DR. CHEUNG: In many ways, I think to determine how to deal with the hypo-responsive patients depends on whether you believe that ESA is harmful by itself or not, the dosage. So, we heard a little bit about using the IPW techniques. There may be a U-shaped or J-shaped relationship. Then we heard I think from the Amgen presentation that if you correct for case mix there was less of an effect of dose on mortality, and if you corrected for co-morbidity it even almost totally goes away.

I would like to hear some independent statistical expertise to give us a little bit of an idea which way of dealing with it gives us some glimpse or idea about what is harmful or not. I recognize that the data we have is not a well conducted randomized trial.

DR. PLATT: So, we might ask Dr. Klassen and either DR. Zhang or Dr. Hernan to speak to those issues. I am not sure we have somebody who would be considered truly independent in the room.

DR. KLASSEN: If I may, I would like to ask Dr. Ken Rothman to come up. Ken Rothman is

well-known in this field and can address this question.

DR. ROTHMAN: Good afternoon. I am here as a PI of a program that Amgen has initiated.

DR. PLATT: Dr. Rothman, would you just identify yourself for the record, please?

DR. ROTHMAN: My name is Ken Rothman. I am vice president for epidemiology research at RTI Health Solutions. I am the PI of a program investigating confounding by indication, which is a program sponsored by Amgen and which has four independent academic units that are conducting research projects.

This program is aimed at evaluating the role of confounding by indication and exactly the problem that we are discussing. What we have heard today about confounding by indication illustrates that among the patients that we are talking about this is very clearly a problem. We have seen analyses that have used conventional methods, methods controlling for time-dependent variables and methods that control using marginal structural

models, all of which illustrate that there is serious confounding by indication and that, to some extent, it can be removed.

So, we know that it exists and, furthermore, we know from general principle that you can never remove confounding by indication fully unlessB-well, you can never remove it fully because you need perfect measurement of all confounding factors and, as Miguel Hernan said earlier, we don't have perfect information.

So, what has been explored in the project that I just mentioned is newer techniques, including marginal structural models, and also using data that are more detailed, that have more frequent measures of time-dependent variables like hemoglobin and have other information that isn't available in USRDS. The analyses we saw were from USRDS, but from dialysis providers we can get other data that might be potential predictors of outcome, as well as more frequent measures, under the theory that with more information or better information we can remove even more of the confounding by

indication that you have seen.

So, at this point I would say that the analyses to control for confounding by indication show some promise. Though all speakers have indicated that this is not going to be the equivalent of a randomized trial, I would remind everyone that randomized trials can be conducted over a period of long time, many years but basically in the end examine one question, the question that was designed according to the random allocation and if you have other questions which come up you are going to have to fall back--even if you use the trial data or if you use the other available data you are going to have to fall back on methods that involve the same techniques that you have been talking about. So, we think that ultimately by refining these methods and applying them with better data we are going to come much closer to the answers than we have come to today.

I hope that illuminates a little bit where I think the methodologic questions lie. I think that what we have learned is that we have

confounding; that it hasn't been fully controlled yet but that we are making a lot of progress and that ultimately I expect that we will get reliable answers from it. Thank you.

DR. PLATT: Thanks so much. Is Dr. Hernan in the audience? Or, Dr. Zhang, do you want to speak to this topic, please?

DR. ZHANG: Great, thank you. I want to point out two differences between our analysis and Amgen's analysis. One is that they are doing basically associational studies by looking at association between dose and patient mortality. But in our analysis, just like I said in my presentation, we try to mimic an RCT by using inverse probability rating. So, we are not simply looking at association. We are trying to have a [?] inference.

The second difference is that in their analysis they show the association between per unit increase in dose and mortality. However, the dose and mortality relationship is not linear. Just based on our own analysis, it is very clear to say

that actually for a dose level lower than 15,000 units/week it is negatively associated with mortality. However, for a dose greater than 15,000 units/week the increase in mortality is greatly increased.

So, since the association is not linear, by reporting the results with per unit increase in dose it is very misleading. Thank you.

DR. PLATT: I know we could spend a long time on this topic but, Dr. Cheung, I want to have a sense of whether you have heard enough. I know there are two more experts who could comment but we could spend the afternoon on just this topic and I want to make sure we get your question answered.

DR. CHEUNG: Actually, I was hoping to get an independent statistical opinion but I will withdraw my question. Thanks.

DR. PLATT: So, gentlemen, thank you. I think we will defer for the moment. Dr. Nelson?

DR. NELSON: Yes, you know, by training I am a medical toxicologist and what you just said was interesting because when you start thinking

about getting to these high doses you start to think about the toxic effects of things that you wouldn't necessarily expect to see at, you know, pharmacological doses.

We didn't really speak much about the mechanism by which this might be, which adds to the whole causality issue in terms of biological plausibility and why things might be the way they are. I don't know if anybody has-Bperhaps you doB-some explanation for why these might become toxic. I know there is a lot in the literature now about alternative uses for erythropoietin to prevent and to treat other diseases but, like every other drug that is beneficial, it often has some adverse effects as well. So, I don't know if there are any comments that might go along with that.

DR. KLASSEN: Slide up, please. I can comment very briefly and then I will have Dr. Glen Begley from our preclinical group come up. But the bottom line is that the underlying mechanism, in terms of action of ESAs, is as defined through EPO receptors and we haven't been able to conclusively

determine any other action, other than what is the hematopoietic action through that EPO receptor interaction. I would like to have Dr. Begley from our preclinical department elaborate on that just a bit.

DR. BEGLEY: Thank you. My name is Glen Begley, from Amgen. We have invested a lot of effort trying to understand this, particularly looking at the literature that claims there is effect of EPO on a variety of cell types. We have actually been unable to demonstrate that despite a number of studies that we performed. Part of that is because of the problems that have arisen with trying to assay the erythropoietin receptor. Many of the publications that have arisen have used fundamentally flawed methodology.

Slide up, please. I could just illustrate that with this slide, which looks at the four most commonly used antibodies to assess the erythropoietin receptor. You can see in front of you a Western Blot showing that each of those antibodies detect a multiple band and, in fact,

very few of them detect the erythropoietin receptor itself, which is the most intense blot in the second line in each of those gels. So, the band that is being looked at in most of the studies is actually not the erythropoietin receptor. It is actually a protein of a larger size and has been variably demonstrated to be Hitchcock protein 70 or Hitchcock 90 but not the erythropoietin receptor.

The next slideB-if you want, we can continueB-goes on to demonstrate that this is the case and that when the knockdown experiments are used, in this case using inhibitory RNA, we can demonstrate that the erythropoietin receptor band disappears but the band that is being detected by the antibodies does not. In the panel on the right you can see that the specific band that is recognized is actually Hitchcock protein 70, not the erythropoietin receptor.

So, based on these and a variety of other studies that we have performed, we actually don't have any evidence that the erythropoietin receptor is expressed on endothelial cells or on

cardiomyocytes despite the literature that makes claims to the contrary. Again, we are concerned by some of the limitations in the reagents that are being used to perform those studies.

DR. NELSON: It is an interesting point. You know, many of the things we think about now as biologicals-BI mean, insulin would be a good exampleB-have effects that are well described that don't necessarily involve a surface receptor that we would classically consider, you know, drugs working by. So, while it is important to look at these things, many people out there are claiming certain anti-inflammatory and other effects in terms of protective effects and things that have been suggested perhaps. So, you know, it is good to look at these receptors but I am not necessarily sure they would answer all of the questions in terms of toxicity.

DR. BEGLEY: That is a fair point. So, in addition to those sorts of studies we have looked at, for example, the action of erythropoietin on endothelial cells or on angiogenesis again, where

there are reports that erythropoietin is active.

If I could have slide YB-5 up, please? That demonstrates one of the series of experiments that we have performed, looking at the effect of erythropoietin to stimulate angiogenesis. The top panel shows a corneal model. A little plug is implanted in the rat cornea and the plug is being embedded with VEGF, in the middle panel, or EPO, on the extreme right. You can see that eh VEGF is able to stimulate the ingrowth of vessels in the rate cornea. That is not taking place in the panel on the right even though the doses used here are 100,000 times greater than the maximal doses that are able to be achieved clinically, and that is quantitated in the graph underneath.

We have similar sort of data looking specifically at endothelial cells, Cardiomyocytes, and so on. So, in addition to being unable to demonstrate the receptor on the surface of the cells, we are unable to demonstrate any consistent, robust biological response on those cells although, to be honest, I would be delighted if we really

thought there was an action of EPO on, let's say, Cardiomyocytes. But our attempts to try and demonstrate that have really been unsuccessful, and not for lack of trying.

DR. NELSON: If I could just make one more comment about this, you know, one of the problems with the hypo-responders is that, you know, obviously you raise the dose considerably in order to get them to respond and when you get to these high doses we may be looking at effects that aren't necessary EPO receptor mediated.

I guess my question is rather than giving once a week dosing in a fairly substantial dose, has there been consideration of looking at split doses over several days, several times a week perhaps, or even more of an infusion pump type of scenario where people get low levels over long periods of time?

DR. KLASSEN: Epoetin alfa is dosed most typically three times a week with hemodialysis and that is typically how it is given. There are other longer-acting agents, darbepoetin alfa for example

can be dosed certainly at longer intervals, weekly, every other week, etc. And, the safety profiles between those two, for example, have not been appreciably different, as evidenced in the approval programs for each. So, epoetin alfa was compared to placebo, again, in adequate and well-controlled placebo studies in terms of the safety endpoints. Then, darbepoetin alfa was compared in a non-inferiority fashion to achievement and maintenance of hemoglobin as compared to epoetin alfa in over 2,000 patients in Phase 3 and the safety profile for those two compounds are identical.

