descriptive hypothesis-generating exercise in a database. At this point I would want to be comparing between randomized groups so even if that question was looked at from the data from a randomized trial, it would be a non-randomized comparison. So, I think doing something like a split sample or taking a group of studies and looking for potential ways to identify hypo-responders and the relationship between dose and mortality in those, and then looking to validate that in a separate data set would be how I would think about going about it.

DR. PLATT: Dr. Nelson, do you want to speak? Go ahead.

DR. NELSON: Briefly. I would just remind everybody that the sponsor actually gave some thought to this as well and made a recommendation, which seems very reasonable despite the fact that maybe we have some changes in the number to which, you know, we would target the hemoglobin. There is no diagnostic test, obviously, for this group so we are going to have to do some sort of clinical

decision-making to decide if they are and if you give them the drug and they don't respond, which is essentially what the sponsor is suggesting, that seems like the only way we are going to be able to do it for now.

DR. PLATT: Dr. Cheung?

DR. CHEUNG: I think, no question, this is an extremely important topic. As clinicians we are always confronted by this and we don't know what to do. Regarding the sponsor's slide, I think they give a very, very good start. Although it is already somewhat in clinical practice, I would just modify it slightly to say that I would not wait until you actually see the non-responder to try to identify those things. Iron deficiency, of course, is easy. Although it might still happen, I think it is an easy one that you can deal with even before you watch for the three months to see if they respond or not respond. But much more important are the hospitalized patients or the grossly infected patients and whether we should increase the dose, continue the dose in order to

avoid apoptosis or actually decrease the dose because it is futile. I do not know how to deal with that.

DR. BLACK: Yes, I also want to say I think the sponsor gave this a lot of thought and has a reasonable proposal, and we don't have anything else that is any better necessarily to go on. We might look, if we could profile the hypo-responders' outcomes, to see if we can maybe refine who we look at a little bit better but I think that is going to take some work with the observational database.

DR. KRAMER: I think by nature of the other decisions that we made that the label will likely have a target hemoglobin, this is a very serious problem because if you just leave it the way it will be these patients who are hypo-responsive will be pushed in terms of the dose. I realize that there is a tremendous amount of confounding that you can't separate out, but the practical effect is that they will have toxic effects from having the dose pushed. So, I think it is critical that

something be put in the label as soon as possible in terms of this issue, and it seems to me the best way to proceed is to use the observational data to come up, as the sponsor has started to do, with some definitions. And, those definitions, in my opinion, should be tested in an actual randomized trial so that we know the answer to this question. But prior to that I would put at least a caution in the label, to the extent that we can, describing the fact that we need to avoid pushing the dose when patients really aren't responding.

DR. NEATON: The part about the sponsor's proposal that I like is the new research. I think the problem in looking at hypo-responders in the existing trialsB-it is just fraught with problems in both what the FDA did and what the sponsor did. I think the idea of kind of doing a run-in period with a challenge and looking at kind of the etiology, if you will, of hypo-response and then understanding ways to manage them is the way to go.

DR. TEERLINK: So, I would like to agree with my colleagues, as well as myself with what I

said earlier in terms of including a statement about the poor outcomes in patients who have had poor responses to the EPO. I also concur that it is important to do a trial where you first address reversible causes of the hypo-responsiveness and then take that patient population, and I would randomize them to a strategy where you just let the physicians do what they will with themB-standard of care, compared then to after 12 weeks you start pushing and, you know, you then can select the maximal dose that achieves the maximal hemoglobin and you stay thereB-or the minimal dose that achieves the maximal hemoglobin and you stop at that point. Then look at the data you have right now and if, in fact, this event rate is as high as we keep sayingB-oh, these hypo-responders do so poorly, you may actually be able to do a very effective outcome trial to establish the benefit of this different treatment strategy. So.

DR. LESAR: I want to mention some of the data that Dr. Zhang presented. There is some very interesting data that could probably be used to

inform a decision in looking at dose versus mortality and correlating that with the hematocrit response to a given dose, and if you tie it in with the data on the actual average EPO dose with the achieved hemoglobins and things match up pretty well despite the different populations. So, I think that can be used to perhaps come up with some warning statements that make some sense based on that evidence.

DR. KASKEL: Again, the reasons for hypo-responsiveness will differ whether a patient is on hemodialysis or perineal dialysis, and I think that the sponsor should look at KP studies that haven't been done yet to see if there is even a dose response to EPO administration that may involve pharmacokinetics that haven't been identified. Certainly, in the CKD population the stages of CKD may be correlated with hypo-responsiveness. There is a template for this analysis that was done when the FDA approved recombinant growth hormone in the use of children with kidney disease, kidney failure and growth

failure, and an algorithm was set up looking at nutritional assessment, acidosis, anemia, correction nutritional abnormalities prior to the administration of recombinant growth hormone to maximize their response to it. So, this hypo-responsiveness has been evaluated in another system in CKD and it may be reasonable to apply to the population at hand.

