begin with or, at least if they were, they did not remain sick by 2002. Is it possible that there were a thousand facilities that changed their practices and outcomes by cherry-picking and getting rid of their difficult patients? That is up to you to decide.

This suggests that changes in practice did occur and they led to biologically lower mortality. We need more granularity here however. The previous result was published in AJKD. Now I am moving on to analyses which have not been

published. We are looking at more granularity in hemoglobin. We have hemoglobin ranges along the horizontal axis and on the vertical scale we show the percent of patients across the United States at 4,500 different facilities in each of those categories. You can see that 11.5 to 12.5 is the most common range. About a third of the patients are there.

However, facilities aren't all average. The box and whiskers there shows the range among facilities, among 4,500 facilities, and the fraction of patients in each of those categories. We examined that variability to see if facilities that had more patients in certain categories had correspondingly higher or lower mortality.

That is shown in this slide, right here, where we look at the relative risk, on the vertical scale, associated with having 10 percent more patients in any of these categories at the expense of moving them out of the reference category. What you see on the right-hand side of the reference category which we chose as 11.5 to 12 is excess

mortality ranging between four percent and nine percent. That is between 1/25 and about 1/11 excess deaths associated with having higher hemoglobin levels for these patients. At lower levels, below 10.5, we see excess mortality associated rates of 9 percent to 21 percent. That is 1/11 up to about 1/5 excess deaths.

We did this same analysis looking at changes in practice patterns as a sensitivity analysis. That is shown here. This does not compare one facility to another; it compares facilities to themselves as they changed their practices, and you can see similar mortality risks corresponding to changes in practice patterns.

In conclusion, anemia practice defined by percent of patients varies widely among facilities and it allows us to study mortality. It is lowest in the range of 11-12. It is elevated up to 10 percent per 10 percent more patients as you move to higher hemoglobin levels, but up to 20 percent higher mortality...

DR. PLATT: Thanks so much. We are ready

for speaker number four, please.

DR. PROVENZANO: Ladies and gentlemen of the committee, thank you for allowing me to speak today. My name is Robert Provenzano. I am a practicing clinical nephrologist in Detroit, associate professor of medicine at Wayne State University, the past president of the Renal Physicians Association and a member of the Office of the Chief Medical Officer of DaVita. My financial disclosures today, I have been a medical director for DaVita and Fresenius, and have had a speaker bureau relationship and research relationship with Ortho Biotech, Advanced Magnetics, Roche and Acumax[?].

I am here today on behalf of not only over the 1,200 practicing nephrologists serving as medical directors for DaVita but for all practicing nephrologists. DaVita is a dialysis organization responsible for the care of over 100,000 patients with chronic kidney disease undergoing dialysis. We serve patients with CKD and ESRD, who are a unique and distinct group whose morbidities and

responses to ESA therapy, as heard today, sets them apart from all other groups, specifically cancer sufferers as well as HIV patients. On behalf of DaVita, myself, my patients and practicing nephrologists, I do appreciate this opportunity to address you.

Concerns raised by recent studies showing higher patient mortality and/or cardiovascular events with study target hemoglobins of greater than 13 g have resulted in much scientific and public scrutiny of the treatment of anemia in our patient population. DaVita has taken this opportunity to focus and analyze our patient database to determine what, if any, impact these studies have had on real-life management of anemia in our patients.

As many of my colleagues will be focusing on other important aspects of concern today, I will limit my comments to our data on the results of withholding ESAs and then briefly on patient quality of life with anemia improvement.

DaVita performed a retrospective

longitudinal examination of all of its hemodialysis patients receiving epoetin alfa therapy between January 1st and June 30th, 2007. Within this patient group we identified two cohorts by level of baseline hemoglobin, either 12-13 g/dL or above 13 g/dL. Within each cohort we reported the epoetin alfa doses administered at each dialysis treatment and calculated percent changes in doses from baseline during the first four weeks of the study period. We then evaluated changes in hemoglobin from month one through six of treatment according to the percent epoetin alfa dose reduction.

What you see here is that our results confirm the experience of most experts in this field as well as practicing nephrologist, that withholding epoetin alfa doses or making large-scale dose reductions in these patients who lack endogenous erythropoietin produces, in turn, both below target hemoglobin and subsequent above target hemoglobin, a phenomenon referred to earlier as cycling. You can see that again here.

Recently, a publication in the *Journal of*

the American Medical Association provided information on hemoglobin levels, utilization of epoetin alfa, magnitude of dose reduction and ownership of dialysis facilities. The data published in this report showed that high month to month dose reductions are associated with higher average weekly epoetin doses. Taken together with other findings, these results suggest that excessive dose reductions should be avoided and that large-scale dose reductions or withholding epoetin may actually increase epoetin utilization.

Further analysis of this data confirms a second observation, that regardless of ownership, facilities that use higher epoetin doses have a higher proportion of patients with hemoglobin levels above 11 and that facilities, likewise, with the lowest epoetin utilization, on the other hand, showed the highest proportion of patients with hemoglobins 11.

