Bleeding Disorder Collaborative
April 20, 2016

Woman: Donna asked if I would run the meeting today.

Donna Sullivan: Yes, please.

Woman: Do we need to do introductions so that…

Donna Sullivan: We should do introductions and then I want to… we are recording the meeting for our transcription of our minutes. So I ask that you speak into the microphones and state your name before you speak so that the transcriber can identify who is speaking. Thank you.

Lisa Humphrey: Lisa Humphrey, Health Care Authority.

Dan Lessler: Dan Lessler, Health Care Authority.

Donna Sullivan: Donna Sullivan, Health Care Authority.

Leta Evaskus: Leta Evaskus, Health Care Authority.

Dana Mathews: Dana Mathews from Seattle Children's.

Amanda Blair: Amanda Blair from Seattle Children's.

Sarah Roberge: Sarah Roberge, Blood Works Northwest.

Michael Recht: Michael Recht from Oregon Health & Science University.

Rebecca Kruse-Jarres: Rebecca Kruse-Jarres from Blood Works Northwest.

Mike Birmingham: Mike Birmingham from the Bleeding Disorder Foundation of Washington.

Stephanie Simpson: Stephanie Simpson with the Bleeding Disorder Foundation of Washington.

Woman: That's it? First we want to approve the meeting minutes from last time. Did everybody get a chance there at the back of the folder… did everybody get a chance to review them or did we want to take a couple minutes and then I'll be happy to take motions.

Mike Recht: I move to approve the minutes.

Woman: Second?

Amanda Blair: Second.

Woman: All in favor?

Group: Aye.

Woman: Anybody opposed? There you go. The minutes are approved. All right. Then we wanted to approve the met report and Donna, I think you wanted to talk to that.

Donna Sullivan: Okay. So we have it up on the screen. So this is… we've discussed this on several of our phone calls. This is the first three questions that we had discussed with OHSU at the Center for Evidence-Based Policy about doing a research survey or a literature survey and defining the literature and we have revised it now where they are going to go ahead and identify evidence-based practice guidelines, evaluate those guidelines, and bring back a report. So this is the updated proposal with the changes that we had from the previous meeting. We're moving the brand names from the table and then also making sure that the… I think it was the European practice guidelines were included in the evaluation. So this… really what we need to do today is just formally approve and adopt this project proposal so that we can move forward with that evaluation. So we just need a motion to approve and a vote.

Rebecca Kruse-Jarres: Motion to approve.

Donna Sullivan: Second.

Woman: All in favor?

Group: Aye.

Woman: Anybody opposed? Approved. All right. I think then we can jump to the meat of the meeting and that's the actual research proposal. The goal today is to really finish this as much as possible and be… have a research proposal we're all happy with. Donna wanted us to talk… or to approve it today. I think that's going to be difficult since Judy is not here. She's on vacation. And since she's a major stakeholder or as somebody who is going to be conducting the clinical trial I think we need to give her some time. But I think during the next telephone meeting we can then see whether we can actually approve it. But the goal today is to really go through it step-by-step and make sure we are okay with this proposal and we do the research based on that.

What we have right now is definitely a draft. I worked on it some more. There are definitely some bigger questions that we need to answer and agree on and take it from there. I just filled in a little bit of the background, but basically our hypothesis is that if we're using ideal body weight it's probably going to give us recovery [inaudible] or reasonable. We're… recovery… we're defining that as 66% and that is up for discussion. Is that enough to us? This is a figure that I took from the International Immune Tolerance Study and this is something that has been accepted in the community, but I definitely think we need to discuss that here and maybe that's the first point of discussion.

Man: Can I go back to the primary outcomes?

Woman: Yeah.

Woman: Let me talk about the primary outcomes since… so I changed the primary outcomes a little bit. That was after I talked to our [inaudible] and we have one on board that's been working on this. She's at Blood Works Northwest. And we looked at various ways of potentially looking at the question and then the outcomes, but basically what we want to do is we want to compare how somebody is doing if we dose them –

what their recovery is. Those on ideal body weight versus actual body weight. So… and we really want to do this in people 12 and older. We may also want to do some as a secondary outcome in younger patients. We can talk about that later, but that's really in hemophilia [inaudible] 12 and above. We want to compare the two. But then we also secondary… as a primary outcome want to make sure, what is our chance of, if we're doing… placing somebody on ideal body weight, but we're under dosing them, and what is the chance of, if we dose somebody with actual body weight that we're overdosing them? Because those would be important things for us to know. If we're doing ideal body weight and we see that 50% of cases are then under-dosed that might not be a good dosing strategy. If we see that on actual body weight 50% of people are always over-dosed then that's also a caution and we have to discuss the actual numbers we want to put in there. But that's what the statistics are based one. Does that make sense?

Man: Yep.

Man: I want to talk to you about the decision to use 100 units per kilo.

Woman: I'm sorry. Absolutely. 50. I'll change that.

Susan: Good afternoon. I just wanted to let you know that Susan [inaudible] and Valerie King have joined from the Center for Evidence-Based Policy.

Donna Sullivan: Hi Susan, this is Donna. Thank you for joining us. We've actually moved past the… we've approved the proposal from OHSU. So feel free to stay on the line if you guys want to listen, but I don't think we need you for the rest of the meeting unless you want to stay.

Susan: Okay. Great. Thanks, Donna. Bye, bye. Have a great day.

Donna Sullivan: Bye. Did you guys say to change the BMI greater than 50?

Woman: No. Go ahead and go way up to the primary outcome. Yeah, change that to 50.

Donna Sullivan: 100 to 50?

Woman: Yeah. I had it as 100.

Man: That same mistake is in a couple different places.

Woman: Just making sure that you're paying attention. Is everybody okay with those two outcomes as… and it's recovery only. And it's hemophilia A, all severities, 12 and up, BMI over 25.

Man: And by recovery you mean a 30-minute post level?

Woman: Right. Uh huh.

Man: Okay.

Woman: And then secondary outcomes would be… and we have to discuss that. Do we also… so based on that I talked to Katie who is the [inaudible] and she thought if we get 16 patients in we could probably reach this statistical significance depending on how, you know, what we say is too much over dosing and too much under dosing. She's going to come back with the numbers for us. She's working on that right now. Is it reasonable to think that we can get four overweight patients per institution on that [inaudible] on average? 12 and up? Which probably would mean that, you know, you have both pediatrics and adults. So I know that I should be able to get that [inaudible] or with children together we can get eight. Do you think? Do we think that we can get maybe two or three patients from Children's that are overweight that we think would participate in this?