DR. PLATT: Other questions, group? Are there any topics that are of a general nature, not sufficiently close to one of the questions we are going to vote on, that you would like to bring up now for discussion, remembering that they have to be something that would inform our discussion of the following questions? So, if it could be bundled with one of the questions, let's do it that way.

DR. HUNSICKER: I didn't see that it was bundled with one of the five questions. I think that the issue of the relevance of quality of life instruments, the types of quality of life instruments that might be used and the legitimacy of the current quality of life data, the validity, or whatever you may want to say, should be addressed because I think there is a substantial public interest in this question.

DR. PLATT: I know that there is. Unless someone is going to bring additional quality of life information to us, I think that we can certainly note that fact but we are not in a position, I think, to have sort of a full explication at a level that would really make a difference to our decision-making. So, I want to make sure that we sort of follow your thought in a way that will be useful to the committee.

DR. HUNSICKER: Well, let me be a little bit more precise then. We are going to be talking about targets. We are going to be talking about mortality data. We are going to be talking perhaps

about avoidance of transfusion data. But as I read these questions, they say nothing about how we should or should not be using existent quality of life data and whether or not these would be important in the future, except perhaps in that last question which is, you know, what do you want to do in the future. I am not actually proposing that we should use it. I just think that it needs to be discussed explicitly.

DR. KLASSEN: Mr. Chairman, if possible, I would like to call Dr. John Ware.

DR. PLATT: You want to sort of note for the record that we are not discussing it?

DR. HUNSICKER: I personally would think that there should be some discussion as to whether the quality of life data, as presented, are persuasive and, for the sake of the public, if one feels that they are not overwhelmingly persuasive as presented, and that happens to include me, that this be explained because I think that it would be very puzzling to the public and to many of our practitioners to throw out, as it were, evidence

about quality of life. I think if we are going to not use it, we ought to explain more precisely why we don't think it should be used and that, yet, at the same time quality of life issues may be very important.

DR. PLATT: Good. Thank you. Dr. Rieves, do you want to speak?

DR. RIEVES: Yes. One of the reasons that we did not choose a question directed specifically at quality of life is that our review is ongoing, as Dr. Trentacosti noted. We have received data even within the last couple of weeks or so that we really need to verify and to explore a bit more thoroughly. So, in that sense, we are not ready to essentially independently verify, if you will, some of these nuances and some of the details.

But the point is well taken. It emphasizes our need to focus on those as potentially important components of the label and we plan to do that. But at the present time though, I think we would be somewhat handicapped in terms of substantively talking about data that we

have really not vetted thoroughly.

DR. PLATT: Others want to speak to this question? So, asking the group, shall we take a few minutes to discuss this topic? It is an important topic. We clearly hear what you are saying, Dr. Rieves. Do you want to start, Dr. Findlay?

DR. FINDLAY: Just for clarification, I thought there was some change in the labeling already with respect to quality of life. Can you clarify that, FDA? Or, if it has not been changed already, is it proposing to be changed? Has the manufacturer proposed changes in it? I remember seeing in the document some redlining of the label.

DR. RIEVES: Right. That is part of our ongoing review process between FDA and Amgen to revisit the current labeling. Of course, labeling should be updated as new information becomes available and as old components are regarded as inappropriate for inclusion, and that process is actually going on. But in terms of actually altering the statements that are in the label,

there have not been any changes in the, quote, quality of life components in the epoetin alfa. That is only in the epoetin alfa label.

DR. EISENBERG: Just to be clear, Rieves is correct. It is only in the epoetin alfa label. Amgen has been reviewing that with FDA as part of the post-marketing commitment quite actively, and we have proposed significant decreases in what is in the label.

If I could have the slide on, these are the changes we proposed, and I would actually ask Dr. John Ware, who is an expert in this area, just to make a few comments. I think they are pertinent to the instruments. He has helped us review the quality of this and we believe this is supported by the data.

DR. PLATT: Dr. Ware, let me ask you to speak very, very briefly to this, please, because I think we are not in a position to have sort of the substantive discussion about the quality of life issues so much as talk about the relevance that these things could or should have to our

discussion. So, the very briefest comment, please.

DR. WARE: Two minutes. Thank you. In a risk/benefit evaluation, of course, all benefits should be considered. I think we have heard from several different perspectives this morning. We have heard from the public some rather dramatic statements about what it is like to have this condition. We have seen those sponsored studies, both objective physical performance measures of things like physical functioning, and we have also heard from the agency some serious concerns about the validity of the measures that were used in those double-blind, placebo-controlled trials.

So, since I am not responding to a particular question I am just going to make some general statements. Dr. Klassen earlier this morning reported the objective physical performance data. In that same trial patient-reported measures, the SIP and the KDQ, were used to replicate those findings in a placebo-controlled trial and also to expand those findings to include patient-reported outcome measures. The criticisms

of these relatively crude toolsB-these are the tools from 20 year ago-Bthe criticisms lodged by the FDA as being not reliable and valid, those tools, despite how crude they were, produced significant differences between placebo and treatment groups.

So, I think the issue here is, well, how do we interpret those differences. Well, physical functioning measures clearly measure physical functioning. The vitality and other symptom measures clearly, whether you want to call it vitality or you want to call it fatigue or you want to call it energy-Bthose are the words that are in the tool, and it is very clear what those tools measure--

DR. PRATT: Dr. Ware, I am your yellow light.

[Laughter]

DR. WARE: Well, my biggest concern is, and I would voice disagreement that if you apply the FDA preliminary guideline documents for patient-reported outcomes, as recommended this

morning to these tools, and included in those tools are well validated measures such as the Sickness Impact Profile. It was said this morning that it does not have content validity. I didn't develop the Sickness Impact Profile but I was on the site visit team that funded it 30 years ago. From an Anthropologic point of view, it is the most comprehensive, 12-dimension description of generic health, you know, that we have in the field, even more comprehensive than the SF-36 tool which I developed. So, to say that it is not content valid is obviously a mistake.

So, if the application of the FDA draft guidelines to those tools leads to the conclusion that they are not valid, I would have to call into question the validity of the guidelines themselves. In conclusion, I would say that the net effect of these mistakes is to throw out all of the PRO data...

DR. PLATT: Dr. Ware, we are really done. Thank you. Dr. Cheung, did you want to carry on?

DR. CHEUNG: I just have a related question

and it is very pertinent to these questions we are going to be asked, that the guidelines in the blood transfusion I am not familiar with so could, please, the FDA help us a little bit? What are the current indications for transfusion, and should they be applied to this particular population?

DR. RIEVES: Actually, we may defer. Amgen did a very nice review of transfusion guidelines in part of their briefing document, I think, or some of the preparation for this committee. But, in essence-Band correct me, other people who are more familiar with this, the guidelines for transfusion in general incorporate heavily symptom considerations. Candidly, off the cuff, I am not aware of specific numeric triggers, if you will, in transfusion. But we had a nice review of that information from Amgen.

DR. CHEUNG: Is quality of life an indication?

DR. RIEVES: FDA does not set up guidelines for transfusion and that is more of a practice of medicine consideration.

DR. KLASSEN: I can answer that very briefly. Slide up. The answer is yes, transfusion guidelines strongly acknowledge symptoms of anemia and physical function. So, the guidelines for transfusion are to avoid symptoms and the guidelines for ESAs are to avoid transfusions.

Committee Discussion and Questions to the CRDAC/DSaRM

DR. PLATT: Thank you for raising that. We are going to start talking about the five questions for discussion. Dr. Phan, the discussion we are having now is on the record, is that correct? So, to the extent that any of us makes comments during this discussion that isn't leading to a vote, we can consider it to be comments that explain or support our vote, though we could change that later. I say that just to emphasize the fact that we don't have to repeat our discussion when we start voting. We can discuss and we can discuss more when it comes time to vote but we don't have to discuss the same topics over again.

Can we put the questions up? Our first

question has to do with the hemoglobin target for hemodialysis, then the next one will be the same question for the non-dialysis population. So, we can have a large discussion on question one and then a smaller discussion on question two that is the effect modification piece of that, or we can do this as ever seems appropriate. We can do this any way you like, but one would be to start at one end of the table for comments or discussion on one and then come back on question two. Is that all right? Is that agreeable? I am being asked to read the question into the record, but can't I do that when we actually vote, Dr. Phan? I can. So, in order around the table, only if you want to speak because you can be silent and thoughtful and vote without comment. This won't be your chance. We will go around until we exhaust the question or we run out of time. Dr. Day?

DR. DAY: I just want to comment that it should not exceed a certain level for patients on hemodialysis, the level associated with better survival. So, we are only being asked in this

question to look at better survival and not increased risk. That is just an observation from the language.

DR. PLATT: Dr. Findlay?

DR. FINDLAY: I think I will pass for now and look to benefit from the discussion as it goes along. It is certainly a fascinating discussion today around a decision of three numbers-Btwo numbers really, 11 and 12.

DR. PLATT: Dr. Good?

DR. GOOD: I don't have much. I guess for me the struggle is trying to work between the two studies, Normal Hematocrit and CHOIR. They are fairly similar. The targets were a little different, and where the patients ended up was a little bit different. I think that is where I am sort of struggling with, trying to figure it out. I want to be as evidence-based as possible. I also want to recognize that it is very difficult. There is a lot of patient variability and in real practice, you know, patients don't stick at one hemoglobin and it is really difficult to keep

patients at a particular hemoglobin. And, I really do think that this issue of cycling is a real problem and I think that that is where a lot of the patients that have adverse events, that is where the problem is, you know, this going up and down and adjusting doses of ESAs. You know, in some of the slides that were up there you see these wide swings in ESA doses that is really frightening and that is what we should, hopefully, try to avoid. So, if we set a target level we want to try to come up with something where we avoid these sorts of things.