Compelling evidence that achieving this benchmark and other CMS ESRD clinical performance measures lowers the risk for mortality in dialysis

patients is important in the interpretation of the safety of achieved hemoglobin relative to target hemoglobin. That 19 should be 17, by the way. The overwhelming benefits of anemia treatment with ESAs in this patient population over the past 18 years should be acknowledged as having a major contribution to the marked improvement in patient mortality despite increasing patient age and co-morbidities.

Taken together, this data supports the following statement which would replace the current black box warning for patients, and provide both necessary and sufficient instructions for managing anemia safely in ESRD patients: That Epogen should be administered at the lowest dose needed to achieve a hemoglobin greater than 11; that the dose should be decreased if the hemoglobin exceeds 12 or the hemoglobin rate of rise exceeds 1 g/dL every two weeks or 2 g every four weeks.

Finally, one cannot help by shake one's head as we debate any suggestion that quality of life is not positively impacted by the use of ESAs.

Many practicing nephrologists, myself included, recall the days, as mentioned earlier, where severe anemia so negatively impacted the lives of patients that many of them questioned whether or not dialysis was really worth their effort. The life-altering improvements that occurred after correction of their anemia can be attested to by thousands of patients noting their improvement and sense of well-being, ability to interact with their families and to remain gainfully employed. Any inadequacy in our tools to measure these changes should be looked at suspiciously.

In conclusion, I hope that the information provided today, gleaned from real-life clinical practice and supported by published literature, advances our shared goal of providing safe and effective care to all ESRD and chronic kidney disease patients. We hope that the agency creates policies and warnings that are specific to this population; that you consider the dangers associated with withholding ESAs rather than incrementally adjusting their dose; accept the CMS

ESRD clinical performance measured hemoglobin target of 11-12; and carefully consider any policy decisions not be made without overwhelming evidence that they are appropriate and based on accurate understanding of all available evidence; and take a broad, common sense view as to the definition of quality of life as it pertains to patients who would otherwise be severely anemic without the appropriate use of ESAs. Thank you for your attention.

DR. PLATT: Thank you. Our next speaker is number five, please.

DR. LAZARUS: I am Dr. Michael Lazarus. I am the chief medical officer for Fresenius Medical Care. I am employed by Fresenius Medical Care. I am an associate professor of medicine at Harvard Medical School.

I would like to review with you some of our experiences in our 120,000 patients and 1,600 dialysis units in our company. First, I would like to stress that ESRD or dialysis patients are different from CKD patients, and are particularly

different from cancer patients.

I have enumerated a number of reasons here but, in the interest of time I will not go through them. I will simply point out that we believe that FDA must develop separate and distinct indications, dosage recommendations and warnings for erythropoietin for these three categories of patients.

With regard to the randomized, controlled trials, you have see this data, I will only point out that all of the randomized, controlled trials, both in pre-dialysis and dialysis, patients is a hemoglobin above 13.5 goal. In four of those six studies the goal was achieved; in two it was well above 12. There may be evidence of death risk in dialysis patients that achieve hemoglobin values of 13 to 13.5 but that information comes from one of three RCTs. There is no scientific evidence for a safety concern for a hemoglobin level of 12 in dialysis patients.

The curve of hemoglobin values that Dr. Wolfe showed you earlier is reproduced here. This

curve we have seen repeatedly over the past seven years. This is USRDS data in the CPM, clinical performance measures project of CMS. You can see that it is a broad distribution curve of hemoglobin values. It does not change in shape over the seven years, but you will notice that the curve has shifted to the right. That, in response to pressures from CMS and other quality organizations to reduce the percent of patients below 11.

Another way to look at this is the intra-patient variation. This is a particularly important issue with these patients. We looked at all patients that had ten hemoglobin values in a period of a year, of which there were 48,000, and plotted the standard deviation of those patients. You can see that there is a skew to the right. If one examines those patients at the 75th percentile, that means that that patient, in the period of a year, would experience a hemoglobin less than 10 or greater than 13 one-third of the time. There is marked variation and variability of patient response to erythropoietin. This is not an easy

therapeutic model for a physician.

Another way to look at this is the study that we reported in 2007 in response to the CMS EMP policy. That was a billing policy that put a restraint on hemoglobins above 13 by payment. The distribution curve is flipped on its side. The yellow boxes are greater than 13, blue is 12-13, the green is the target of 11-12, and purple is less than 11. You can see that over a four-month period that distribution does not appear to change despite the fact that as we followed patients over that four-month period they rapidly cycled in and out of different categories or buckets. There was marked management of patients up and down and, despite that, at the end of the four months the distribution curve appears to be exactly the same.

So, the variable response of ESRD patients causes a distribution curve with a mean standard deviation of 1.1. The distribution curve is stable. Although there is marked movement of patients within that curve, physicians have been unable to change the shape of the curve. That is,

we have not been able to eliminate patients at the extremes and narrow the curve. And, there has been a shift in the curve both to the left and to the right in response to Medicare, Medicaid, FI policies and soon to be an FDA policy.

If we modelB-this is a model and I took the patients in our current distribution in our company, which is the blue curve, and we say that no patient may exceed a hemoglobin of 12. No patients achieve a hemoglobin of 12. That curve will shift to the left and is represented by the red curve. That means that 60 percent of the patients will be less than a hemoglobin of 10; 64 percent less than 11; the mean will be 8.7, with a large percentage of patients below 8.