Man: Over 12, right?

Woman: I would have to take a look at our list and think about which ones of them are big. A couple come to mind.

Woman: And just from the [inaudible] I've spent here I've certainly… [inaudible] think of at least five probably, and obviously not everybody is going to participate.

Woman: Especially if they don't live close.

Woman: We'll talk about that later due to budget and travel and reimbursement [inaudible]. But do you think you could get four or five patients?

Man: I don't think that's going to be a problem at all. The question would be, when we do all of our outreach [inaudible] in some of our lower social-economic areas the incidence of obesity is higher, whether we'll have the ability to draw and process the labs appropriately. If we can do it during outreach it will be no problem.

Woman: So this would just be, again, hemophilia A, 12 and plus. So I'd talk [inaudible] last time. I talked to Maggie [inaudible] during the [inaudible] meeting because they have this similar trial ongoing and they are 18 and up. So we have this opportunity of having younger patients in there. We have the opportunity of also looking at patients less than 12, which I think would be really important. I think we should do that. I think maybe as a secondary objective also have an arm where we do less than 12 or 2 to 11. But I don't think we're going to get enough patients to make, you know, those 16 patients that we need for statistical significance. But I'm thinking while we're doing that it would be nice to also do that as a secondary [inaudible].

Mike: I guess the question would be, if we have limited resources, which we do, do we want to spend those resources on part of the study that we know is not going to give us power… appropriately powered results.

Donna Sullivan: I'm going to interrupt for a minute. Can I get you guys to speak into your microphones?

Mike: This is Mike and the question I raise is if we know that the study isn't powered appropriately to get valid results in those under 12, should we not be recruiting for that age group and concentrate our efforts in the 12 and above, initially, and then have another study that we would look at in the younger people?

Woman: If we have another study, you know, who is going to fund that? When are we ever going to get to do that again? Doing it in a younger population, I don't know how many people we can get together and maybe we need to down scale what we really want to get… do we even see a difference or is there just no… and what do we find as interesting that, you know, those with higher… actual body weight that it, I don't know, 20% more than the ideal body weight? Just to show a proof of principle, because nobody has looked at that in kids.

Man: That's right.

Woman: And that is where we can add to what is happening in the trial world right now. But it is open to suggestions. We don't have to do this.

Amanda Blair: Are you thinking we would need 16?

Woman: To show the same thing, yes, we would, unless we just say, well, maybe we just want to show a difference in… if we show the, you know, like… I said what is the percentage of under dosing and overdosing that we're doing with the bigger adult trial? Is it enough for the kids to just show while we do see a significant difference or not in the different dosing and I can ask our biostatistician what we would need for that; what number. I just don't think we're going to get 16 patients together that are less than 12.

Woman: That would be my…

Woman: Yeah, and it's hard to do those studies in kids because of the blood draws.

Woman: I still don't totally grasp the timeline. Part of me wants to say, well, we could do an interim analysis in the adults and see what we are getting. See what the ballpark is and if it looks like ideal body weight dosing is looking like a major win, and depending on the timeline, and the budget and how much this is all costing, whether or not it might be worth making a greater effort to get kids in the second half of the timeline. I mean I'm all about kids, obviously, but if we have limited

resources I would hate to put our… the over 12 study that is the primary endpoint at risk.

Woman: What we can also do is just look at the budget, now that we know that we need the 16 patients. For the adult study we can say, well, if we… I have this later on my agenda in my head, is that we need to think about, you know, what is in the budget and see how much do we have leftover and what not? And do we have the money to actually look at the kids, as well? Should we just table it until then? Okay.

The same question is with hemophilia B. Again, much harder to get to numbers. There are not as many patients. We're not going to get 16 patients. Do we want to drop hemophilia B completely and let that be a different study? Do we want to include them and not pay attention between A and B? Just throwing it out there.

Mike: I think not paying attention to A or B is going to muddy things significantly.

Woman: I agree.

Mike: And not that the biology is that different, but the products are very different. The expected recovery [inaudible]. Factor 9 products are very different than the expected recovery [inaudible].

Woman: Right. And I would say that maybe the recovery is not… since they are not being dosed as often the recovery becomes less important than the half-life and we're really looking at recovery. So should we just stick with hemophilia A for this? And if this is a positive study, which I hope, then propose that we're going to do this for hemophilia B.

Mike: I think the cleanest way to do this would be to have as tight of inclusion criteria as possible. So severe A…

Woman: I was not going to make it just severe. I am not sure, even though… I mean I definitely think we need to look at it whether somebody had moderate or a mild, but I would include anybody in that.

Mike: So A is over 12 years old.

Woman: Uh huh. And then not even… so I'll scratch all the hemophilia B out of it.

Mike: Amanda and Dana, what do you think about not having kids initially… under 12 kids initially?

Woman: I think that's going to be the best way for us to be successful and [inaudible] patients in the short time span we have to accomplish this. I think if, you know, like you said, if it is a positive outcome in the very small group then it would hopefully allow [inaudible] to look specifically at children and [inaudible].

Woman: I think that the children… we can still see whether potentially, depending on the budget we have, whether we can pull them in here or not. But I think for B I personally would say let's not make this about B at all.

Donna Sullivan: I just want to remind you guys to stake your names before you talk. I know it's awkward, but you'll get used to it. Thanks.

Rebecca Kruse-Jarres: What I just said.

Woman: Then I think we should just take out the… all the hemophilia B parts of this.

Woman: So, Donna, just limit it to patients 12 and over in this current draft that's up there.

Donna Sullivan: Is that what you guys just were talking about?

Woman: Leave it. Well, for now you can do that. Let's see what budget we have and whether the budget would allow us to, as a secondary goal, also look at patients less than 12 years of age. Because I think that's a really important question, one that is not being answered anywhere that I know of. I mean we're going to add anyway to the study that's being done in Pittsburg right now because we do have patients less than 18

years of age. Their study is not huge and they do not have long-acting products in their…

Donna Sullivan: I just made a comment so that we'll… I'm trying to track the questions that we're thinking that we're either going to make changes or answer those questions at a later date.

Woman: I'm making some… I really apologize. I forgot my computer, but maybe it's a good thing, but I'm scribbling down some thoughts here too that we can then combine.

Donna Sullivan: Okay. Thank you.

Rebecca Kruse-Jarres: Something that as a secondary outcome then I would look at different severities, but I would not stratify it to begin with because, again, we're not going to come up with a useful end. Do you agree Amanda and Dana?

Amanda Blair: I agree.

Rebecca Kruse-Jarres: Dana?

Dana Mathews: Yeah.