DR. PLATT: Dr. Hunsicker?

DR. HUNSICKER: Well, a couple of comments first and then a puzzlement. First of all, I agree that the issue is about two numbers but I think I might disagree on what the names of those two numbers are and I would say the upper and lower range. I think those are the two numbers that we are interested in.

With respect to the upper range, I thought coming into the meeting today that we had sort of

an agreement between the FDA and the sponsor that an upper limit of 12 seemed reasonable, an upper limit of 12 I will get to in a minute. We don't have a lower limit. The reason we don't have a lower limit is that there are now experiments which show at what point peopleB-well, there are now some data on what level people cease to need transfusions so much. At the risk of irritating my chairman, I will say that I don't think that this is independent of the issue of symptoms or quality of life, that, in fact, the reason that we transfuse people historically, as I with my grey hair well remember, is that they felt like hell and they felt better when they got transfused.

But up to where? Maybe 10. I wondered whether I should say 10, anyway. Well, 10 was the number that we dragged out of our back pockets years ago when we figured out how much we should transfuse people up to. Transfusion targets have changed over the last several years and we would be in a very difficult situation right now were we to use the currently existing criteria for transfusion

in these patients. I think we have to start with that because we don't transfuse people now if they are a little symptomatic and even with a hemoglobin of 7 in a young person otherwise healthy. I wouldn't transfuse them. Would I not transfuse a chronic renal failure patient? I wouldn't transfuse them, I would give them EPO. So, we have to start with that.

So, what is the upper and what is the lower? My thought is that when we look at the upper we have experiments which have compared 11 with 13. And, 11 seems to be better than 13. I think that the data supporting that are fairly strong, although I look for further information from my good friend Marc, over there, in the future. What is 12? Well, I don't know. Is that half way to 13 or is it about the same? I don't think we have any data to decide whether the upper end of the target should be 11 or 12. There are no data there.

On the bottom, I sort of like the data that Preston presented that showed that the risk or

transfusion goes up substantially when the hemoglobin is less than 10. That is nice because it conforms with my bias that we probably should not let the hemoglobins go below 10.

So, I feel sort of comfortable about two numbers, 10 and 12. But then we get here to what we are asked, what should the target hemoglobin be? My problem is that I haven't the faintest idea what we are supposed to do with the target. I would say the target hemoglobin should be 11, plus/minus 1. The question is what do we do when we get to the top and what do we do when we get to the bottom? That is the question that you have asked, Richard, how do we avoid cycling.

It says down here any such hemoglobin target necessarily assumes achieved excursions in the 12 g/dL range. Well, big deal, we get above 12. But that is achieved, that is not what was tested. What was tested was the target, and the target of 13 is not good but achieved of 13 is okay, as far as I can see. So, what that it means that occasionally people get above 12? I don't see

that this is a big issue.

So, when I look at this issue of target I would really like the FDA, and I would like the sponsors to tell me what the hell they want me to do with the target.

[Laughter]

DR. PLATT: Perhaps after we finish this round we will ask what the hell they want done with this target. Thanks. Dr. Crawford.

DR. CRAWFORD: Very brief, just as is written, based on the available data, primarily based on one study, maybe where the limitations have been pointed out as well the contributions, it would be difficult for us to make a recommendation. I am also not quite sure, based on how the question is written, is that little squiggly mark meaning approximately or is it specifically for these 11 and 12 figures we are seeing from the FDA?

DR. PLATT: So, clarification, the squiggly mark is intended?

DR. RIEVES: Approximately, right. It takes into consideration-Bagain, we are looking at

the lower hemoglobin groups. The upper limit was 11 in Normal Hematocrit and 11.3 in CHOIR.

DR. LINCOFF: I have a few comments and I think I somewhat disagree with the idea that we are working with two numbers. I think we are really working with one number and I think that is the upper limit because the upper limit gives a physician the discretion to deal with this clearly important quality of life for this individual patient.

What is really the issue that would be the constraint is if the upper limit is too low, and I am compelled by the reality of the Gaussian curve that if you set this limit to 11 you will have a sizeable proportion of patients who will, just falling on that Gaussian curveB-the limit as a target, will actually achieve a hemoglobin that is in the range that will diminish quality of life. So, I am more comfortable with 12 from that standpoint.

I also think that we are dealing with an issue here that is complicated from the standpoint

of this hypo-responsiveness and dose, and I think we can't walk away from the idea that dose is important. As the statistician from Duke had pointed out, the hypo-responders are going to be equally distributed in the two randomized groups of these trials that suggested worse outcome in the higher hemoglobin target. So, what was different was the fact that those hypo-responders were flogged more. They received more dose in an attempt to get them to their target. Clearly, how hard you push to get somebody to a target is a factor so we can't ignore the targets.

On the other hand, in the end we are faced with evidence-based medicine, and the evidence is we don't have anything that says 12 is worse than 11. We have evidence that suggests 13 might be and 14 might be and those probably relate to the extent of how hard one is pushing on the dose. But we don't have anything to help us discriminate that dose and where it becomes a problem in a hypo-responder and, in the absence of what we don't have, I think we should be working with what we do

have and what we do have is a Gaussian curve and what we do have is admittedly observational data that suggests that 10-12 is a reasonable range.

I am less interested in the 10. I think our goal is really to find out where we think it is safe to target to push, and I think that in the absence of other data 12 is a reasonable number.

DR. PLATT: Sp, in fact two numbers/one number. I think the problem is that we have no number. To step back for a moment, I think it should be extraordinary that after hundreds of thousands of individuals have been treated neither the patients, nor clinicians nor our society really knows how best to use a very important therapeutic agent which, everybody recognizes, carries considerable harms as well as benefits. The reason I say it should be extraordinary but isn't is that exactly this kind of information gap pervades so much of therapeutics. And, if there is a larger lesson to take from this, it is that as individuals and as a society we should demand much better evidence much earlier on rather than let clinical

practice evolve the way we have. So, we are in a very difficult situation here, being asked to advise in the absence of data. So, I agree with several of my colleagues bout that.

Secondly, it seems to me we are being asked whether there is enough information to, in a sense, adjudicate a disagreement about 12 versus 11 because I am sure that we wouldn't be having an advisory committee meeting if the agency and the manufacturers agreed on an upper level. And, my sense is that as good as observational data may be, they are not good enough to help us with this kind of very fine distinction. It may be. I think we have heard some very impressive presentations, none of which was finished, none of which was peer reviewed, and it is conceivable that as that becomes more mature that would be very helpful.

So, if we are being asked to decide on the basis of evidence, I too would say there isn't enough to support an affirmative statement about making a change to any number. I guess I will say that if FDA decides that the public is better

served by having a number than having the existing guidelines there is really no evidence for anything higher than 11 based on the limited data that are available.

I would say two other things. One is that, just as what data we have come from the treatment of groups with an intended target, a guideline might also be aimed at groups. Those groups might be the values of the population treated at a dialysis center or a renal failure clinic rather than individuals because that is the guidance we have, and that would accommodate the fact that there is a great deal of heterogeneity and would avoid the perception that there will be great penalties if any individual exceeds the nominal threshold.

My final comment is that important as this question is, it seems to me that the largest opportunity for improving the ratio of benefit to risk might really result from much more attention to understanding how to prevent the excursions both above and below the targeted range. So, if we

posit that there is a big gap in the way these compounds are used and ways in which we could improve the welfare of individuals with chronic renal disease, the big gains might lie in the area of understanding how better to keep people within whatever target range we choose. Next?

DR. KASKEL: I would like to concur with what was said thus far. I think putting a number as the ultimate absolute value will set us up for fluctuations and cycling that we will come back later to look at and realize there my be increased risk. So, I would not be in favor of changing or lowering the number at all.

So, I would recommend that because of the limitations in the data and the studies thus far, I think we need to develop algorithms to define how we look at the rate of rise in the individual patient and then assess to make critical periods to determine as, again, each patient is different and we will need their individual assessment. So, I think it is very difficult to put an absolute value on this, but from my experience, I think if we go

below the 11 we are going to get into trouble.

DR. LESAR: Tim Lesar. I am just trying to untangle a number of things here. I think that what struck me is some of the confusion between achieved and target but I think we need to be quite clear that people who are going to deal with the number is so they can see what was achieved; they are not going to think about what their target is.

The second thing is, to reiterate some points about the dosing, I think the issue is that the data is pretty good that higher hemoglobins improve responses, but I think the question really comes up is at what cost and how did you get there. I think that goes back to some of the issues related to dosing. I think any number has to be tied to what was the process by which you achieved your goal, if you have achieved it. That is, achieving a goal may not be a good thing for a for all patients because the potential adverse effect of high doses of EPO-BI think there is some strong evidence here that total doses and possibly related to dose increases and rates of increase may be

actually problematic. So, how you achieve that goal is extremely important. So, again, I think that algorithms in guiding prescribers on how to get to a goal, and whether getting to that goal is worthwhile given possible the total dose of EPO that is required to do that. So, I think guidance in terms of how to achieve that goal, and even if that goal is then worthwhile given the potential risks to achieve it are important.

DR. TEERLINK: So, I would like to emphasize I do think the quality of life and symptoms are an important aspect of this discussion, as well as avoiding transfusion. But those I think do speak to the lower end of this range that we have been dancing around.