Well, perhaps you might ask the question how low is too low? That has been discussed here. There are no randomized, controlled trials at the low end but there are observational, retrospective studies, this one from Li and Collins of USRDS of 50,000 patients. You have seen these slides before. This is a relative risk below a hematocrit

of 33. This is our own data in which these patients were case-mix adjusted, again showing a relative risk of death below a hemoglobin of 11 in 82,000 patients.

And, this is the DaVita data that you have seen earlier. Even with a randomized, controlled, case-mixed line on the bottom there is significant increase in the risk of death. How low is too low? That is yet to be seen but we have to rely on the retrospective data.

With regard to transfusions, you have heard this discussion at great length. I will only point out that because of risk of iron overload, hepatitis, AIDS, sensitization physicians vary in their response in how they transfuse patients. I do not believe that physicians transfuse to some frequency to pre-identified hemoglobin level.

In summary, ESRD dialysis patients are vastly different from CKD and cancer patients. A hemoglobin of 12 is not scientifically supported as the level of adverse event concern. Variability of response of these patients to ESAs demands a

distinction between the target and achieved hemoglobin levels. It makes the concepts of approaching that target and avoiding transfusion confusing and impractical to physicians. Transfusion is a treatment, not an outcome, and its avoidance is poor guidance for clinicians. Thank you.

DR. PLATT: Thank you. The next speaker is number six I believe.

DR. VANWYCK: Good afternoon. I am David VanWyck. I am a professor of medicine and surgery at the University of Arizona College of Medicine. I am co-chair of the NKF K/DOQI anemia workgroup. I am a part-time employee for DaVita, and I have received less than $5,000 in speaker fees from Amgen and Bio Tech over the last year.

Thank you for the invitation to be here. Our topic today is the recently published K/DOQI hemoglobin target update. The K/DOQI hemoglobin target update involved both the evidence review team and the anemia workgroup. The evidence review team are independent methods experts contracted by

the NKF to extract evidence from the literature and appraise its quality and consistency. The K/DOQI anemia workgroup includes interdisciplinary membership from the U.S., Canada and Mexico.

We undertook the current update because five trials were published in the past year that compare hemoglobin targets above 13 to those below 12 in patients with chronic kidney disease. From the evidence presented by the review team we composed three guiding statements.

The introduction to the three statements reads as follows: The hemoglobin target is the intended aim of ESA therapy for the individual CKD patient. In clinical practice achieved hemoglobin results vary considerably from the hemoglobin target.

This is followed by our first clinical practice recommendation on selection of the hemoglobin target. In the opinion of the workgroup, selection of the hemoglobin target and selection of the hemoglobin level at which the ESA therapy is initiated in the individual patient

should include consideration of potential benefits, including improvement in quality of life and avoidance of transfusion, and potential harms, including the risk of life-threatening adverse events.

This is a clinical practice recommendation and it is followed by a second on selection of the target hemoglobin. In the opinion of the workgroup in dialysis and non-dialysis CKD patients receiving ESA therapy, the selected hemoglobin target should generally be in the range of 11.0 to 12.0 g/dLB-a clinical practice recommendation.

This is followed by the third statement on avoidance of targets and evidence-based clinical practice guideline. In dialysis and non-dialysis CKD patients receiving ESA therapy the hemoglobin target should not be above 12 g/dL.

Let's briefly review the evidence. We reviewed results from 27 RCTs comparing lower to higher hemoglobin targets in patients with chronic kidney disease, 12 in dialysis, 15 in non-dialysis CKD. This chart shows the targets in whiskers for

each trial. You can see that for the first decade, bottom going up, the upper targets were the treatment ranges and the lower targets were the placebo controls. The treatment ranges for the first ten years became the lower targets for the second ten years of RCT experience, and the upper targets then were in the range of 13 to 14 or 15 or more.

Note here that the evidence of harm is limited to three trials in the upper treatment arms all greater than 13, and that the recommended treatment target, in the blue shade, is in a prudent range, well below that.

We must distinguish target hemoglobin from achieved hemoglobin. Target hemoglobin is the aim of ESA therapy. Target, that word, defines the action points for increasing or decreasing epoetin doses. The safety of a hemoglobin target is evaluated by between group comparisons in RCTs. Achieved hemoglobin is the result of ESA therapy. Achieved varies from target. The safety of achieved hemoglobin is evaluated by within group

analysis in RCTs, by prospective and retrospective longitudinal cohorts, by cross-sectional observational studies, all among patients treated to the same target hemoglobin.

Because the same target hemoglobin has been 11-2 or greater than 11 in this country and others for over 10 years, we have abundant information on that and what you have heard, more to the point, is that facility-specific performance matters to patients in this regard. The percentage of patients with hemoglobins greater than 11, facilities that perform better on that, as we have just heard, are safer places for our patients to be.

Let us review the evidence for the statement that hemoglobin targets should not be above 13 g/dL. We can considered all the trials that compared hemoglobin targets greater than 13 to those with lower targets. These RCTs all tested the hypothesis that a higher target would prevent adverse cardiovascular events or mortality or cause mortality, and none showed a benefit in those

outcomes.