Woman: So that stays in. Severity. So then as a secondary I would then also look at the half life because that's not going to be a primary goal, but obviously we're doing… we're not just doing a recovery. We decided we're going to do half-life studies, too. Right? Correct?

Mike: Yeah.

Rebecca Kruse-Jarres: Then we're also going to not from the get-go stratify normal half-life versus extended half-life products, but we're going to do it on the product that the person is on regardless of what that is. All agree?

Mike: Yeah.

Rebecca Kruse-Jarres: And then we were not going to stratify by overweight versus obesity. But go ahead and look at that after the fact, as well. Again, for reasons of [inaudible].

Donna Sullivan: Rebecca, can you point out… where are… are we looking… am I at the right spot?

Rebecca Kruse-Jarres: We're in the secondary outcome. Yeah. That was the last… sorry, I should probably sit next to you. Yeah. They are all good. So we are basically keeping all of those in. But if you're going, I think to the second point, to compare something in hemophilia B and hemophilia B, so point 2 and 3 you can take out. Yep. There you go.

Dana Mathews: And move it to 50 units per kilo on the top line.

Rebecca Kruse-Jarres: Thank you. We're good with the primary and secondary outcomes then?

Mike: Yes.

Rebecca Kruse-Jarres: So the inclusion criteria have…

Man: This is a non-hematologist speaking. And this is just definitional. Under primary outcomes, just to help, to compare the response, can…

Rebecca Kruse-Jarres: Recovery.

Man: That is recovery and it is this 30-minute post level. Is that what we're talking about in terms of recovery? I think I heard Mike say [inaudible]. So I'm just… I'm wondering if you just want to actually specify it to that level rather than [inaudible].

Rebecca Kruse-Jarres: And I think we should do that in the study methods because otherwise the sentence becomes really, really long. So what we can do in here is to compare the recovery, maybe in brackets. I would keep response to 100 dah, dah, dah, in brackets, recovery. Or response… you know what I mean? I mean it's not a recovery to.

Mike: Our primary outcome is going to be between the recovery…

Rebecca Kruse-Jarres: Right.

Mike: So that's what I would say.

Rebecca Kruse-Jarres: Okay.

Woman: You could say recovery parenthesis yield or something in parenthesis almost in terms of…

Rebecca Kruse-Jarres: I think we all know what recovery is. We'll define recovery under methods and say exactly [inaudible] needs to happen.

Man: I know you guys all need, but I think, you know, to the extent that others actually care public and so forth and may not know that it's a… and so it sounds like it will be defined… there will be some sort of glossary or, you know, it's defining terms.

Rebecca Kruse-Jarres: So that's why I had response in there at first because I figured that is what the public will understand. They might not know what a recovery is.

Man: Not to belabor it, but I think the public might think response is you're actually going to measure whether or not there is more bleeding occurrences and that's not what you're… you're measuring a biologic outcome here.

Rebecca Kruse-Jarres: Yep. So recovery is good with me and we'll define it in the methods section.

Are we good with primary and secondary outcomes? We can let them live? We're forever happy with them?

Woman: Uh huh.

Rebecca Kruse-Jarres: Good. Let's talk about the… go over the inclusion/exclusion criteria. So we're going to take in the inclusion we're going to have to decide in the

end whether that's going to… the age rage is going to change. We're going to take out hemophilia B. We are… it's going to be males only even though we could potentially have female patients, but I don't know that we have any that's going to… be messy. And then either overweight or obese. Any other additional inclusion criteria?

Mike: Just to talk about the language in the document up to now. So there are some parts where it says less than 12 years of age. Others that say above age 11, and then in the inclusion it says 12 and over. So if we can just keep consistent with that [inaudible].

Rebecca Kruse-Jarres: Let's go with the 12 whatever. I noticed that as I was reading it, right before we came over.

Mike: I think it should be 12 and over.

Rebecca Kruse-Jarres: Yep, I agree with you.

Mike: Above age 11 could be 11 in one day.

Rebecca Kruse-Jarres: Yep. Got it. Donna, can we go through. Yeah, I'll comb through the document again, too, and make sure that that's all consistent. I agree. Any other inclusion criteria we need?

Mike Birmingham: If you're only including people who are overweight do you have a control group for that?

Rebecca Kruse-Jarres: They are their own control. Right? So in these patients we are first giving them a dose based on their actual body weight and then we give them a little bit of washout and then we give them a dose based on the ideal bodyweight or the other way around. So everybody is really their own control. Does that make sense?

Mike Birmingham: Yeah. I'm just wondering if it would be different [inaudible] a real control group where they are not overweight.

Mike Recht: I think that's a good question, but that's not actually the question we're asking. We're not asking does the recovery in someone who's

overweight equal the recovery of someone who is not overweight. We're asking the question does the recovery in someone who's overweight… is the recovery in someone who's overweight different if you base on actual weight versus ideal weight.

Rebecca Kruse-Jarres: I couldn't do the study in somebody who is normal body weight because it would be the same.

Mike Birmingham: Thank you.

Rebecca Kruse-Jarres: Does that make sense? It's a really good question.

Mike Birmingham: Yep.

Donna Sullivan: And so just to make this more… I think specific, I changed the BMI for overweight to be 25 to 29 and then obese to be greater than or equal to 30.

Mike Recht: You're missing 29 to 30 then.

Donna Sullivan: Greater than or equal to 30?

Rebecca Kruse-Jarres: I have the official from the CDC guideline. I have the actual numbers how they stated it.

Mike Recht: It's 29.9.

Woman: There's 30.1.

Rebecca Kruse-Jarres: I'll bring them to you.

Woman: Just leave it the way it was.

Donna Sullivan: Okay. Sure. It just makes it look like you are overlapping, potentially.

Woman: No, you're not because it says greater than or equal to 30. Or less than 30.

Donna Sullivan: Got it.

Rebecca Kruse-Jarres: So exclusion criteria I don't think we want to include anybody with an inhibitor. If they have another bleeding disorder, if they are… have another prolonged APTT reason such as lupus anticoagulant, if they are female. I think we need to exclude people that had a recent bleed and I… is it one day? Is it one week? We need to decide on that. I think one day might not be enough, but I definitely think you have a different… if you had an acute bleed within those… maybe a week I think you're going to consume your factor differently and then you're not going to get adequate PK studies.

Mike Recht: Do you want to exclude them or just…

Rebecca Kruse-Jarres: From the day you do the PK there has to be at least… they couldn't have had a bleed the week before, but then they can do it a week later.