I would encourage the FDA when they do these analyses to try to find perhaps a middle way between a draconian adherence to 2007 standards of evidence and applying them to 1980 data. I think that if we were to do that to most labels currently approved we would be in trouble in terms of having any approved drugs. Obviously, balancing that with

basing claims on truly poor data. So, hopefully, some middle way can be charted between those two extremes.

This is an interesting issue because typically when a sponsor comes to us with trials and they say, look, this is what we did in the trial and this is what happened, and we say, okay, what happened was either good or bad and we approve that drug at that dosing regimen for that indication. So, actually it is interesting that we are discussing this because it seems like the dose is actually the targeted hemoglobin of 11 or 11.3. We can, you know, fudge over that. And, our concerns areB-and that is what was established by the clinical data, the randomized, clinical trial data that we have, and that is the only data we actually have to work on.

So, this range thing I think is bringing in the safety concerns and the safety concerns I think need to be addressed through finding out more information on this cycling phenomenon. You already have data from these trials. You have,

well, how did these patients cycle in the trials. What were the things that were done to either help or prevent them from cycling? Then you have a direction for future trials in terms of actually looking and seeing prospectively if we pick a target of 11, how do we hit it and how do we prevent these bad things from happening. And, the same thing can happen with the hypo-responders.

I am confused as to where 12 can from actually. I am not seeing it anywhere. I see some epidemiologic studies but those were achieved doses not target doses. I think that what we need to do is actually give the clinicians a target dose to work from and then work on giving them information on how to adjust doses to appropriately hit that target dose. So.

DR. NEATON: It is interesting, I have sat on a couple of treatment guidelines panels and my clinician colleagues always tell me they want numbers. We want cut-offs. We don't want to just leave it to clinical judgment. But I look at the early trials and I guess there are some concerns

that remain to be addressed with the physical function measurements. I mean, I am less concerned about the instruments that were used and the tests that were performed as the completeness of the data that was alluded to in the FDA summary in terms of the potential for bias and what appears to be rather remarkable differences when you compare the strategy of 9.5 to 11 as well as 11.5 to 13 versus placebo.

I think a range is in order. A range, as I understand it, has been used both in those early trials looking at transfusion and these functional measures and in the Normal Hematocrit study it is roughly 10-11 versus 14-15, the strategies compared. So, I am comfortable with a range between 10-12 to allow some variability in the hemoglobin, or if we are going to choose a number I guess I would choose 11. But I think it is very different and I wouldn't mix the non-dialysis population in with the dialysis population because I think the epidemiological data that was presented today, the wealth of it and the number of different

ways that have looked at it, it kind of comes up consistent in my mind that around 11 is pretty good. So.

DR. KRAMER: My interpretation of questions one and two really gets down to the issue of the hierarchy of evidence. As I read between the lines, I think what the FDA is really saying to us is if we believe that randomized, controlled trials data is the highest level of evidence and we have these two, granted they are two different questions but we have the dialysis population and the CKD population, and we demonstrated a statistically significant improvement in outcome against what we posited at the beginning. The observational data led us to believe that normalization would be better. However, we have clear-cut evidence that is consistent between these two large studies that showed statistical superiority of a lower target.

I agree with people like Dr. Teerlink who commented that we have to be very careful about the distinction between target and achieved hemoglobin, but these trials tested a target hemoglobin and we

are trying to come up with recommendations for the population, not for the individual patients. We are not now talking about ESA responsiveness; we are talking about an overall recommendation and I think the question is quite reasonable. I would say that if the tables were turned and the sponsor had posited at the beginning that this lower target was superior they would be asking for approval based on exactly what they have done.

Granted, there are some issues with the trials but they are by and large quite convincing and consistent across multiple trials and to me, the answer is, yes, that is a reasonable target hemoglobin. I completely agree with Dr. Platt that it is really unconscionable that we are at this point in time and we don't know any more about dosing algorithms, specific adjustments for patients who are ESA unresponsive, and that is ultimately the responsibility of the sponsor to have done those studies and they have not.

So, I would argue that, yes, I would directly take the results of the randomized trials

to pick a target hemoglobin. And, I would like to make a couple of other comments.

One is I didn't have a chance to comment on this quality of life thing. I think we are at risk today of a tremendous amount of misunderstanding, having listened to what people from the audience and the public session said, that this committee of the FDA is suggesting that quality of life is not important. I, for one, as a member of this panel think that there is no one who is saying that. I think they are saying that it is our responsibility and the sponsor's responsibility to properly conduct these trials so that we can be reassured that we are measuring what we think we are measuring, and when greater than 50 percent of people are missing from the data and you look at the details of these analyses, they really are inferior.

So, I think we think they are important but we need to do the right studies so that we can get it in there, and we need to be reassure patients that we understand the importance of

quality of life.

Secondly, I am very concerned, and this relates to these questions and the discussion this morning. There are many people talking as if we are talking about maybe we don't need the ESAs. I don't think anyone is saying that. Specifically with the issue of transfusion, as I read the briefing packet and you look at the randomized trials, I was really struck that there wasn't as much of a distinction between actual transfusion requirements in the two arms as one might think there would be because everyone is saying, oh, we can't use this lower target because we will have all these transfusions with all the types of things that were raised in the public session about the risk for antibody development, etc. But in the Normal Hematocrit study in the high target arm 30 percent of patients were transfusedB-in the high target arm. In the low target arm 38 percent. In the CHOIR study there is hardly any difference, 8.8 percent in the high hemoglobin target and 10 percent in the low hemoglobin target, and no

difference in quality of life between those two arms.

So, we need to be careful not to use our notions and our fears but use the data, and I think the data supports the low target arm in both of these trials.

DR. BLACK: Well, this is a hard place to be with so many erudite people. I even agree pretty much with what Larry said, which is unusual. I think there are a couple of things I would like to talk about. I think having a single number with an approximation in front of it for a biological variable that is as variable as this makes no sense whatsoever. It has to have a range and I actually like the 10-12 range, which I guess Jim did and others have and Larry first suggested.

We could abdicate our responsibility and that would be very easy to do right now. We are asked to give guidance with a number which hasn't existed for 20 years and we could simply say the data is not good enough to do that, thank you very much and come back to us in two years when we have

that. I don't think any of us really wants to do that, and I think we are going to have to take some stand, based on the quality of the data we have, and include the observational data in our understanding of what to do, understand what I like to call EPO resistance, like we talk about insulin resistance, rather than hypo-responders. I think it is not surprising that we sometimes have an active drug that we have to give more and more and more of and find that people get into trouble when we do that. So, that is a caveat with anything where we have such a heterogeneous population and we can't necessarily expect that the single drug we use and the single dose we use is going to achieve that.

If we are going to change the label, we have to make clear that there are some people who will respond very well to low doses and they are a little bit different as far as people who require very high doses to get to the same number, and maybe we are not doing them any good by cutting back the dose. This gets a little bit complicated.

I don't think we should have a target dose. I think we should have a target hemoglobin if we are doing that because we are going to end up in exactly that situation. As a clinician, we sometimes have to put a number, for example for blood pressure 141 is bad, 139 is not and that doesn't really make biological sense either. So, we have to have some range and I am tending to go with the 10-12 range, understanding that we don't really have all the information we might like in order to make that distinction.

I think what we do with the label, how we talk about how to push it, how we educate clinicians to do it-Bso, I am afraid that there are going to be some people who would strictly adhere to a single number and that we would certainly get people into trouble doing that.

DR. CHEUNG: I fully support to have a target, just like blood pressure, and dialysis dose for people on hemodialysis, etc. Even though I fully believe in randomized trials, I also am mindful that how you achieve the target in a

randomized trial, the algorithm to get there, could be very, very different in clinical practice, especially when you have something like ESA, as we heard earlier, and you have some different ways of getting to the target, for example giving lots of iron.

In terms of what the range should be and some question why it should be 12, I think that we should have a large enough range so that we would not fall into this problem with the excursions. So, I am comfortable with 12 even though perhaps, based on what data we have, 11 may be the safe range. I emphasize the word "maybe" but you have to have certain excursion allowed to get up to 12.

Finally, whether we should have a lower range or not, I don't really feel strongly but I would just bring up two scenarios. One of them is I am so afraid that, say, people look at the label and say, well, we should give EPO only if we need to avoid transfusion and that is so nebulous, because of avoiding transfusion with a hemoglobin of 18. So, I think what is the mean transfusion to

have the patient be able to get out of bed or actually to go and be gainfully employed. I think that is a very, very important issue to me as a practicing nephrologist. So, if you want to choose to have a lower target, I would also make sure that the doctors understand that you don't have to achieve the target, especially when the patient is a hypo-responder. Likewise, if you that you don't have a lower target the patient doesn't have to wait until the hemoglobin is 4 before you get EPO.

DR. NELSON: There are two issues I see we talk about here, which are safety and we talk about efficacy. The efficacy seems to not really be a big issue here today and we seem to talk about safety. I think when we start looking at our patients in these studies we are really looking at those patients who respond the way we expect them to an ESA, and I think they become less of a concern and we are really looking at efficacy in those patients. We want to make sure that they are going to get to their target hemoglobin without any problem and they really won't have a problem

getting there. I think when we really start to talk about safety we have to start looking at the population that doesn't respond very well because those are the patients who get these very high doses of ESAs and do suffer some of these real adverse consequences that we are talking about. They really make up the bulk of the patients we are talking about today.

I think that the data is pretty clear when you break it down in these subgroups that this hypo-responder population really would benefit from the safety perspective by keeping their hemoglobins at 11, or at some level in that range. Pushing it to 12 is probably exceeding the level that the data would support as safe. So, I am very comfortable saying that we should keep a target hemoglobin of approximately 11, particularly for the hypo-responders. Again, the clinical guidelines that follow could work out what you might want to look at in terms of efficacy for other groups of patients. But I think the safety perspective really has to be our focus here today and we have

to look at the patients who are really at risk, and I think that is the group we are looking at.