DR. PLATT: I strongly support the notion that any labeling change to identify a target has to have language that that target doesn't apply to hypo-responders, and until there are better data best expert opinion ought to guide the identification of those hypo-responders and the way they should be managed. I too support the importance of developing additional data.

DR. LINCOFF: I agree with what has been said essentially. I think the key is that it is not just the hypo-responding status but it is pushing the hypo-responders to try to achieve a target that is the problem, and it is either a lower target or not a target. And, I agree with

all the drive to have a prospective evaluation of what is the best way to evaluate the hypo-responders and what is the best way to try to dose them.

DR. CRAWFORD: I agree with what everyone has said.

DR. HUNSICKER: Well, I will start out by agreeing with the general principle that this is, or at least appears to be a very important issue and it needs new research. To do research in a consistent way you need a consistent definition and I am not sure at all that there is a community consensus on a definition. Preston suggested oneB-I think it was Preston who suggested one possible definition but, as I understood Dr. Unger's presentation, it wasn't at all clear that initial unresponsiveness has been correlated with unresponsiveness later in the course of treatment.

I think that we may be at the point where to say we have a way of defining this is just premature. So, we know it is a problem. We don't know how to study it yet. That is generally a

recommendation for what I would call free communications or what you would call investigator-initiated research. You need a lot of ideas and it is too early to close off how we are going to look at it.

I think once we get a definition that is testable, or whatever, we have to bear in mind that it still is not in any fashion demonstrated that there is what I would call an interaction between EPO and responsiveness and EPO toxicity. We don't know whether the increased mortality that is associated with EPO responsiveness is simply characteristic of people who are EPO unresponsive. We have no evidence that it makes any difference how you dose them. Before we get too panicked about things we have to understand that we have-Bwhat did I just say?B-no data on that. So, I don't think that we should yet put in, you know, arbitrary upper limits on anything because we have no data behind it.

The final thing is that I do think that a caution, and I rather like the idea of best

opinion. It was my chairman's suggestion, that there is a best opinion. I don't have a very high opinion of best opinion but it may be better than nothing, that suggests that these people are really at particular risk and that, therefore, the issue of dosing in them should be approached with some sort of caution. And, that is about as much as I would say in the current indications. What we get in the future God only knows.

DR. GOOD: Just ditto to those comments that have been raised. I don't know that we have good ways to identify nicely the ESA hypo-responders but I clearly think there needs to be something in the label. I think the data that has been presented on the association--talking about causality, the association of adverse outcomes with these ESA hypo-responders is quite compelling so I think there should be something in the labeling cautioning about dosing in these patients.

DR. FINDLAY: I agree strongly that there should be discussion in the label with emphasis on

the adverse effects and heightened risk.

DR. DAY: It would be great it someone could think of a creative way to pull apart the contribution of toxicity and lack of response, and thinking of a way to study that would be terrific. In the meantime, we need some cautionary statements about the hypo-responders.

DR. PLATT: We are doing pretty well for time all of a sudden. Do any of the committee members want to do a second pass on this? Dr. Cheung?

DR. CHEUNG: I am not at all surprised that the initial non-responder at baseline is different from later in the follow up because dialysis patients get a dialysis catheter and I think it will change all the responsiveness. I am not sure we are really at the point to actually do randomized trials yet before we identify the percent of patients with readily correctable hypo-responsiveness and what are the biomarkers, etc. that would identify the patients who may be more difficult to respond. But even after we are

ready to do it, I have a slight disagreement with the control arm being the current practice. I don't know what the current practice is at all over the country. Even in my hospital everybody does it differently. So, I would rather have something a bit more structured in the control arm than just routine practice.

DR. NELSON: For what it is worth, it is probably not inconceivable that there is a diagnostic test for this, and it might be as simple as taking, you know, some peripheral blood, finding a stem cell, or something and mixing it with some EPO and seeing what happens. I mean, it is something that is probably worth looking into. I don't know that that is FDA's job. It certainly may be a recommendation for the sponsor to start thinking about easier ways to make a diagnosis than a mini clinical trial of one.

DR. PLATT: To our FDA colleagues, have we helped you enough with this question?

DR. RIEVES: Yes, that is very useful. In the last few moments, questions three and six are

actually tied together very closely. They are just dealing with other design considerations for clinical studies.

DR. PLATT: Okay, so I will just note that we have taken our last vote as a committee. Right? So, we can just be smart again. Dr. Kramer?