Woman: I think that's a good question. You put someone on the study and they are going to be getting two infusions. So you'd… this language doesn't make sense to me. You might say a patient who has had an acute bleed within the one-week prior to planned PK testing will have it postponed or something.

Rebecca Kruse-Jarres: We can also leave… I just wanted to put that somewhere that… because I think it's really important that we don't do a PK study in somebody with an acute bleed. So what we can do… because at the study entry it's not going to… maybe we need to put it in the methodology. So why don't we take it out here and move it down somewhere in the methodology for right now so we don't lose it. And then see how the wording needs to be.

Mike Recht: Do we want to consider something about people who have had a poor… a documented poor recovery in the past for unknown reasons? Or do we want to include people who clinically act like they have an inhibitor, but we can't measure an inhibitor, you know, they are really very soft.

Rebecca Kruse-Jarres: Right.

Mike Recht: I guess the documented poor recovery in the past when it…

Rebecca Kruse-Jarres: And how do you define that?

Mike Recht: Under 66…

Rebecca Kruse-Jarres: And I would put that under exclusion… I would put it actually inhibitor of over .6 and then [inaudible] twice in the past, or abnormal recovery.

Donna Sullivan: You lost me at the number.

Rebecca Kruse-Jarres: If you go exclusion criteria. The very first one already says inhibitor… no, I'm sorry. At the passed go to the very end of it. Yep, comma or abnormal or documented abnormal recovery of less than 66% in the past. Sounds good? And I thought of one more that we probably do not want to include underweight patients. We wouldn't do that anyway. Never mind.

Mike Recht: That could be an exclusion criteria – normal or underweight. BMI less than 25.

Rebecca Kruse-Jarres: It's already in the inclusion so we don't need to mention it in the exclusion, obviously. Okay. Any other exclusions you can think of? So recruitment is going to be through the participating centers and we can… did I not have them listed somewhere? Maybe not.

Donna Sullivan: Do we know the centers? We could type them in now.

Woman: They are in the trials design on the first page.

Rebecca Kruse-Jarres: I thought they were somewhere. Yeah, there you go.

Okay. Study design. So for the primary outcome we already defined the population. Patient will be randomized and we have to decide on how we want to randomize. Is it just every center… per center the first one goes into this, the next goes into that? Or do we centrally randomize or how do we want to go about that?

Mike Recht: Did you talk to your statistician about the best way?

Rebecca Kruse-Jarres: No. I have not, but I can do that.

Mike Recht: I think that would be… like we can have a central randomization program.

Rebecca Kruse-Jarres: We can do that or we can say every site the first one that goes in does the ideal body weight first, the second one per center that goes in does the…

Donna Sullivan: It's not random.

Woman: You could have… there's ways of generating card sets for each center that are random A or B or whatever. I mean 1 or 2 and whatever.

Mike Recht: Exactly.

Woman: I think that might be the… I think a central randomization will be painful because you have to have someone you can contact right that moment whereas if you have a card deck or something, I don't know, there's various ways.

Rebecca Kruse-Jarres: If you have a card deck then you just pull it up?

Woman: You get assigned a card deck and it's random. There's a bunch of cards that are randomly, you know, X or Y or 1 or 2, whichever, and then you just take the next one out for a patient and that's what you do. You might get three in a row that do ideal body weight or whatever, but then it's completely random, but yet we don't have to call and get a new random… just something like that maybe.

Mike Recht: It should have some kind of central tracking at least to make sure that we're not skewing one direction.

Amanda Blair: If you have one person who makes the card deck… like you just make your whole card deck [inaudible] to each center and then each center has…

Rebecca Kruse-Jarres: How do I know how you're keeping, I mean, I don't know. I've never done this better. How do I…

Woman: Random is supposedly random and, you know, I mean if you flip a coin 16 times you might get 5 heads and 11 tails, if I can do my math. And that could happen to us, as well. So I don't know if it really makes sense to be tracking and make sure that we're having good randomness. I mean, again, I agree with talking to your statistician.

Mike Recht: If the statistician [inaudible] results before, I mean after…

Rebecca Kruse-Jarres: I think she has experience with [inaudible].

Mike Recht: She'll know how to do a multi-center random small study size…

Rebecca Kruse-Jarres: I'm looking at Sarah.

Woman: She's kind of new. I don't know.

Donna Sullivan: Again, I haven't read through this, but is the idea that we're going to give them one infusion based on ideal body weight and a second infusion based on actual body weight? So my question is, does it matter if it's randomized or not if they are all going to receive two infusions?

Rebecca Kruse-Jarres: It's not huge. It's just in the name.

Mike Recht: It's just better.

Donna Sullivan: Okay. That's fine. I was just…

Mike Birmingham: [inaudible] one before the other that might affect…

Rebecca Kruse-Jarres: That's where I say every center… but then you're right it's not randomized, but every center the first one that comes in does it this way and the next one you do it the other way around. The next one goes back to the… it's not randomized, but it assures that we're going to get enough or the same amount of people who do it one way versus the other. That would be the other way of doing it. But then I guess we can't call it randomized. Or we can randomize it.

Mike Recht: I think you should talk to your stats. I'll talk to the stats person that I work with and we'll see… I guarantee you they have some… they'll know easy the system.

Donna Sullivan: Because you're not blinding it. Right? So, again, then you'll know that you used ideal body weight one time and actual body weight the next time. So if you're trying to get rid of bias and, again, speak to the statisticians, I guess I'm trying to figure out how that's preventing bias by randomizing which one you do first.

Rebecca Kruse-Jarres: I think it's not the randomization. I think that's what we are talking about here. It doesn't need to be randomized or not. I do, however, agree that we should mix it up. And if we just say in every center one does A, B. The next one goes B, A. The next one goes A, B. Then I think we're going to exclude that bias.

Mike Birmingham: It sounds to me like you want to assure that it's 50% rather than randomized. 50% go one way, 50% go the other way.

Rebecca Kruse-Jarres: Yeah. That would be fine with me. Yeah. So should we just… I mean we can do it that way. I'll ask you… I'll ask too, but I think… you're right, it doesn't need to be randomized. All right.

And here randomized to receive… where are we? Oh yeah, can you change that to 50 units again?

Donna Sullivan: So you want to make it… so when it's factor 8 they get 50, but if it's factor 9 they get 100?

Rebecca Kruse-Jarres: We don't do factor 9 in these.

Donna Sullivan: Got it.

Rebecca Kruse-Jarres: Then we need to decide on what wash out period we want between the two meaning the time between doing the first PK and the second PK. I put two weeks in here, but I brought this up for discussion.