I think another big area we have to focus on, and it is not necessarily our purview at this point but we really have to find a way to avoid this phenomenon of cycling and of this daily variation. I mean, I am sure if you measure my hemoglobin three times today it is going to be different each time you measure it. Just given the fact that the laboratory has some variation and even if I don't have a glass of water all day and my hemoglobin rises during the period of time, etc.B-so, there are so many things that fit into this variability.

I think that one of the things we have to think about, and I kind of touched on this a little bit but it is the way we have to view the pharmacokinetics or at least the clinical pharmacokinetics of how we use the drugs. I am not necessarily saying we have to put an infusion pump in everybody but giving the drug several times a week. I think there is a lot of good data out

there that says that continuous dosing versus this intermittent, particularly large bolus dosing, probably isn't necessarily the best. And, when we start looking at these hypo-responders with these huge doses that they are getting, I am not convinced there is no toxicity of this drug yet. I mean, I understand the data doesn't necessarily say there is but I am not sure the data says that there isn't either.

DR. KOPP: I also favor a range. I have been reviewing the specific ranges in the three trials we have heard the most about. For the Normal Hematocrit the low target started out at 10.5 to 11 and then was increased to 11.3. For the CREATE study it was 10.5 to 11.5, again the low target. And, for the CHOIR it was 11.3. Where that takes me is something nobody has suggested before, which is not focusing on an integer but considering the possibility of 10.5 to 11.5. I do think a range is important, in part for the reason that you and others have made, that if we give a single number the tendency will be to have

clinicians try to treat up to that number with the risk of some increased toxicity.

There is the issue of cycling that has been brought up a number of times, and by keeping a relatively narrow range of just 1 g/dL there is a risk for more cycling. On the other hand, a range of 1 is what we have heard the FDA proposing in question one, 10 to 11. So, I don't insist by any means. This is not a firm statement but I would be inclined to go to 10.5 or 11.5.

DR. HENNESSY: The current label says that the hemoglobin concentration should not exceed 12 g/dL. So, my view of the question is whether that number should be changed. If we were sitting here when EPO was just being considered for approval based on the randomized trial data, I think I would say that that number should probably be 11.

I have also heard a lot today about the differences between randomized trials and non-randomized studies. I think the non-randomized studies here probably provide the best information on the relationship between hemoglobin level and

mortality between the 10-12 range. In slide 39 from Dr. Zhang's study, my look of this is that mortality bottoms out between something like a dose of erythropoietin of 10,000 units/week to about 12,000 units/week. If you match that up against Dr. Zhang's slide 29, it looks to me that that ends up being a hematocrit or about 35 to 36, which is a hemoglobin of about 12. So, given that we don't have randomized trial data telling us whether 11 is better than 12, but we have well done, although perhaps not perfect observational data suggesting that mortality may be lowest at 12, I am hesitant to reduce the number in the label to 11. I think when a number is out there a degree of conservatism is warranted to protect against unintended consequences.

In terms of what happens to non-responders, I think that in addition to having maximum hemoglobin to titrate to, having a maximum dose in addition to that may be the best way to express that, although I don't think we have seen the data to know what that best number should be.

So, I also think that randomized trials are unlikely to come up with that best number.

If you look at slide 39 again, there are 30 points on this curve. It is unlikely that we are going to see a randomized trial of 30 different regimens and the maximum dose, or at least some information about what the likely maximum dose is going to be is probably going to need to come from observational studies and, luckily, with the USRDS that is eminently feasible.

From a research ethics perspective, I am fascinated by the USRDS. I don't know much about it. I know there is a lot of talk now about the need for informed consent even in large database studies. So, if you are going to be in an HMO you can either check, yes, your data can be used or check no if your data can't be used. I don't know whether patients in USRDS have to give consent for their data to be used. I think that doing so would reduce the utility of such data and in particular its utility in improving the health of the people who are in the program itself. Thank you.

MS. SCOTT: I don't have a lot to say on the issue besides I think that having 11 as this magic number wouldn't be practical, and I say this from personal experience because I am a dialysis patient and I know that if I had a hemoglobin of 11 I wouldn't be here, sitting here with you right now. At 11 I am not in the bed but I feel like, you know, most of the day is spent in the bed. I function more at a level of 12. I function better and I am able to work.

I don't come from a scientific background. Like I say, I am doing this from personal experience and, from working in a dialysis center, I think that a lot of the other patients feel the same way that I do, and in keeping this range from 10-12 you open it up for the people that may not respond to EPO at 11 that may, you know, start feeling sick but may not be bedridden at that point for the people who have to have that 12 number.

DR. NARVA: I think we need a range, even if it is a narrow range. Regardless of whether we pick a range or a single target, a range is what

will be adopted as a performance measure by CMS and that will actually determine what happens to our patients.

I am ambivalent about what the target should be. With the lack of prospective data to identify the best target and potential adverse effects with higher doses, I feel that suggests that we should endorse a more conservative goal. But given the reality of how things work in a dialysis unit, I would be very worried that a more conservative target would result in a lot of patients, as shown by Dr. Lazarus' data, ending up with hemoglobins very low. Perhaps that could be reduced by better dosing algorithms, better ways of identifying people at risk of becoming EPO resistant.

If we have learned anything in dialysis care in the last 15 years, it is that we don't need to be married to the kind of disparities in care that we have tolerated in the past, and I think we probably can do better.

I think regardless of what we recommend,

we need to acknowledge that certain individuals will benefit from higher hemoglobins, including people who live at high altitude and there are a few thousand people in the western United States who live above 6,000 ft. and probably shouldn't have the same target hemoglobin as those of us who live at sea level.

DR. PLATT: Okay, folks, and extremely thoughtful conversation. We are five minutes over the time for the break and although we agreed we would move on to discussion of the other topics and then vote, there is some sentiment from the lieutenant commander on my right that we consider voting on this question now, before the break. I see nods. Does anyone want to hold off? So, we are going to vote.

DR. BLACK: Excuse me, Dr. Platt, could you clarify exactly what this means. Is it about 11? Does that mean 10-12?

[Laughter]

DR. PLATT: Dr. Rieves?

DR. RIEVES: Just a few points. Firstly, a

historical perspective, when we changed the label in March we essentially tied the recommendation to a transfusion trigger. There have been many comments here that that is not appropriate. So, we are looking for something better. There have been other comments that clinicians want numbers and we agree with that. We have been told. So, we are looking to try to walk away with a range, if you will, or a number.

The next point is the number 12. Remember, if we vote to choose a range, 10-12, if you will, I want it to be clear in our understanding we are acknowledging the weight and the benefit associated with observational data because we have essentially two clinical studies, 11 versus 13.

The last point is that on the slide up here, this proposal actually a range, sufficient to avoid transfusion and not exceedB-the key words are "not exceed" approximately 11, if you will. It is to "not exceed." It could be lower but that is one interpretation. We offer this as a pivot point.

If the answer is no, then we are looking for you to develop a proposal.

DR. BLACK: So, if we think this should be 10-12 we vote no.

DR. RIEVES: That is correct and we will be looking to you for a specific proposal. We don't want no answer; we want a proposal.

DR. PLATT: And we have four more questions and we end at 5:00. Any other points of clarification? Dr. Cheung?

DR. CHEUNG: Yes, I need a clarification on how to vote. If we have a number, let's call it 12, I want to make it clear that doesn't mean that the practicing nephrologist will have to cut the dose when it reaches 12.1.

DR. RIEVES: Your point is well taken. This gets into engineering the specific language. For example, one of the criticisms in the earlier label was that any hemoglobin above 12 was unacceptable. That was not the intent. We understand that, that variability is inherent and we anticipate working with Amgen to get that

language in the label to reflect clinical practice, if you will.

DR. PLATT: Dr. Kramer and Dr. Nelson?

DR. KRAMER: Based on what you just said, I just want to make sure I understand it. As I read this, it says the target hemoglobin should not exceed 11. But the way you said it a moment ago, you said it shouldn't go beyond 11 as if you were talking about achieved. I just want to make sure you are talking about the target.

DR. RIEVES: I am talking about a target. I don't want to confuse achieve and target. We are talking about target. You are exactly right.

DR. KRAMER: And could you clarify whether there would be any instruction for the clinician to explain what you should do with the target?

DR. RIEVES: To do with the target?

DR. KRAMER: For instance, reiterating what the instructions were in the trail that studied it in terms of, you know, how they should manage to a target.

DR. RIEVES: For example, one could

envision language along a target, if you will, sufficient to avoid transfusion and not to exceed 11, and then the language could go on state describing persistent elevations above 11 and define persistent, if you will, and prescribe a dose reduction paradigm in that line.

DR. KRAMER: When you say sufficient to avoid transfusion and avoid higher than 11, it sounds like you are inching into achieved rather than target. So, it is confusing.

DR. RIEVES: You are exactly right, and that confusion is why we are looking to the group for some clarity there. Again, we offer this as one proposal. We are not offering this as the best proposal; we are offering it as an example.

DR. PLATT: Right. I think all of us are aware how difficult it is to wordsmith a policy in a large group setting under tight time constraints. Frankly, I am not optimistic that we are going to come up with something better in the time that we have if this one doesn't make it. Dr. Phan is wondering whether this squiggle might be assumed

not to meaningfully change 11. You want us to vote on this. Let's just vote on what you have given us. Dr. Kaskel?

DR. KASKEL: I want to reiterate that in children and adolescents there is some evidence that they may need higher hemoglobin targets and levels for the process of growth. So, we need to take into account that this range has age-dependent factors as well.