DR. KRAMER: In reading question six, I was trying to think about the question that Dr. Rieves posed to you, Rich, in terms of characterizing what happened today and question six is really asking whether we need to do more studies of dosing algorithms. And, I think the hesitance of the committee in voting on the first two questions was the idea--even though we had randomized trial data, the idea of picking one number, which was, you know, the arm that was successful in Normal Hematocrit and CHOIR for those two questions, and depending on that because it gets all mixed up with the target and the achieved hemoglobin.

So, I do think one way to interpret the confusion or the differences among the committee votes was just that people were uncomfortable with

the potential misunderstanding of one small, narrow target. So, anything that can be done to actually test different specific dosing instruction algorithms so that clinicians know what it means when you say a target is, you know, and if it was here this is what you should do and if it is there this is what you should do. So, I think to the extent we can get data on this it would be very helpful, and I don't think that we really were that different in our views on those first two questions when I think about it.

DR. PLATT: I suggest that we go around on this and it would be okay to sort of speak to both questions three and six at the same time. They are tied together. We have 11 minutes so I don't think we will have a chance to sort of consider them separately. My short-term memory is gone. I don't remember which way we started. I think we started with you, folks, last time so why don't we start with Dr. Day. Once again, it is not required to comment.

DR. DAY: I need a moment to put three and

six together, as I assume other people do. Would it help to start with six and include three as relevant or some strategy like that?

DR. PLATT: Fair enough. Dr. Findlay?

DR. FINDLAY: No.

DR. PLATT: Dr. Good?

DR. GOOD: No.

DR. PLATT: Dr. Hunsicker won't let us down.

DR. HUNSICKER: No, Dr. Hunsicker won't let us down. I just want to make a comment about number six, that this is a very unusual way in medicine, very much constrained by the billing practices and by the CMS rules for reimbursement. You have to understand that the way we go about treating things has in large measure been tailored to the reimbursement patterns, and if we are going to be free to try different patterns we can't be absolutely-Bwhat is the word?-Bforced into a certain pattern. Particularly, the suggestion is implicit I think in everything that we have said that we are what I used to call as a kid

over-driving: The level goes up; we stop things. The level goes down; we push things. What we need to do is to adjust the doses in very gradual ways in order to get something so that the dose is the same every week. This is well-known to everybody who has even either driven a car or tried to dose warfarin.

Right now we are less constrained than we were in the past but we are still substantially constrained by the billing rules, and I just think when the FDA is looking at these things they are going to have to work with their CMS colleagues to make sure that, in fact, we have enough room to adjust our treatments in a rational way to achieve over the long haul a consistent level.

DR. PLATT: Dr. Narva?

DR. NARVA: Actually, I think CMS is holding its breath, waiting for this meeting.

DR. CRAWFORD: Given the lateness of the day, I don't quite remember so I guess it is more my just asking could we get a reiteration? At a certain point during the sponsor's presentation, I

don't remember if it was on dosing or cycling, but they absolutely acknowledged amenability to including studies. Dr. Rieves I believe, someone from FDA stated that it was good to hear what the sponsor was saying. Would this fall under what you were stating? If so, is it possible for them to just reiterate what they were thinking?

DR. PLATT: I think you ought to say what you think is important.

DR. CRAWFORD: I just don't remember. I mean, what they said. I am a little confused with the two questions.

DR. PLATT: I think we don't have time to have comment. So, I am happy to have you say what you think we ought to do.

DR. CRAWFORD: I believe they should continue with that study they have in mind, and talking with the agency, of course.

DR. PLATT: Dr. Lincoff?

DR. LINCOFF: I think initial studies shouldn't be directed outcomes but just to assume, at least for the start, that reducing variability

in dosing and reducing variability in hemoglobin levels is desirable, and use parameters as endpoints that are measurements of variability. Once one achieves algorithms which appear to be effective in that way, then is the time to do outcome trials to answer perhaps question three, that is, are there better ranges of hemoglobin that we might want to shoot for. Since we have decided we don't want the higher ranges and we know we don't want to be below 9 or 10, do we want to refine that further, but I wouldn't do that because it has been very clear that the studies that exist seem to be flawed by this wide variability, until we nail the variability and try to achieve better dosing regimens. I think that is the first goal.

DR. PLATT: I will speak first to question three. I think there is a great, great need to prospectively evaluate the utility, both the benefits and the risks of hemoglobin targets of 10, 11, 12. It just makes no sense at all to have this be such an important therapeutic question and for us to be guessing about 12 and 10 and to focus all

of our energy on we know something about 11 or 11.3.

I think given the magnitude of the issues involved, it warrants formal prospective clinical evaluation of the full range of hemoglobins that we have been discussing. And, I fully support the notion that we should be able to develop more thoughtful dosing algorithms to identify those who can respond, and for those people to keep them close to their target without having to require physicians to make ad hoc guesses.