A meta-analysis performed by the evidence review team supported our concluding statement. This included all RCTs with greater than six months of follow-up, no restriction on study size. We used a random effects model. We separated dialysis from non-dialysis CKD trials, and then we combined all cardiovascular disease events for analysis of cardiovascular risk.

Here is what we found for mortality in non-dialysis CKD. Mortality risk is dominated, by Singh and Drueke in 2006, non-significant, no harm signal. Cardiovascular events in non-dialysis CKD, here an evidence of harm. You have seen these. I will just go though them briefly. Mortality in dialysis CKD, all hemoglobin targets here greater than 13 no statistical increase. Cardiovascular events in dialysis CKD.

In conclusion...

DR. PLATT: I am sorry, we have to move on. Thank you. Our next speaker is number seven.

DR. KLINGER: Good afternoon. My name is

Alan Klinger. I am president of the Renal Physicians Association, the professional organization of clinical practicing nephrologists. I have no financial relationships to disclose.

I am speaking on behalf of both the RPA and the American Society of Pediatric Nephrology. The RPA and the ASPN appreciate this opportunity to address you. Each day thousands of our member nephrologists care for hundreds of thousands of patients on dialysis and those with chronic kidney disease. For most of these patients we prescribe ESAs to replace the disease-induced absence of patient's own erythropoietin.

You are holding this hearing and making recommendations to the FDA because recent studies have shown a higher risk of death or cardiovascular events with target hemoglobin levels of 13.5 than with lower target hemoglobin levels. We, nephrologists, use evidence-based guidelines to inform our prescribing practice and these studies have surely raised our concerns, just as they have raised yours.

With this in mind, we wish to make several points and ask you to consider four issues as you formulate your recommendations. First, consider uses and warnings that are patient and population specific. Cancer patients with anemia are very different than patients with chronic kidney disease or those on dialysis. Children are different and more vulnerable than adults. Low EPO levels are a life-long problem for kidney failure patients. Before ESAs were available we regularly gave our dialysis patients blood transfusions to treat their anemia. Blood transfusions can cause infections such as hepatitis and can induce antibodies, making future kidney transplant difficult or impossible.

Those of us who practiced before ESAs were available remember the debilities so common in our anemic patients and the complications of frequent blood transfusions. As we seek to prevent cardiovascular events associated with high hemoglobin targets, please remember the hardships to our patients that would result if policies and warnings around ESA use were to drive hemoglobin

levels down to low levels again.

Second point, we know that different patients respond differently to treatments with ESAs and iron. Adults' needs vary and children's needs differ than those of adults. Despite our best efforts, there will always be a distribution of achieved hemoglobin levels, a bell curve of hemoglobin. Warnings or prohibitions at the high end will surely shift the curve to the left, increasing the number of patients at the low hemoglobin end.

Should physicians be warned that hemoglobins should not be greater than 11? We know that the number of patients with hemoglobin less than 9 or even less than 8 will increase substantially. Hemoglobin targets should not be above 13. We urge you to make recommendations that do not impede the ability of nephrologists to achieve the target hemoglobin range as recommended by evidence-based guidelines, 11-12.

Third, please preserve improvement in the quality of life as an indication for ESA use for

anemia in kidney disease patients. In the 1980s so many of our patients saw the introduction of EPO as life altering. It was the most important improvement in dialysis care that I saw for decades. This clinical experience is confirmed by the limited by consistent published evidence on quality of life, particularly at the lower end of the hemoglobin curve. Please listen to what our patients say about the importance of these ESAs to their lives.

This brings me to my final and perhaps most important point. Each patient is unique with their own risk profile, biologic and psychological response to anemia, and their own opinions and their own choices about their treatment. Good medicine is done one patient at a time where one doctor and her patient make best treatment choices. Clinical research and practice guidelines inform these decisions but do not dictate them.

A recent meta-analysis that we have seen, published in *Lancet*, reported that a hemoglobin target of more than 12 was associated with a 17

percent increase in mortality risk. We have also seen the KDOQI meta-analyses that show a two percent non-significant increase in mortality risk for CKD patients and a 12 percent non-statistically significant increase in mortality for dialysis patients.

Patients and doctors weight these risks against the benefits of treatment, and in some cases choose that risk to avoid worse consequences for that individual. Some of our ESRD networks have already received patient complaints that their physician has cut their EPO doses for fear any patients will have hemoglobins more than 12. The complainants say that they feel much worse with lower hemoglobin, and these patients are willing to sign releases to allow better EPO dosing for them but their doctors refuse. Please help us to reverse this fear among nephrologists. Do not create the kinds of warnings and policies that cause patients to rise up and beg for more medicine. Each doctor and informed patient should be allowed to determine best dosing.

In summary, one, create policies and warnings that are patient and population specific. Two, remember the irreducible biologic variation in response to ESAs and create treatment policies that expect this variation and do not induce overreaction to the dangers at the high end. Three, preserve quality of life as an indication for ESA use. Remember patient experiences in the pre-ESA era. Finally, respect the rights of patients and their doctors to consider risks and benefits, and to make best individual decisions.

Thank you for allowing me this time and for your attention.

DR. PLATT: Thank you for your comments. Our last speaker in this session is speaker number eight.