Mike Recht: Two weeks before… between the two PKs or it's two weeks between doses?

Rebecca Kruse-Jarres: That's what we need to decide. We need to define it somehow. I don't care how we do it, but we need to assure… so I said after the period and I was thinking about the actual dose given that it's at least two weeks between that does, but no more than two months.

Mike Birmingham: How are we accounting for those people who are on prophylaxis and get it every other day anyway? Are we asking them not to treat?

Rebecca Kruse-Jarres: Right. We need a wash out period before. So if somebody would… would have to skip a dose of prophylaxis. So that's one thing for both the extended half-life. So wash out prior…

Mike Birmingham: So it's not just a matter of them not having to [inaudible] before we start doing this. They also [inaudible] treated before we do this.

Rebecca Kruse-Jarres: Right. And we need to decide on how long of a period… now we're just… it's just for hemophilia A.

Mike Birmingham: That means that you either are talking to people who are treating on-demand only or you are asking them to not treat their regular prophylaxis?

Mike Recht: Not necessarily. For example, for people who are on a standard half-life… if you have a wash out of 72 hours you should be under 1% and that is a Friday until Monday time period. So you don't miss a dose [inaudible] care on a three-day-a-week prophylactic schedule, but you're refusing Monday, Wednesday, Friday if you go from Friday until Monday you're not skipping any prophy dose.

Rebecca Kruse-Jarres: And I would argue…

Mike Recht: And I agree with you. You don't want to interrupt standard of care.

Rebecca Kruse-Jarres: No, we don't.

Mike Recht: For a clinical trial.

Rebecca Kruse-Jarres: But, does it really matter if we still have a little bit of residual factor? It doesn't, because it's just a recovery. So I think to say… I would propose that for regular factor that it has to be at least 48 hours.

Mike Recht: I agree.

Rebecca Kruse-Jarres: That's even on somebody who is taking prophylaxis every other day. We would not interrupt it. So they would just come in for their next prophylactic dose.

Mike Recht: Right.

Dana Mathews: I would agree. I mean if you think about it we want real data. We want to know what happened for someone on prophy who has a surgical procedure on a Tuesday. And that person would probably get prophy on Sunday morning and get their corrective dose on Tuesday morning before their procedure. So I would agree. I mean if we're looking at the difference between a 2-1/2% drop versus a .5% drop that's not a…

Rebecca Kruse-Jarres: Even if they are at 5% I don't care because it's a recovery. Or no factor for at least 48 prior.

Man: Yes, yes.

Rebecca Kruse-Jarres: Then what about the extended? Four days?

Mike Recht: [inaudible] between their regular prophy dosing. So if someone is on every three-day…

Mike Birmingham: Some of us are on every four-day, but we do twice a week instead.

Mike Recht: Exactly.

Rebecca Kruse-Jarres: Right. So then we would just get around the four. Right. So then I would try and go for the four-day.

Donna Sullivan: I just want to clarify because it's not quite clear what we're… at least for me, not knowing the lingo. So you're saying you'll get a dose of 50 units per kilogram a factor and you will have a pharmacokinetic test drawn after that. Then it says after a period of at least two weeks, but no more than two months, and the period I know we're talking about, so are we really saying after a period of a certain amount of time goes by you will then receive a second dose of 50 units per kilogram and a second PK test will be performed? Because that's not stated here.

Rebecca Kruse-Jarres: Right. No, it's not. So while one thing that we're discussing right now is what is the time period from their last factor dose… there are two things here. So one thing what is the timeframe from their last factor dose when we can actually do the PK? And the other question we have to ask is, how long is the time period between doing the first PK and the second PK? What's the minimum time and what's the maximum time? Because we don't want the second PK study to be done a year later.

Back to the first question, which is… so for the normal half-life we grade on 48 hours. For the extended half-life…

Man: 96?

Rebecca Kruse-Jarres: Yeah, I think that's…

Amanda Blair: Wouldn't you include like maybe 72 to 96 hours for the people who do every three days? I mean if you're going to include children…

Rebecca Kruse-Jarres: Do you have anybody on every three days?

Amanda Blair: The younger kids might. Yeah.

Rebecca Kruse-Jarres: I'm good with that. Again, it's a recovery so…

Woman: You're not going to be very high at 72 hours for most of these given [inaudible]. So I think in… you're looking at recovery.

Man: [inaudible] 18.

Woman: It's shorter for sure.

Man: Correct me if I'm wrong, but the important thing here is to make sure that it is consistent between the two doses. So if you get it three days before one dose you want to get it exactly three days before the other dose so you can see exactly how it behaves. Right?

Rebecca Kruse-Jarres: I don't know that that's as important because it's the recovery. It's how far do you go? And that shouldn't really matter how much you have in your… so if you have 5% left in your blood and you go up by 100% you should go to 105 and then the next time let's say you start out with nothing then you just go to 100. So I'm looking at the incremental rise.

Man: [inaudible] the way the body reabsorbs the factor, though, affected by how much factor is in the body.

Rebecca Kruse-Jarres: I don't think it is.

Man: Okay.

Man: That's a really good question. I don't know any data that would support that.

Rebecca Kruse-Jarres: I don't know any data that supports it nor does it make biologic sense that it would to me. But it's an important question to ask.

Dana Mathews: It's also the case that I think that I we sometimes get a bit of an illusion about the precision of our [inaudible] and there probably is such a difference between the 5 and 2% trough, but I'm not convinced there is a difference between 105 and 100%. I think, you know, we're looking for big differences, not subtle differences, especially if we think we may

make an impact on costs. So I think we want to make this… we don't want to set this design in such a way that it puts a lot of barriers in patients' participation. So I think… I totally understand why you're asking. I think it's a great question. But I think if it was… and ideally I think it would be great to have it be the same, you know, four days after their prophy dose for each of the two rounds of PK, but I think the only thing that worked for the family was to do it three days on one and four days on the other. I still we could get information.

Rebecca Kruse-Jarres: I can say 72 to 90… at least 72 to 96 hours, preferred 96. Or should I not even say that?

Man: So if we're going to put a range we shouldn't put a [inaudible]. We should just say [inaudible].

Rebecca Kruse-Jarres: Okay. 72 it is.

Donna Sullivan: Is it 72?

Rebecca Kruse-Jarres: 72.

Donna Sullivan: Okay.

Rebecca Kruse-Jarres: So the next question then is how close can the second PK or should we even say? And what is the longest… so what I have right now, and that's randomly chosen, was that there has to be at least a two-week period in between and maybe there really doesn't have to be one at all. But I would say no longer than two months, because of body change and weight and habit changes.