DR. HUNSICKER: As we vote, are we allowed to make comments or is it just simply a word?

DR. PLATT: This is the time for comments.

DR. HUNSICKER: Now is the time for comments.

DR. PLATT: That is my understanding. Let me tell you what my understanding is of the process once we start it. These are the rules as of July 11, 2007. I read the question and then all the "ayes raise their hands and while your hands are still up we go around the table and you identify yourself as an aye. Then all the nos raise their hands and all the abstains. Then we move on to the

next question. So, this is the time for comments.

DR. HUNSICKER: So, is one two questions? I mean, are you going to do these separately?

DR. PLATT: Yes, we will vote and then the nos will have an opportunity. Help me out, FDA. Is this the way we should do this?

DR. RIEVES: That is okay. Just remember this is somewhat a two-part question. If it is no, then we go to the next slide.

DR. PLATT: Yes, yes, understood. I am a little worried about the time that we are taking. It is all good but we are going to be very compressed in a moment. So, only the critical things now, please.

DR. FINDLAY: Well, I think this is critical. Don't we have a dilemma? I think that if we put this exact thing, this exact wording up for the vote there is a good chance it is going to go down and FDA is not going to get the specificity, and you seem to have indicated a moment ago that any change in the wording is not going to get anywhere. I wonder if we shouldn't

think is there a change in wording, or as we go around to propose a potential tiny change in wording that would reach a consensus, then you would get what you want and we won't have wasted a day. I think there is enough consensus on certain parameters but maybe not that exact wording, given the squiggly, etc.

DR. PLATT: I am only expressing a personal opinion about how hard it is to make small changes that have no consequences.

DR. FINDLAY: And we would all agree with that.

DR. PLATT: But having said that, my understanding is the committee can do what it wants. So, we can change the wording but let's decide quickly.

DR. TEERLINK: May I make a suggestion? The way we handed this on another recent committee is that everybody voted but then, if you were a no you had a chance to say why you were a no as you went around. So, that will give us a chance to modify.

DR. PLATT: All right.

DR. HUNSICKER: I am fine as long as I can explain my vote when the time comes. Why don't you explain your no vote now?

DR. HUNSICKER: My no vote is related to the specific things "and not exceed." I have a great deal of difficulty basically crowding us less than 11 in the absence of data that 12 is worse than 11. If they were to excise that and say should be approximately 11 g/dL, even though that is not a range, I would buy that because approximately is up for grabs later on as you folks negotiate the label with Amgen. I just don't want to crowd us below 11.

DR. PLATT: Dr. Good? So, I will modify my statement. These kind of things can come up. When you vote no we have to help FDA with something new so why don't we reserve those kinds of comments to there?

DR. GOOD: Dr. Kopp had a suggestion which was also my suggestion that I didn't bring up, which was an alternative thing to float which would

be 11.5 as a suggestion as a target which sort of splits the difference and it actually is evidence-based at least for CHOIR as a target, which was 11.3. So, it is pretty close and people are saying, like, 11-12.

DR. PLATT: That is a part two comment. Are we ready? I am reading the question: For patients on dialysis, based on the available data, primarily derived from the Normal Hematocrit study, should the ESA product labels be changed to state that the target hemoglobin should not exceed approximately 11 g/dL for patients on hemodialysis, the level associated with better survival in the Normal Hematocrit study? Any such hemoglobin target necessarily assumes achieved excursions in the 12 g/dL range.

By a show of hands, those who vote yes on this, raise your hands now, please.

[Show of hands]

Keep them up, keep them up. I have five. State your names for the record, please.

DR. FINDLAY: Steven Findlay.

DR. GOOD: Chester Good.

DR. LESAR: Timothy Lesar.

DR. KRAMER: Judith Kramer.

DR. NELSON: Lewis Nelson.

DR. PLATT: The nos?

[Show of hands]

I have 14. Keep your hands up so we can know who you are. Dr. Day, will you start off by saying that you are D. Day?

DR. DAY: Ruth Day, no.

DR. HUNSICKER: Larry Hunsicker, no.

DR. CRAWFORD: Stephanie Crawford, no.

DR. LINCOFF: Mike Lincoff, no.

DR. PLATT: Richard Platt.

DR. KASKEL: Rick Kaskel, no.

DR. TEERLINK: John Teerlink, no.

DR. NEATON: Jim Neaton, no.

DR. BLACK: Henry Black, no.

DR. CHEUNG: Alfred Cheung, no.

DR. KOPP: Jeffrey Kopp.

DR. HENNESSY: Sean Hennessy.

MS. SCOTT: Malazia Scott, no.

DR. NARVA: Andrew Narva.

DR. PLATT: We are tallying the votes. Are there abstentions? There are no abstentions. I am suggesting we take a break. We are scheduled for 15 minutes but I don't think we have 15 minutes so 10 minutes, not to exceed 10 minutes.

[Brief recess]

DR. PLATT: Looking to FDA, can we proceed or do we need to wait? We can go. So, we are going to deal with the second part of question number one, which is for the people who voted no. I am sorry, I am supposed to announce the results. The vote we just took was 5 yes, 14 no, no abstentions.

Let me read the second part of question one: If no, provide a target hemoglobin and the basis for this suggestion. Describe the role that the Normal Hematocrit study contributed to your recommendation.

My suggestion is we go around. Everyone can state very briefly, since the question failed it doesn't matter, in my interpretation, whether

you voted yes or no. The question is what is your instruction to FDA and you have to be brief about it because we have to go home. Is that agreeable? A short recommendation. We are not going to try to get to consensus; we are just, each of us, going to say what we think the appropriate thing should be. You can stand with your original yes if you think that is what it should be. So, starting at the end, please.

DR. NARVA: I think the target should be 11.5.

MS. SCOTT: I guess I am not understanding but I think the range should stay like it is now on the labeling from 10-12.

DR. PLATT: My understanding is that the current label does not have a range. It just says treat not to transfuse. That is the current label.

DR. HENNESSY: The current label says do not exceed 12. I just read the label that was on line.

DR. RIEVES: It says the achieved and, again, let's distinguish target from achieved, the

achieved hemoglobin should not exceed 12. That is the current labeling. There is no language about a target in there. Essentially, the implicated target, if you will, is the transfusion trigger. We are looking for something better.

DR. HENNESSY: I want to change the current label.

DR. KOPP: I say 11.5. Again, the Normal Hematocrit study started with a target up to 11 and changed it to 11.3 and then the other two studies, CREATE was up to 11.5 and CHOIR was 11.3. So, all three of them are moving over 11.

DR. NELSON: I think I said yes. I know I said yes but if I could just comment, I mean, I have no problem switching it to 11.5 but I think the problem with a range is that it effectively become the top number with a "less than" in front of it. So, if we are saying 11.5, since we have kind of the little line in front of the 11 it really means about 11, which could be 11.5 anyway.

DR. CHEUNG: I suggest 10-12. I think 12 is one or two points below the Normal Hematocrit

study and the CHOIR study and we have to allow range for excursion.

DR. BLACK: I think we should take out the word "exceed" and have it say target hemoglobin should be 10 to 12.

DR. KRAMER: I feel strongly that we shouldn't be making up something now. I think it should be driven by the data from the Normal Hematocrit study, and that it should reiterate the target hemoglobin from that study, and a description of how the target was used, and the dosing instructions in the trial that created these data.

DR. NEATON: I am in favor of a target of 10-12 based on the Normal Hematocrit study and the epidemiological data we were presented.

DR. TEERLINK: I voted no because I think the words "not to exceed" are inappropriate. It should be changed to "should be approximately" whatever, you know, 11 or 11.3 from the study. If we are making a general statement, then 11 to 11.3. Also, it is interesting that the safety data from

other indications might be informative in terms of this upper level, and we haven't even talked about that but that is another issue. Then, also, I think a statement saying something along the lines that large variations in hemoglobin and/or erythropoietin dose have been related to poor outcomes and should be avoided as well.

DR. LESAR: I guess I agree with Dr. Teerlink's statements that I believe the numbers should be around 11 or 11.5 and it should be the target, but maybe there should be some statement related to the recognition of the variations from hemoglobin to hemoglobin in a patient. So, I think we should stick to the evidence.

DR. KASKEL: I would like to recommend that none of the decisions that will be reached regarding any changes in levels will apply to children up to the age of 19 years of age. There are no studies, no scientific data, and to assign these values to the pediatric population is not appropriate without the data.

DR. PLATT: I would remove "should not

exceed" and say that the target hemoglobin should be approximately 11, and would qualify that to say that the target should be applied to groups of individuals as a way of determining compliance.

DR. LINCOFF: I would emphasize that the Normal Hematocrit study was not the study that led to the approval of this drug. It was designed to test a higher target. It was not designed to rule out the existing target which previously was 10-12. So, I don't think that that informs that decision. I think the range should be 10-12. Although I said I don't believe the lower limit is as important, I think a range is useful in helping to prevent some of the fluctuation because if someone is aiming for a single number I think there will be a tendency more to try to fluctuate around that number.

DR. CRAWFORD: I would just add that if there is a target I cannot suggest a number and I would also support the inclusion of a statement that a target has not been established for all populations, such as the pediatric one, we have an

example of in others.

DR. HUNSICKER: Firstly, I don't think we should not change the label. The current label, as it is existing, suggests, at least to me as I read it, that we should be treating with EPO only if the alternative was transfusion and I think that was not what we really mean at all. So, I think it is important that we change the label, the question is to what. I obviously agree with myself.