MS. HARTWELL: I have no financial interests to disclose. Dear Chairman and Members of the Advisory Committee, my name is Lori Hartwell and I have lived with chronic kidney disease for the past 39 years. My kidney failure was caused by an E-coli bacteria infection. Since then, I have

survived 12 years of dialysis including three kidney transplants and two rejections.

I also founded and represent the Renal Support Network. Our patient-run non-profit organization is devoted to helping improve the lives of people with chronic kidney disease and providing hope to fellow patients.

The Renal Support network is deeply concerned that patients will suffer tremendously if the FDA limits the hemoglobin level to a level that is below what is recommended in the National Kidney Foundation's KDOQI guidelines. This concern was accentuated by the recent national coverage decision for oncology which determined that treatment of anemia could not be initiated until a hemoglobin falls below 10. Patients with chronic kidney disease are permanently affected by anemia because kidneys produce the hormone that helps create red blood cells. As a result, effective anemia management is key to a kidney patient's ability to survive and thrive.

I would like to urge the committee to

consider how your decision will affect the patient's quality of life. You have heard about the clinical data that showed the relationship between hemoglobin level and patient quality of life. For my part, I would like to tell you about how patients actually feel. I currently have a kidney transplant but rely on EPO to feel well since without it my hemoglobin would be extremely low and it would be impossible for me to continue working and performing the daily activities of daily life.

In my case, I do not feel normal and cannot function as well if my hemoglobin level is below 12. Many studies have shown that treatment outcomes and quality of life suffer when hemoglobin level falls below 11 and my own experience confirms this data. At a hemoglobin of 11 I can feel the difference. Daily activities become difficult or impossible to perform. Shortness of breath and fatigue are constant reminders that I have chronic anemia.

Many people who have chronic kidney

disease have related their experiences of how anemia has affected them. We receive many letters from patients but here is a sampling from quotes from Renal Support Network members:

Heather Powell stated, when I was first diagnosed I had to have blood transfusions every month in order to fight anemia. EPO did not exist at this time. The introduction of EPO had a huge impact on my life. I was healthier, more productive. I was able to complete college, work full-time and enjoy life.

John Garcia stated that when I was anemic I was always tired, listless and cold. My family couldn't get me to do anything.

Katie LeBeau says when a have a hemoglobin level below 10 I can't walk as far as the mailbox, grocery shop, do much housework or find the energy to go to work.

There are currently hundreds of thousands of other patients with chronic kidney disease, and we have had the benefits of a hemoglobin level above 11 for almost 20 years. I urge the committee

to consider how the quality of a kidney patient's life will suffer if your decision forces us to ignore 20 years of progress and regress to a hemoglobin level where it is near impossible for us to remain productive citizens. I would contend that regaining our quality of life is as important as preserving our lives.

Quality of life is centered on the foundation of hope and the belief that life is still worth living. Initiating any of the healing arts has at its core a belief that life is still worth living and an expectation of improving quality of life. Otherwise it is pointless. Everything from replacing a limb for an injured soldier or providing physical or occupational therapy for an elderly person with a fractured hip to taking an aspirin for a headache is done to improve quality of life. Failure to consider quality of life as a goal in managing anemia is tantamount to ignoring the patients.

Renal Support Network is also concerned that lowering the patient's target hemoglobin level

will result in a dramatic increase in the number of patients with low hemoglobin levels, resulting in the increased need for patients to receive blood transfusions and to be hospitalized. Blood transfusions can have a significant and long-lasting negative impact on our health, and even increase our risk for death. Blood transfusions can severely affect a patient's ability to receive a kidney transplant. The reactive antibodies received from blood transfusions result in fewer potential kidney matches from donors.

Melissa Daniels has had chronic kidney disease since she was a small child, and received a number of blood transfusions before EPO was available. Even though she has not received a blood transfusion in some time, the effect of those transfusions continues to haunt her, and she currently has a reactive antibody percentage level of 81 percent.

As a result of blood transfusions, the number of potential kidney donors that are a

compatible match is severely limited. The transplant team at her center is not confident that they will ever find her a match. There are thousands of other patients like her across the country who will find it extremely difficult to find a suitable kidney if their antibodies levels increase after receiving a blood transfusion.

I would like to emphasize that I am not downplaying the safety results of the trials that have been published. All drugs carry risks, and patients deal with these risks every day in every facet of medicine. However, patients are also acutely aware that the potential risks associated with drug therapy need to be weighed against the benefits.

I would like to reiterate that anemia is one of the most devastating conditions that affect those of us who have chronic kidney disease. Physicians should retain the ability to individualize EPO therapy in response to an individual patient's needs. Patient's visit doctors in response to how we feel. We simply have

no other way to communicate with our physician.

The hemoglobin of 11-12 that is currently recommended by K/DOQI gives patients and clinicians some latitude in the treatment of anemia so that if we experience an infection, need to be hospitalized or lose additional blood during hemodialysis, which is not uncommon, we will not be as threatened by the risk of receiving a blood transfusion or a reduced quality of life.

In the past, many of us have had witnessed the battle days and we don't want to go through that again. If these therapies are restricted and the patient is forced into a lower quality of life, what is the point? Quality of life is measurable. Patients measure it every day. Please consider this.