Mike Recht: For a couple of reasons. We want to make sure we do this as efficiently as possible. So I think two months makes a lot of sense in terms of the maximum period. I have no problem having the two PKs done a week apart.

Rebecca Kruse-Jarres: Okay.

Mike Recht As long as we satisfy that at least 48 or 72 hours between… before the dose.

Rebecca Kruse-Jarres: So we can say no more than two months after they will have to repeat PK testing.

Mike Recht: Right.

Donna Sullivan: So I'm going to be technical and picky. Do you want to say two months or 60 days or…?

Woman: You work for the state.

Donna Sullivan: I do work for the state, but I'm just trying to be very, you know, I write a lot of documents and I'm just trying to be technical on… because not every month has 30 days.

Rebecca Kruse-Jarres: Sixty days it is.

Dana Mathews: So one week is enough for a long-acting? I realize many of them have shorter half-life, but if give, you know, 100% correction dose, or even more possibly, if it's on actual body weight, are we really okay with a long-acting factor starting one week later?

Man: Let's say in the best of all worlds the half-life is 24 hours, which it's not. So we would be fine by seven days.

Rebecca Kruse-Jarres: Would you put then at least a week before we do it? So then that… I'm sorry.

Man: Remember, we're saying it just has to be 72 hours from before your previous dose. So…

Man: What is the purpose of making it different from the previous dose?

Rebecca Kruse-Jarres: There is something getting confused in there right now.

Donna Sullivan: I'm lost on what does the 72 to 96 hours or that 48 hours…

Rebecca Kruse-Jarres: So after a period of at least 40…

Donna Sullivan: What happens after 48 hours or 72 hours?

Rebecca Kruse-Jarres: [inaudible] totally randomized to receive… they will get their…

Donna Sullivan: Are you trying to say that you will draw the PK test 48 hours after the dose?

Rebecca Kruse-Jarres: No, no. So this means that they will get their PK testing. The dose and the PK testing there has to be at least 48 hours for standard half-life or 72 hours extended half-life before that can be done, of their regular factor use.

Donna Sullivan: Before what can be…

Rebecca Kruse-Jarres: Before they can get their…

Donna Sullivan: Second dose?

Rebecca Kruse-Jarres: No, even the first one.

Woman: For each PK dose they have to be at least 48 hours for standard half-life and at least 72-hours for extended half-life products from their last dose. So you put that whole description there you actually described that as being for their second PK dose, but that's not what we meant.

Donna Sullivan: Okay. So the first test must happen 48 hours for standard half-life products and at least 72 for… I'm sorry, for extended half-life products before their previous dose. So the first testing… okay.

Rebecca Kruse-Jarres: I would do a highlighted section, timing of dosing for PK testing, colon. Exactly. You got it.

Donna Sullivan: Is that what you're trying to say?

Rebecca Kruse-Jarres: Last dose is fine. It doesn't need to be PK testing. Then do the next… is timing between PK 1 and PK 2.

Man: Yes, perfect.

Rebecca Kruse-Jarres: So you have the timing of dosing…

Donna Sullivan: So are you saying that… so for the first dose you're going to wait at least 48 hours for standard half-life, at least 72 hours for extended half-life and then they can have a dose, a factor, and they will get a PK test. Does that not stand true then if, for the second dose, could be that same time period could go by for testing or do you want a longer period in between?

Rebecca Kruse-Jarres: But it could be for… but we need in the second dose the timing between those two doses cannot be longer than two months. That's what we're trying to get at.

Donna Sullivan: That's what this says. So it says after a period of at least 48 hours for standard half-life products and at least 72 hours for extended half-life products, but no more than 60 days the patient will receive a second dose of factor at 50 units per kilogram based on the alternate dosing strategy and will have a second PK test.

Rebecca Kruse-Jarres: I think that works.

Man: So they don't have to wait a week or two.

Rebecca Kruse-Jarres: No.

Dana Mathews: I wonder if we want to flip those a tiny bit. To me it seems confusing. We've been sitting here discussing it, but to me I would have, as you say, the section that says timing of PK dosing and just for each PK dose have the 40 or 72 hours. And then timing between PK studies and then have that. I think having it the way it is now is a little confusing.

Rebecca Kruse-Jarres: I think it is [inaudible] things and I know exactly what you mean and once I have… it's kind of difficult because Donna is not usually… so what

I will do is when we are done with this, in the next day or so, I will just go through it and make it so it is more readable and make sure that we really captured what we're saying here and then send out that version to everybody and make sure it's clearer so we're not spending our time here on semantics. Does that sound fair? Okay. All right. Do we need to put in the exclusion criteria that people cannot be on a diet? I know it's silly, but…

Man: In case they lose weight in between?

Woman: Are you concerned that within 60 days they are going to become no longer overweight or obese?

Rebecca Kruse-Jarres: What if they are on a crash diet and they really changed from overweight… I don't know, some people lose crazy amounts of… I'm just throwing it out there.

Woman: You're so optimistic.

Rebecca Kruse-Jarres: There are crazy people out there.

Woman: So I think if you were to say cannot be on a diet you will exclude a whole lot of pure potentials.

Rebecca Kruse-Jarres: Okay. I brought it up here…

Woman: Maybe you could argue something like… it pushes you to want to keep the two PK doses pretty closely together. As you can only change your body mass so much in two months, you know, maybe you could say if there is… by the second dose they have dropped below our criteria they… I don't know.

Rebecca Kruse-Jarres: What you could do… right. I mean if they have lost a certain percent of their body mass by the second PK…

Donna Sullivan: Is it more likely that they would actually gain weight? You have it both ways. Whether they lose weight… their weight changes.

Woman: How about if there is a greater than 10% change in body weight between the first and the second PK…

Man: Or BMI.

Woman: BMI, right. That would be really hard, but it just shows that we're thinking about it in both directions. We would still probably analyze. We would have the information even though they wouldn't be able to… I mean if that person, just saying, if that person got the ideal body weight first and they had a 100% yield that would be information.

Man: Right.

Donna Sullivan: If you just do an intention to treat then you just keep them in the ideal… the obese or overweight and not worry about it. You can note it for, you know, evaluation and comments in it, but maybe just say that they won't be excluded, that you'll still do it, but you can discuss it because you intended them to be in one weight class and they changed to another.

Rebecca Kruse-Jarres: All right.