[Laughter]

I think that what we should do is remove the statement that it should not exceed. I like it should approximate 11. I have a marginal preference for an approximate single number rather than a goal because I think goalsB-I mean spreads are sort of confusing. I want to reiterate what I think was first brought up by Dr. Kramer, that I think it is essential that if we say that the goal is thus and such we say what we mean when we say the goal is thus and such, i.e, what do you do when it gets to where. That probably should be developed from the existing data that we have.

DR. GOOD: I would vote for a target. Whether the target is 11 or 11.5 is fine with me. I do think we need to accept that the best evidence does come from two randomized, controlled trials that were both halted prematurely because of safety concerns, and I think that we need to remember that and, because of that, I feel strongly that setting the target at either 11 or 11.5 is most appropriate. But I do think that is quite reasonable to include the verbiage that says that we do assume that there are going to be excursions. That is, a gram per deciliter above that target is also quite appropriate.

DR. FINDLAY: I agree with removing the words "should not exceed" and replacing that with "should be in the range of 11 to 11.5."

DR. DAY: I agree with some range and "should be" rather than "not to exceed" and I would like to just make an additional comment, that the language has to be a lot simpler than what it is now. If you take what it is now and you put everything all together, you have five terms of

quantification in one sentence. This is taking one of the statements in the sponsor's briefing material saying what the current dosage is, and that is the lowest ESA dose--So, that is going downB-to increase hemoglobin concentrationB-that is going up--his is all one sentenceB-to the lowest level sufficientB-going downB-to avoid the need forBso that is going to zero--

DR. PLATT: Dr. Day, it is great but--

DR. DAY: I am sorry, but it is very difficult to vote on these things for a particular change when it is in the context that still may not be communicating well enough.

DR. PLATT: Fair enough. This draws to a close the discussion of question number one. So, we are ready to discuss question number two. I make us to have 52 minutes to discuss five more questions. This was all very well worthwhile. I don't mean to be facetious but we do need to have sort of a different tempo for our discussion from now on.

Let me ask, with a show of hands, how many

folks on the committee want to have a separate discussion on question number two? So, how many folks will want to comment separately on question number two before we start to vote? Dr. Hunsicker and Dr. Black. Dr. Black, why don't you start?

DR. BLACK: I think the concept isn't really that different but I think the numbers might be, and I think we saw different numbers so we might want to talk a little bit about what those numbers should be.

DR. PLATT: Fair enough. We will ask you to comment on it. Let's take the rest of the comments.

DR. NEATON: Well, I guess I think mixing CREATE and CHOIR and Normal Hematocrit is a mistake. This is a different patient population, a much lower mortality rate overall than in the Normal Hematocrit studies, and also not the large database from the USRDS to kind of look at. So, given the quality with which those trials were done, I think there is a great deal more uncertainty about the kind of range in the lower

level. So, I just want to put that on the record.

DR. PLATT: Good. Dr. Hunsicker?

DR. HUNSICKER: Actually that was almost exactly my comment so I will just simply repeat that I think the targets are the same based on what we have, but I think we have to recognize that the data are much less thorough and much less net convincing for the non-dialysis patients than they are for the dialysis patients.

DR. PLATT: Dr. Black, do you want to pick up on your comment?

DR. BLACK: I may well defer to people who actually practice nephrology right now-BI used to, as to how much this really matters. It seemed to me that these people live better with a somewhat higher number but that may be a misinterpretation or an over-interpretation.

DR. PLATT: Good. More discussion on this topic? With the committee's agreement I will read the question and then we will vote. So, this is question two. Based on the available dataB-so this is patients not on dialysisB-primarily derived from

the CHOIR study, should the ESA product labels be changed to state that the target hemoglobin should not exceed approximately 11 g/dL for patients who are not on dialysis, the level associated with fewer adverse cardiovascular events in the CHOIR study? Any such hemoglobin target necessarily assumes achieved excursions into the approximately 12 g/dL range. Show of hands. Everyone who wants to vote yes on this, raise your hand, please.

[Show of hands]

Five. Now for the record state your name, please.

DR. FINDLAY: Steve Findlay.

DR. GOOD: Good.

DR. LESAR: Timothy Lesar.

DR. KRAMER: Judith Kramer.

DR. NELSON: Lewis Nelson.

DR. PLATT: The nos? Hands up.

[Show of hands]

Fourteen. You get to state your names, the hands up group.

DR. DAY. Ruth Day, no.

DR. HUNSICKER: Larry Hunsicker, no.

DR. CRAWFORD: Stephanie Crawford, no.

DR. LINCOFF: Mike Lincoff.

DR. PLATT: Richard Platt.

DR. KASKEL: Rick Kaskel.

DR. TEERLINK: John Teerlink, no.

DR. NEATON: Jim Neaton, no.

DR. BLACK: henry Black, no.

DR. CHEUNG: Alfred Cheung, no.

DR. KOPP: Jeffrey Kopp.

DR. HENNESSY: Sean Hennessy.

MS. SCOTT: Malazia Scott.

DR. NARVA: Andrew Narva.

DR. PLATT: We will wait for the tally. Five yes, 14 no. Did I ask for abstentions? No abstentions. Now we will do part two of this question.

Since the answer was no everyone can state his or her recommendation. If no, provide a target hemoglobin and the basis for this suggestion. Describe the role that the CHOIR study contributed to your recommendation. Why don't we start on this

side? I think we started on the right side so why don't we start with you, Dr. Day, please?

DR. DAY: No comment at this time.

DR. FINDLAY: I would suggest the same wording that I did for the previous one, which would be to remove the "should not exceed"B-it does say that, right? Yes, to it "should be in a range of 11-11.5."

DR. GOOD: 11.5.

DR. HUNSICKER: Remove "not exceed" and then 11 or 11.5 or 10-12. I don't care.

DR. CRAWFORD: No further comment.

DR. LINCOFF: I don't think it should be different in the absence of data from end-stage renal disease on dialysis, so 10-12.

DR. PLATT: I will stay with my comment for the "no" part of question one.

DR. KASKEL: Same as before. We need studies in pediatrics.

DR. LESAR: No additional comments.

DR. TEERLINK: As per my previous comments.

DR. NEATON: I think there is too much

uncertainty to establish a threshold here. That is why I voted no.

DR. KRAMER: I think it should exactly mimic the CHOIR study. It occurred to me since my last comments that I think the label should also include discussion, since the analysis was done in the CHOIR database, that higher achieved hemoglobins was associated with better outcomes so that clinicians understand that the target is not the same thing as achieved.

DR. BLACK: I think it should say what the CHOIR label did as well, which is not exceed 10-12.

DR. CHEUNG: 10-12 as the last one. I also want to qualify for both dialysis and non-dialysis all the caveats about children or high altitude, etc. That will be in finer print.

DR. NELSON: Nothing additional.

DR. KOPP: Same as before, 10.5 to 11.5.

DR. HENNESSY: I don't think we have seen data warranting a change in the label.

MS. SCOTT: The same as my previous comment, 10-12.

DR. NARVA: Also the same.

DR. PLATT: Clarification, Dr. Good, could you restate your vote? There is some confusion.

DR. GOOD: I voted yes initially but I said I would vote for 11.5 if it went for a re-vote.

DR. PLATT: Okay. Dr. Kramer?

DR. KRAMER: It just occurred to me that we have dropped the discussion about needing more data and instruction on ESA responsiveness, and I think that all of our comments on this should have that as an underlying theme, that that is needed.

DR. PLATT: I think we will come to that soon. Dr. Phan is saying that our vote on question two is four yes and 15 no, which is different from question one which was five yes and 14 no.

DR. GOOD: I am sorry, I voted no. For this I voted yes. Have you got me as yes or no? I voted yes but I said if it went for a re-vote I would vote for 11.5.

DR. PLATT: Could we just see the yeses again, please? The yeses on question two?

[Show of hands]

Five, same as number one. This is why we do paper trails on these. We are going to move to question number three. Question number three, for better or worse, is not a straight up and down yes or no vote. So, if you are agreeable I will read it, but I think that we are talking about a discussion, and since we don't have a lot of time we may be talking about going around the room and stating our views. Is that agreeable to the group? It says there is a vote and there are question marks but--

DR. RIEVES: Dr. Platt, in terms of getting the most useful information we can defer this question. In fact, the subsequent voting question, number four, is perhaps a little bit more--

DR. PLATT: Okay, with the committee's agreement, we will do question four next. In the interests of time, let me read it and then we can discuss. Question four is are the ESA dosages used to achieve the hemoglobin levels in the lower target groups in Normal Hematocrit and CHOIR sufficient to form the basis for ESA dosage

recommendations? So, that is going to be a yes or no. Any such recommendation necessarily recognizes the difference in dosage between subcutaneous administration to patients not on dialysis and intravenous administration to patients on dialysis.

It is a substantive question and we need to move with dispatch on that. I think we can't do better than to invite comments around the table, understanding not everyone might feel compelled to comment. So, can I look for eye contact from those who want to-Bgood, Dr. Hennessy?

DR. HENNESSY: I don't think anybody was happy with the amount of data that we had available to make the vote so my guess is that number four is going to be no.

DR. PLATT: So, you are telegraphing your intention to vote. Moving around, I see Dr. Black. Anyone between Dr. Hennessy and Dr. Black? This is discussion so there can be comment or discussion.

DR. KRAMER: It seems to me that when you have inadequate data the best you have is the data

you have. So, I would suggest that it should be in the label in terms of what was the experience in the trials that showed one group that did better. It is not ideal, we don't have everything we need but I would vote for having it in there.

DR. PLATT: Others?