DR. PLATT: Thank you very much.

[Applause]

Committee Discussion

DR. PLATT: On behalf of the committee, I want to thank all of the individuals who have spoken during the last hour. Their comments have

been extremely thoughtful and helpful in the considerations we are having.

I am required to read this statement: The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address consideration of the data before the committee as well as the public comments. Stephanie?

DR. CRAWFORD: Thank you, Mr. Chairman. I just wanted to ask before we go into any specific questions could we continue, if we didn't quite have the chance before lunch, to ask some questions of the presenters?

DR. PLATT: Right, so I think our very next order of business is to decide how to use this next block of time. One suggestion for our consideration is that we see if there are any additional questions directed to the presenters or others, and that we spend the bulk of our time considering the questions on which we will be asked to vote but not voting. That is, we would work our

way through those questions to the extent that we think that it is appropriate. If that notion seems reasonable, before we start doing that, we might identify any other topics that we think, as a committee, it is important for us to discuss on the way to dealing with those questions that wouldn't automatically be included in the five questions that we are asked. So, if there are additional topics for discussion that would inform that, we probably ought to identify those after the questions.

So, looking around the table for nods or let's do something else? Okay, seeing not too many heads shake no, just before we go to the additional questions let me ask the FDA if there are any things you would like to bring to our attention before we launch into this section.

DR. RIEVES: Dr. Platt, just to reiterate to be sure that everyone understands, we, here, are hoping to walk away with some solid advice on how to improve the label in terms of addressing this target hemoglobin and that the current label

actually does not contain a target hemoglobin, and we are looking to accomplish something today to improve that labeling.

DR. PLATT: Thank you. How many of the committee members have questions you would like to ask? Two? Good. Stephanie?

DR. CRAWFORD: Thank you, Dr. Platt. I needed to hold my question until after lunch so I could take my expensive magnifier to see of these slides again, and what I learned is that I needed to spend more money for a magnifier but I do have a few questions.

With respect to potential changes that might be considered with labeled indications on dose responses, it is somewhat unclear to me from the presentations as to the scope of the problem. But I am going to give different examples that were presented to us. I guess I would ask if there could be a brief response from any presenter who can make this more clear. Because so many different things were compared, I am truly trying to understand the scope of how much is considered a

problem with some of the dosing. Dr. Zhang's last slide, 43, on the relationship between epoetin dose and one-year survival among incident elderly hemodialysis patients, 61 percent of the study cohort received a dose higher than the FDA dosing range.

My question to her would be was this typical for this special population of patients, even though it may be atypical when I compare that with Dr. Singh's slide 36, which he did not have the opportunity to discuss with us because of time constraints. It showed the figures for hemoglobin and EPO dose over a 15-year period, 1991 to 2006. It was based on USRDS data and I wanted to ask because I can't tell from the slide, is that more general population data? I couldn't see the exact number but it is definitely an average dose of less than 8,000 units.

In the open public hearing just now, speaker number four for the DaVita data made some recommendations with respect to dose that he said would be regardless of age or other special

populations. But speaker number seven made quite a call that if this joint committee made any considerations that we should definitely consider different patient populations. Lastly, Dr. Eisenberg's slide CC71 that discussed ESA responsiveness in a risk management plan talked about physician and patient educationBthis is almost a given question for me when anything is so vagueB-about what? Specifically about what? Especially if you would mean with respect to dose.

So, could we have anything that would help us understand the scope of the problem a little more clearly from any of the presenters?

DR. PLATT: Dr. Singh, it looks as though you have a comment to make on this.

DR. SINGH: Thank you. The data that I didn't present but which was USRDS data--

DR. PLATT: Could you speak more directly into the microphone?

DR. SINGH: Yes. The data with regards to hemoglobin values showed the average hemoglobin values in the USRDS population for dialysis

patients. The slide next to it showed the GAO, General Accounting Office, average epoetin dose that has been used in the first six months over a similar time frame.

I think the issue about dose, which I think was emphasized by a number of the public speakers, basically relates to what level of dosing is associated with risk. I know that Linda Szczech, and we work together, suggested that there may be a dose relationship but that dose relationship appears to be different between the high and the low hemoglobin arm, and that it is important to consider those people who actually achieve the hemoglobin versus those that don't achieve the hemoglobin.

So, it appears to be a complex relationship. At least from the CHOIR data which is not the USRDS data, in the CHOIR there doesn't seem to be a clear-cut relationship between dose and outcome. It seems to be a relationship that is different in the different groups of hemoglobin and whether you achieve the hemoglobin or not.

DR. PLATT: If Dr. Zhang is in the audience, still with us, and wants to speak, that would be fine. Dr. Klassen, do you want to comment?

DR. KLASSEN: I think, first, it is clear that these are complicated and confounded issues. But if I could have the slide up, in terms of what Dr. Eisenberg presented for ESA responsiveness as a working definition and, again, this is something that we are interested in as feedback from the panel as well, of course, as FDA, but a proposed definition of hypo-responsiveness in product labeling could be someone who is unable to achieve a hemoglobin target within the range of 10-12 despite appropriate use of ESAs over an appropriate period of titration.