Donna Sullivan: You guys can keep going. I'm just trying to capture the…

Rebecca Kruse-Jarres: That's really, really important. So then after that there's just a little graph here and obviously… yeah, so we're going to see… a total of 16 patients and that's what…

Man: Are we going to stop after 16 or if we have…

Rebecca Kruse-Jarres: Yeah, I mean if we have more I think we should have more… yeah.

Man: If we have the funds can we keep going?

Rebecca Kruse-Jarres: I would rather have more patients in it. I just figure this is the minimum we can come up with and that's why I decided that's why we're going do the…

Mike Recht: Maybe on the graphic we could say minimum of eight patients on both of those.

Woman: Is that eight patients over 12?

Man: Over 12.

Rebecca Kruse-Jarres: Total between all of us. But… 16. Right? It's 8 and 8.

Woman: So you're not going to have a certain amount of patients you need from each site then?

Rebecca Kruse-Jarres: No, we don't. No. This was just to kind of see can we even come up with 16 patients between… because Judy is also… I don't she's going to have four patients. So that means that we're going to have more patients. Because pediatrics is only 12 to 18 so the pediatric sites are going to have a harder time getting those patients. We're going to have more adults or more 18…

Man: [inaudible] Spokane.

Rebecca Kruse-Jarres: You can scratch that secondary outcome because we're going to have to just remove it for now. Then I think somewhere in there we need to do a definition and not have that in the document. So you don't have to worry about that because I can put that in… the one that I forgot at my desktop at home. The definition of body mass index, I think we should put that in there. And I just took it from the NHLBI website. The body mass index calculation being calculated by kilogram per meter squared. And I think that should be true for everybody. And that's from the NHLBI and CDC websites. And for body mass calculations, also… so they are different in people 20 and over and less than 20 years old. If you look at the CDC website. They give you this calculation for BMI calculation in 20 years and old, which is kilograms per meter squared, but for children or less than 20 years old it is different and they differentiate that between girls and boys. I cannot, for the life of myself, find the calculations.

Man: It's just the same calculation, but it's just percentile.

Rebecca Kruse-Jarres: Right. And then they… do they… okay. So the question is, should we… because there are really nice calculators on the CDC website. Should we actually write in the protocol that we can use those to calculate the BMI?

Man: Or that we have to use those. So we're all doing it exactly the same.

Rebecca Kruse-Jarres: Right. So I have those websites, Donna, in my… I'll put them in. But they are the actual CDC website calculations and if we all agree that that's what we are going to use, I think that would be a good thing. And then we need to define the ideal body weight calculation.

Man: And that's tricky.

Rebecca Kruse-Jarres: That's really tricky in kids and I pulled an article from 2007.

Donna Sullivan: Maybe I lost something. What are we using for the CDC website? Was that not the calc…

Rebecca Kruse-Jarres: For the BMI. There are two different things here. One of them is the BMI because we need to identify what, you know, can our patients actually enroll in the study? Are they overweight? Do they go into the overweight versus obese bracket?

Dana Mathews: Those BMI criteria don't work in young kids.

Rebecca Kruse-Jarres: That's what I'm saying. So we need to use two different calculators in… and their cutoff is 20 years, actually. So they have the regular BMI calculator for 20 and up and less than 20 they have it calculated or adjusted by percentile and girls and boys are different. That's what I'm saying. I cannot find the actual for how they are coming up with, maybe Mike you know more about it…

Mike Recht: The definition of overweight is 85th and 95th percentile based on age. And the definition of obese is greater than 95th percentile. You can get that from the CDC calculators.

Rebecca Kruse-Jarres: Right. The calculators just makes it easy and, you know, maybe I should not, but it's the CDC so I trusted it. And you just put in the weight, the height, whether they are male or female and it just puts all that…

Man: And their age.

Rebecca Kruse-Jarres: So you actually have to put their birthdate in it because it calculates the age.

Man: Right.

Dana Mathews: So then when we're defining overweight and obesity up front, at the beginning, since we're including over 12 we're going to have to define it throughout.

Man: Participants age 12 to 20 the definition of overweight and the definition of obese is the CDC definition.

Rebecca Kruse-Jarres: So what you're saying is that it needs to go in the inclusion/exclusion criteria. Right? Is that what I'm hearing?

Man: Uh huh.

Rebecca Kruse-Jarres: Because here we have it as BMI 25 to less than… so I'm…

Man: Or 85th to 95th percentile for those less than 20.

Woman: We could just say overweight or obese defined by the following criteria – age 20 or over BMI, but age under 20 percentiles defined by…

Rebecca Kruse-Jarres: Or we just leave it as overweight and underweight and then in the study section actually have a section where we define it.

Man: Either way.

Rebecca Kruse-Jarres: We can put it in both and then it's clearer.

Woman: I think there's some advantage to both. You don't necessarily have to have the calculations in both, but I think just kind of the concept of percentiles for under 20 and BMI for over 20 up there and then having the more precise calculations and links down in…

Rebecca Kruse-Jarres: Okay.

Amanda Blair: Can I ask a question? Is there going to be any effort in trying to make sure that the patient's we're looking at are evenly distributed between overweight and obese as far as categories if we're going to compare?

Rebecca Kruse-Jarres: We talked about that before. It's going to be very difficult to do and, you know, I would love to do that. I would have loved to tease it out completely and say we only have so many overweight and so many obese, but we're kind of limited by how many… what our numbers are. So some of this is just real life and then look at it after the fact.

Woman: I'm sorry. This may all be in the details, but that's a… just to calculate for a BMI for a child and percentile of a child's BMI not of just their weight?

Man: That's correct.

Woman: Okay. As long as we're not capturing tall people who weigh a lot because they are tall.

Man: That's correct.

Woman: Good. It will be easier when I actually see it.

Man: Said by a tall person.

Rebecca Kruse-Jarres: You can actually look it up on the CDC website if you go BMI calculations [inaudible]. Like I said there's no formula attached, but you have to input their height, their weight, their age.

Man: They actually have two different calculators – one for adults and one for children.

Donna Sullivan: Do you want to look at it?

Man: That's the child one and you can see what they require to put in.

Rebecca Kruse-Jarres: So birthday, date of measurement, and that's just for them to calculate the actual and then the sex is in there. Got it. Can you go down some? Then their height, weight, and then that calculates your BMI.

Man: The cutoff line between obese and overweight is 30?

Woman: Yeah. But for children it's percentiles. Right?

Man: Yes.

Rebecca Kruse-Jarres: We should put a test patient in there and see what it comes out with. Can we do that real quick?

Donna Sullivan: How about 12 years old.

Rebecca Kruse-Jarres: No, let's make her 6 years old. I don't care. 12… whatever. I don't care. Yeah.