DR. HUNSICKER: The question there is are we being asked whether there should be advisory information that is not an FDA recommended treatment but, rather, advice as to how to achieve this goal. Is that what is here? Typically, there would be something in the product information folder about what happened in the trial, what the doses were, and stuff like that. Certainly, it is appropriate for that to be there.

DR. PLATT: Dr. Rieves, do you want to comment?

DR. RIEVES: Yes, that is one interpretation. For example, the label could describe the dosages used in CHOIR and Normal Hematocrit, and by notation within the label it is obviously of some importance to the clinician.

DR. HUNSICKER: But it is not meant to be quite the same as what we have just talked about, which is you give the stuff to achieve a target of approximately whatever the heck you can extract out of our comments.

DR. RIEVES: That is exactly right. This somewhat ties into the earlier vote also because a more negative vote earlier somewhat leans towards a more negative vote here because the dosing was to targeting here. One potential usage here would be to cite this even in the dosage and administration section. That would be one interpretation. So, it is difficult to divorce the earlier questions from this question.

DR. PLATT: Dr. Black?

DR. BLACK: It seemed to me we weren't that unhappy with the lower dose group. They seem to have done better so maybe we ought to use those recommendations. I don't know that it would have quite the same authority as we did previously but it certainly should be mentioned.

DR. HUNSICKER: If I might, Mr. Chairman,

Henry, the question in my mind is when we read a recommendation for a blood pressure medicine it says that you are supposed to start with a certain dose and adjust to such and such. This is the way we use it. The implicit thing is we are trying to get to a target and we adjust to the target. I am assuming now that what we have here is some sort of statement as to what the target is and then some sort of comment as to how people got there, in fact using the existing data. That seems to me eminently reasonable.

DR. BLACK: Then looking to Dr. Rieves, does that sound reasonable to you?

DR. RIEVES: That was in the line of thinking, right, of trying to construct a reasonable target or target range, if you will, and how to dose to get there. That is the type of information we would find useful.

DR. PLATT: Dr. Teerlink?

DR. TEERLINK: Yes, so if we were to focus on dosage recommendations where we said this is the range of doses, I would not agree with that. If it

were labeling that said in the CHOIR and these trials this is how they achieved these targets, then I would strongly support that. Does that make sense in terms of the distinction I am making?

DR. PLATT: Dr. Cheung?

DR. CHEUNG: I also interpret this question, and maybe I am just reading it wrong, Dr. Rieves, and it is relevant to the question I asked half an hour or so ago, is there any toxicity with the drugs where you have a limit? For example, if you give an ACE inhibitor at a certain dose your target is a certain blood pressure but what is the maximum dose you should give? So here I wonder are you looking for the maximum ESA dose you should be allowed to try to get to the target?

DR. LINCOFF: If we don't end up with the same recommendations though for target that are the same in the trials, then these dosing regimens that were used in the trials are only of some relevance. They are probably a good starting point. But isn't this where we probably want to make the cautionary notes about avoiding cycling and, you

know, whatever algorithms or steps, without getting into the details of them, that would be designed to try to limit marked dose changes in response to small changes in the hemoglobin?

DR. PLATT: Dr. Good?

DR. GOOD: It seems reasonable to have something to let clinicians know that these were average doses, but I am just wondering how is it going to be used. I mean, obviously if these were average doses some people used higher doses; some people used lower doses. So, how is this going to play out?

DR. RIEVES: Right, we are essentially asking the committee if the conceptual approach is reasonable for using this. We are not positing exact language, if you will, on that and we will take any comments from you to heart in working with Amgen to optimize dosage information in the label. So, we are not talking about specifics at this point on this dosing. The concept, the dosing that was used in CHOIR and Normal Hematocrit, do you regard that as an important as a basis for

construction of some dosage recommendations?

DR. GOOD: That seems reasonable. I guess the concern would be that these might be used as limits to dosing or things like that, and that might be counterproductive.

DR. PLATT: Back to you, Dr. Findlay.

DR. FINDLAY: So, this is just a conceptual question really. You are not looking for actual dose--

DR. RIEVES: That is right, this is conceptual. We are not getting into the specifics. We are not as specific as we were on the earlier questions.

DR. FINDLAY: Thanks.

DR. NARVA: In the area of dosing and route of administration, we know that sub-q EPO works in hemodialysis patients but we don't know its relative risk of adverse effects compared to intravenous erythropoietin, and that would be very interesting to know and I don't think the data exist yet.

DR. PLATT: Dr. Kaskel?

DR. KASKEL: Would it also be important to look at the rate of response, rate of rise in an individual patient to this dose and have it appropriately evaluated with an algorithm?

DR. RIEVES: Yes, it would. Again, it would be placing some emphasis upon these randomized, controlled studies, if you will. We are not talking about specific language at this point. We want a sense of the committee as to how important you regard these two studies, these randomized, controlled clinical trials. Do you regard them as important enough to help inform the labeling, if you will, specifically the D and A section? We are not talking about the specifics of it because we are going to use good judgment with Amgen to optimize the language, but the conceptual approach is what we are interested in here.

DR. PLATT: Seeing no more comments, we will vote. So, we are looking for a show of hands--

DR. TEERLINK: Can I ask one point of clarification? Sorry. So, I just want to make

sure are we voting on dosage, which generally is a range of, okay, you shall give such-and-such microgram per kilogram, which is how it is written, or are we voting on dosing regimen? Or, do you mean dosing regimen by your term "dosage" here?

DR. RIEVES: Dosage regimen.

DR. PLATT: Going once, going twice? I will read it again. Are the ESA dosages used to achieve the hemoglobin levels in the lower target groups in Normal Hematocrit and CHOIR sufficient to form the basis for ESA dosage recommendations? Any such recommendation necessarily recognizes the different in dosage between subcutaneous administration to patients not on dialysis and intravenous administration to patients on dialysis. Going once, going twice? All in favor?

[Show of hands]

I see 14 hands. Let's have them by name. Dr. Findlay?

DR. FINDLAY: Steve Findlay.

DR. GOOD: Good.

DR. HUNSICKER: Hunsicker.

DR. CRAWFORD: Crawford.

DR. PLATT: Platt.

DR. LESAR: Lesar.

DR. TEERLINK: John Teerlink, yes.

DR. NEATON: Neaton.

DR. KRAMER: Kramer.

DR. BLACK: Black.

DR. NELSON: Nelson.

DR. KOPP: Kopp.

MS. SCOTT: Malazia Scott.

DR. NARVA: Narva.

DR. PLATT: The nos, please?

[Show of hands]

Three. Your names?

DR. LINCOFF: Lincoff

DR. KASKEL: Kaskel

DR. CHEUNG: Cheung.

DR. PLATT: Abstentions?

[Show of hands]

And your names, please?

DR. DAY: Ruth Day.

DR. HENNESSY: Sean Hennessy.

DR. PLATT: My understanding is that since we said yesB-do we need to move to no? Do you want to hear from the people who voted not?

DR. RIEVES: Considering the time constraints, we would suggest that we move on to some of the other discussion questions, specifically topic number five regarding the hypo-responders. Dr. Platt, to try to get a relatively solid sense of the committee's perspective on these voting questions, especially with respect to the target information, is it reasonable to walk away understanding that there were mixed opinions, if you will? There was no consensus regarding that target. Is that a fair characterization of the committee's sense of it.

DR. PLATT: I am not sure it is fair for me to characterize, but let me try to say what I think I might do if I were you, which would be to plot the specific recommendations you got which I thought were fairly tightly clustered. Although there was not unanimity, it seemed to me that you could describe the range in a way that might not

look unlike the results of a Gaussian distribution. I don't want to be flippant or misrepresent--

DR. RIEVES: Taking that into consideration then, the committee is giving some weight to the observational data, if you will, in the target range, if you will, because essentially, again, the RCTs looked at 11 versus 13. The committee was not happy with that and looked towards a range, if you will.

DR. PLATT: I heard some committee members saying use that exactly and others saying that they would temper that with other information. But I think almost everybody gave you a numeric response and, if I were FDA, I would give equal weight to the committee members' views on that and I think you didn't get a cacophony there; you got a substantial amount of concordance.

DR. RIEVES: Well, that is basically the message I want to understand clearly.

DR. PLATT: I didn't hear many people who were way off from anyone else. There weren't serious outliers that I heard. So. Steve?

DR. FINDLAY: Just one point, I mean, I think if you wanted absolute clarification you could take the vote on the number of people who said 11 to 11.5 and the number who said 10 to 12, because there was actually probably a clustering around both of those, if you need that. If you don't need it, you have it on the record.

DR. PLATT: Is it your preference that if we could make good use of spending all the remaining time on question five, would you want us to do that or do you want us to allocate some time to the other questions?

DR. RIEVES: This issue of hypo-responders has been a very high profile topic so discussion of that would, hopefully, be the most useful compared to the other topics here. So, if we spend the majority of time on number five.

DR. PLATT: Okay, and if we are having a hot and heavy discussion that would take all the time, we will do that on question five. Folks, we are moving on to question number five which deals with hypo-responders and it is a discussion

question so that is good and bad.

Let me read it. Please suggest ways to identify ESA hypo-responders. For example, is failure to respond to a maximum ESA dose the most important consideration? Are sufficient data currently available to suggest how best to identify and dose these patients? If so, provide recommendations for how best to define and dose this population and your basis for such recommendations.

Why don't we start? As before, this is a situation where not everyone has to express an opinion and, of course, it would be okay to say I agree with someone who has already spoken. Does someone want to start this discussion? Quick show of hands, who is interested in speaking.

[Show of hands]

We will start with Dr. Hennessy.

DR. HENNESSY: There are any number of ways that one could think about defining hypo-responders and the relationship between being a hypo-responder and outcome. So, to me, that makes it initially a