The management for that would be, of course, to evaluate for potential reversible and modifiable causes and if one is still persistently hypo-responsive and you cannot maintain the target that you would like to maintain, to use the lowest dose to maintain a stable hemoglobin value.

We need to do additional work. We discussed some options in terms of both clarifying definitions but also, more importantly, understanding what needs to happen in terms of dosing strategies for these patients. But I think it is important to point out that there is a difference between managing risk in a population and managing risk in an individual. This is aimed at managing risk in an individual.

In terms of managing risk in a population, we believe the best strategy is to actually focus on randomized, controlled trials. The randomization factor is target and the studies that have shown risk have been target hemoglobin values above 13. And, our risk mitigation is to follow the ESA labeling as it always has been and not targeting hemoglobin values above 12 g/dL.

It is very important to understand what we are talking about when we say definitions of target or when to change dose. The question before the panel, in terms of question number two, is a target of approximately 11. It is important to know what

that means. We are advocating a target range of 10-12, i.e., a dose reduction for a hemoglobin value above 12. If by 11 the FDA means a target hemoglobin with an upper range of 12, i.e., a dose reduction for a hemoglobin of 11.1, for example, that will shift the hemoglobin distribution in the population down by about at least a gram per deciliter and 25 percent of patients will have hemoglobin values less than 10. And, I think you heard today what that will mean.

The other piece of randomized, double-blind, placebo-controlled evidence we do have is where we avoid transfusions, and with a hemoglobin target of 10/7 to 12/7, so basically 11 as the lower end of the target, those are the data presented in terms of transfusion avoidance and I hope you have heard today that that matters.

DR. PLATT: Thanks. Dr. Crawford, are you satisfied?

DR. CRAWFORD: For now, yes. Thank you.

DR. PLATT: Dr. Hunsicker?

DR. HUNSICKER: If I am permitted, I would

like to ask a question in follow up of Dr. Wolfe's presentation. Is that permitted?

DR. PLATT: Sure thing.

DR. HUNSICKER: You have used an instrumental variable analysis to look at the impact of changes within center. A generally accepted thing about the instrumental variables is that the instrument should be something which a priori is very unlikely to affect the outcome, and I would hypothesize that center is not such a variable because it could well be that there is an association between achieving hemoglobin, achieving blood pressure control, achieving higher fraction of nadir fistulas as opposed to whatever.

This could be clarified by the extent to which there is concordance within your clusters, your centers based on fraction of patients achieving certain hemoglobins, of other accomplishments that are associated with quality. Is this something where there is independence of the impact of the fraction of achieved hemoglobin from other quality indicators?

DR. WOLFE: Could we move to slide approximately number five in this presentation? What we have here are facilities. These are the same facilities in the yellow bars there are in the pastel blue bars. In 1999 they were doing one thing. In the year 2002 they were doing another thing. They were the same facilities. And, to the extent that there is a facility level effect, if there is a facility level effect beyond the practice when they changed the practice they would have taken that mortality with them as they moved to the right. So, this is one level of evidence that suggests if there is a facility effect, it is not showing here.

But let me address your question more specifically, which was are there other possible treatment things that these facilities are doing? During the same period of time there were substantial changes in dose of dialysis. Dose of dialysis was improved, not as much as anemia but dose of dialysis was improved.

In the same analysis we did a regression

analysis to look at other instrumental level measures, including agreement with dose of dialysis guidelines, agreement with anemia management guidelines and use of fistula. There were independent effects for each of those, suggesting that the practice pattern for each of those matters. It leads to better patient survival if you improve practices. And this level of difference of about 16 percent was not changed when we accounted for those two measured instrumental variable factors, dose of dialysis and vascular access.

Are there other things? Is there a good doctor effect? Maybe they are good docs and they do everything right. Well, these two other things we measures, they are doing them separately and some are doing them right it and it leads to better outcomes. But this is a separate effect from those.

DR. HUNSICKER: Thank you.

DR. PATTON: Other questions? Yes?

DR. NEATON: May I ask Dr. Pfeffer a

question, and just a bit of a dilemma that your group must have faced with kind of the results coming out of CHOIR? So, you have chosen a target of less than 9 in the control where I guess it is open-label at that point. How did you happen to kind of come to that and they stay with it, kind of following the results of the other trials? The target there is quite a bit lower, for example, in CHOIR as well as CREATE.

DR. PFEFFER: As everything in a clinical trial, this is a compromise of what is the best way to conduct this trial to address the question. As I mentioned, the nephrology community wanted an even higher low value to protect their patients. We had enough discussion of not knowing, but we did know that 9 was a magical number. Walking around with 9 was a hemoglobin where people uniformly did not feel well. We have a quality of life expert with us here, Dr. Ware, who could address that issue. We were well aware of that so we felt the patients needed rescue for that. Of course, a physician is always open in any clinical trial to

say your clinical trial is one thing, my patient is much more important and they are able to put a patient on open-label therapy if they feel a patient needs that, not knowing if they were stopping placebo or active therapy. So, that is always an option. But if we want to hear more about the 9 I would defer to an expert, Dr. Ware.