DR. KASKEL: I agree that the ranges need to be studied, and they also need to be studied in pediatrics. Let me just add in terms of number three, I think, because hypo-responsiveness is such a serious consideration, that we do need an algorithm. We need to look at baseline. Patients need to have a checklist for iron, for folic acid, for carnitine levels. Carnitine deficiency in dialysis patients has been associated with cardiac events, and it has been published multiple times. Assessing their degree of acidosis is very

important and I don't think we pay enough attention to the chronic acidosis which will limit any endocrine factors response at a cellular level and, of course, nutritional assessments. So, I think we need a checklist algorithm to be developed for both the CKD and the hemodialysis patient.

DR. PLATT: Dear committee members on the right, if each of you could speak for a minute we would finish five minutes late. Okay? If you speak for more than that time the lights will go off and you will be speaking to an empty room.

DR. NEATON: I agree with our chair about the need to study different doses, although I think it is quite challenging, again, comparing 10 versus 11, 11 versus 12 just in terms of power issues for these kind of outcomes. So, I applaud the studies that are being planned that are what I would say are pushing the envelope in terms of a low level versus a high level and to use that as a basis for further research, the results of those studies.

DR. LESAR: I just thought that the lack of reliable, consistent data on quality of life really

made it difficult to consider the differences between 10, 11 and 12. So, I would urge that quality of life studies are going to be critical in trying to balance risks and benefits with this drug.

DR. TEERLINK: So, if you ask a bunch of clinical trialists whether we should do more trials you know we are going to say yes. So, in terms of kind of a development plan I would really focus initially on this hypo-responsive group. I think it is a hypothesis that still needs to be tested. I won't say that it is necessarily been proven that actually hypo-responders do worse so that is an opportunity there. Then I might be tempted to actually weight the results of TREAT to see if 13 is not any better than lower dose, then you won't be needing to study 13 for any reason but presumably that should be a slam-dunk.

DR. PLATT: Dr. Kramer?

DR. KRAMER: First, I feel compelled to say that I am sorry that only Dr. Kaskel has made the point about the need for pediatric studies and I

just want to support everything he said about the need for pediatric studies. I have commented on hypo-responsiveness. I would like to comment on question three. I agree that we should actually conduct trials and I do think that we should do important outcomes like death and MI and include very well designed quality of life so that we get the answers to these questions in these different target ranges we have been talking about, target hemoglobin ranges.

DR. BLACK: Yes, more studies, especially on quality of life which was particularly unsatisfying as we went through this. I think it is clear we may get a lot of answers from TREAT. It is certainly the best design of the ones we have and I hope the DSMB doesn't have a quick trigger finger so we are not again faced with a study stopped too early without the answers we need.

DR. CHEUNG: I think two of the culprits of cycling, which we all recognize is important, number one, is the fear of getting penalized because you are 0.1 point above the target and,

number two, not recognizing that the patient needs to be individualized, not a healthy response to EPO in the last few months and just immediately change the dose, decrease by 25 percent once it hits a certain value. Both of those can be somewhat corrected by education alone.

DR. NELSON: I will just put in a plug again for new insights into pharmacokinetics and dosing formulations, such as either extended use of sub-q EPO, infusion pumps, things like that. It will level out cycling. It will be probably a little bit better, more of a sustained release form of the drug in a way.

DR. KOPP: I also would like to underscore what Rick Kaskel said about studies in children. It may be important to redo the studies that were done in adults that did not succeed comparing 11 and 13 and look at all the parameters we have mentioned, but also school performance, growth, and so forth, that may yield different results in children than they did in adults.

DR. HENNESSY: I will pass.

MS. SCOTT: I don't have a real comment but to say that I agree with Dr. Platt about we need more data on 10, 11 and 12 hemoglobin levels.

DR. NARVA: I think the RCTs to look at hemoglobin goals should include route in hemodialysis patients, sub-q versus IV. I think there clearly need to be algorithms to reduce variability in hemoglobin. I think those kind of algorithms would be very amenable to a computerized system and most dialysis units are going to electronic medical records. That is easily capable of dealing with any algorithm that could be produced. But I think it also should be tied to Dr. Unger's suggestion that there be routine surveillance for hypo-responsiveness perhaps in all patients, and that should be part of the input to a dosing algorithm.

DR. PLATT: I make it five o'clock and 13 seconds. Dr. Rieves, any penultimate words from FDA?

DR. RIEVES: Thank you very much. We knew this was not going to be easy. This is not your

typical topic for an advisory committee so we really appreciate all the effort that has gone into it, all the opinions. They are highly valuable. Thanks again.

DR. PLATT: On behalf of the committee, let me thank all of the speakers and all of the many people who helped to make the speakers sound as intelligent as they were, and I want to thank my colleagues on the committee.

[Whereupon, at 5:00 p.m., the proceedings were adjourned.]

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