DR. NEATON: Well, let me just ask another question. My readB-and there were several statements today that, you know, randomized trials are the told standard and I think if they are well done that is the case. My general sense of CREATE and CHOIR is that these trials were not well done. I mean, the withdrawal rates and the losses are substantial. So, whereas the evidence both in terms of the size and you indicated the follow-up and adherence is very good at this point for TREAT, this could be a definitive trial in the non-dialysis population. So, to what extent is establishing now, somewhat arbitrarily I might say based on those two trials and the observational data, kind of a threshold for using the drug in a

non-dialysis population going to interfere with the conduct of what might be the definitive study in your opinion?

DR. PFEFFER: Well, I think if we adopt policies that impact research, then we will be conducting 2007 medicine in 2009. I think it is essential that we understand the difference between how we practice medicine and how we ask patients to participate in trials where there is uncertainty. I believe there is a lot of uncertainty here and this trial should continue. On the other hand, you are addressing real patients today. So, I think that is what I love about what we do. We have to address today's patients but we also have to keep our eyes to the future.

DR. PLATT: We have several more questions but could I ask a follow up of Dr. Pfeffer about this? It seems not improbable that the real discussion that we are asked to have focuses on cut-offs of 10 or 11 or 12 and, yet, TREAT will tell us something about very high versus very low. Can you sort of spin out for us how you think the

study you are doing will inform the question that we are asked to wrestle with?

DR. PFEFFER: I think we heard a lot about dialysis patients and there is no new information on dialysis patients except what you heard from people who have registries to over 100,000 patients. I think the question that we are addressing is the people who are not on dialysis, their risk is maybe ending up on dialysis but it turns out their risk is more likely to have cardiovascular events even though they are at risk to progress to dialysis. So, the question is can we interrupt their pathway? So, we are really asking a question of the pathophysiology, the epidemiology that anemia is bad. We have in our hand a tool to address anemia. Should we be applying that tool to interrupt the pathophysiology of cardiovascular and renal disease in high risk patients? It is a very different question.

Of course, we will collect quality of life. Of course, we will collect biomarkers. Of course, we will try to be smarter about these

people. But we are not making the assumption that everyone needs to be treated, and I think that is a big difference between the three trials that you heard about. We don't make the assumption that everyone needs the treatment and that is the assumption we are testing. Should we come back in two years with a study that says we are now helping people; we are interrupting the pathophysiology, then we can fine-tune this and say, well, where is it? Should we have started at 10? But I think until we have that it is an open question, are we interrupting the pathophysiology?

DR. PLATT: Good enough. So, we have in the queue Dr. Kaskel, Dr. Black and Dr. Good. Anyone else?

DR. KASKEL: Yes, I just want to follow up on what Dr. Klinger said and Lori Hartwell. Children are different and all the information that has been presented thus far has not taken into account that we have a significant population of children and young adults with CKD and on dialysis and with transplants, and they are different and we

transition these adolescents to adulthood. So, any future studies or considerations about recommendations in pediatric have to be taken separately. Metabolism is different. The requirements are different. Their growth has to be taken into account and neurocognitive development as well. So, I just urge the committee to think about this, that we need guidelines and we need data on children and adolescents. Thank you.

DR. BLACK: I would like to follow up on what Jim asked. Are you informing the doctors that the hemoglobin is under 9? Because if you are, they may be treating it based on what you told them rather than what we might learn about the symptoms of anemia, which you have a unique opportunity to do.

DR. PFEFFER: We have a point of contact hemoglobin determination in our computer algorithm with blinded syringes. It is a third party who makes the assessment and calls that into the computer. If the patient does drift below 9--it is a double-blinded--they are then switched to an

active without knowledge. At the end of the study we will be able to tell you things about how that patient was feeling and what happened to them but not during the study.

DR. BLACK: So, that is without knowledge.

DR. PFEFFER: Yes.

DR. PLATT: Dr. Good and then Dr. Cheung.

DR. GOOD: I just wanted to follow up with Dr. Klassen, you were talking about if you set a target to 11 the population mean will shift down perhaps a milligram or less hemoglobin. I am just curious where you get that from. Looking at CHOIR, and I understand that the general population isn't a randomized, controlled trial, but looking at CHOIR where they had a target of 11.3 it looks like the average achieved hemoglobin was around 11.5. So, obviously it doesn't sound like a good idea to have people running around with hemoglobins of 9 or 10 or 9.5. So, I am just wondering where those data come from.

DR. KLASSEN: I can speak to the hemoglobin distribution in the patient population. In general

it is fairly standard. Slide up. I believe that Dr. Lazarus spoke to some of this. The distribution that we see throughout time and throughout the dialysis data sets where we have, again, as I mentioned earlier in the day, comprehensive collection on just about every hemoglobin value, every ESA dose in clinical outcomes like mortality and hospitalization, is that the standard deviation is 1.4 g/dL. So, you can use that to calculate what would happen if a target shifted, so to speak.

In terms of the CHOIR and the dosing algorithm that was used, I guess what I can say is that it was not an on-label use. I think it was described by Dr. Singh and then Dr. Szczech as 10,000 units in all patients, which is one of the nice things from a hypo-responsive perspective, as they pointed out. But there was clearly a dose cap. So, understanding the dose distributions and how that actually applies to the general population today is more unclear.

DR. PLATT: Dr. Cheung?