Donna Sullivan: How tall is she?

Rebecca Kruse-Jarres: And then how much does she weigh? 42 pounds? That's not overweight. I was going to do somebody overweight to see how that comes out.

Woman: There's a graph on the website as well. It's a nice age-related graph and what percentiles are as you look. I just found it.

Donna Sullivan: I put in 100 to say they are really overweight.

Rebecca Kruse-Jarres: What did it spit out?

Donna Sullivan: It didn't like that. Apparently you're not allowed to weigh 100 pounds when you're 6 years old.

Woman: That's excellent. This child is obese. Excellent.

Rebecca Kruse-Jarres: It's giving us everything we need to know. I think if we stick with that calculator and all decide that that's what we are going to use. That's going to give us the definition.

Man: And we're going to base the calculation on the day of the first PK and are we going to re-measure on the second PK?

Rebecca Kruse-Jarres: I think for the study inclusion criteria it's the first, at enrollment. And then… and that should be… I guess the day of the first PK. And I think we need to make sure that we get that information again with the second PK to make sure it hasn't changed much, but that's not the category they are going to go into. Right?

Man: So the category is based on [inaudible] bottom line?

Rebecca Kruse-Jarres: Yep.

Man: [inaudible] line and then they [inaudible].

Rebecca Kruse-Jarres: Then they have to stay the same weight. We are not going to differentiate in this study for the primary objective whether they are overweight or obese. I would love to do that in somebody… in a study, but we don't have enough patients to really put that many in this category and that that many in that category. So I think we're just going to lump them together and then after we get all the data we're going to see what…

Man: I could do it twice and just eat a bunch between [inaudible].

Woman: You're signed up.

Donna Sullivan: Are we going to use the CDC website not only to calculate the BMI, but also use their defin… to clarify them as overweight or…

Rebecca Kruse-Jarres: That's the definition… they have the same definition that I already put in my document. So we'll define it in there… have a little box in there too. This is what's defined as normal weight, overweight, obesity. This is where it comes from. Sound good?

Okay. So then we have the next… and that's a dilemma because we said we are then having dosing somebody on actual body weight is easy, but then we're dosing them based on ideal body weight and that becomes a bit of a dilemma for people less than 20 because there are different ways of calculating that. There's an article from 2007 that says ideal body weight calculation in children and it really says that there is no agreement. So there are different methods. There's the McLaren (?) method… what other methods do we have here? McLaren, Moore, and the body mass index method.

Woman: We have nutritionists who tell us what the actual ideal body weight is and when they need their NG2(?).

Woman: I honestly think we just need to pick one. If there's a graphic there that shows kind of like the… how extreme the differences are we might pick one kind of in the middle.

Rebecca Kruse-Jarres: It seems like the McLaren is the one that's in the middle. There's not much of a difference in lower BMIs where they are just overweight. It's… the higher you go, the more difference you see and the McLaren one is the one that's in the middle. So I would opt for going for that one.

Woman: I have no idea what our nutritionists used. Do you know?

Man: No, I have no idea.

Man: Can the pediatrician go back and report back to you?

Rebecca Kruse-Jarres: Yeah, absolutely.

Man: Can you send us a copy of this, please?

Rebecca Kruse-Jarres: Absolutely. I'll send the article to you guys.

Donna Sullivan: I want to make sure… please don't email those to Rebecca. Please email those to Ryan and Ryan will consolidate them and pass them out. Otherwise you're conducting work outside of an open public meeting. You can send them to Ryan.

Woman: [inaudible] nutritionist. [inaudible] we use at Children's. Is that okay?

Donna Sullivan: That's okay for that. Then send that to Ryan. Don't send them to Rebecca. Send them to Ryan.

Woman: Got it.

Rebecca Kruse-Jarres: What the nutritionist said?

Donna Sullivan: Yes.

Rebecca Kruse-Jarres: But I can send the articles out to everybody.

Donna Sullivan: Yes, you can.

Rebecca Kruse-Jarres: For the 20 and up or for the adults that's not going to be a problem. We have a calculation, but for the kids we need to agree on something. There we go. So the McLaren method is where you take the ideal body weight, but then you actually calculate it and then you actually apply it to one of your percentile graphs and that's how you determine it. We need to identify in the method section how we calculate it.

Donna Sullivan: So is that what we're asking the nutritionists information on? Okay. So we're not sure which one we're going to use yet. So I put a comment here that members will reach out to nutritionists to get calculations and send those to Ryan.

Rebecca Kruse-Jarres: Exactly. And then we can put that in.

Donna Sullivan: Right.

Rebecca Kruse-Jarres: When is our next conference call?

Donna Sullivan: Next Wednesday, the 27th at 7:00 a.m.

Rebecca Kruse-Jarres: I'm not going to be here.

Donna Sullivan: Will you be here some other day next week that we can try and reschedule? Okay.

Rebecca Kruse-Jarres: I'm going to be here the week after that. Unless…

Donna Sullivan: That week Ryan and I are not here.

Rebecca Kruse-Jarres: Ah hah. Well, but I… so if they are getting information back from the nutritionists and Ryan distributes that can I then look at that and tell my…

Donna Sullivan: You can look at it and put it into the draft that we can later talk about at a different meeting.

Rebecca Kruse-Jarres: Okay. But that way I could then say, "Well, this is what I think this should be. You can discuss it at the next meeting."

Donna Sullivan: Yes. You can send what your opinion is back to Ryan and then we will discuss what you put in your email with the collaborative members and we can talk about that.

Rebecca Kruse-Jarres: Thanks for keeping us straight.

Donna Sullivan: Okay.

Rebecca Kruse-Jarres: Then I think the next thing we need to touch upon briefly is the PK protocol. So there, again, PK studies will be measured in response to 150… oh no, it's 100… so I would say 50 and it's per kilogram dose. Right? Of the patient's current product. All patients will undergo PK testing twice. And then we can take out all the hemophilia B language.

Amanda Blair: Do we need to include some kind of adjustment based on available [inaudible]? Right? I mean…

Rebecca Kruse-Jarres: Yeah. And I have that later on that we need to talk about what assays we're using because we know that there are problems with those.

Woman: Do we want to have plus or minute there given by all sizes?

Rebecca Kruse-Jarres: Yes. I think I will just give… yes, that's a really good point. So 50 units per kilogram plus/minute 10%. I mean I'm even good with 15% because sometimes you run into vial size problems. As long as we know…

Woman: We'll ultimately be calculating the yield.

Man: Can we make sure we have the same vial size in the studies? If you go 10% up or down that could really skew your results, couldn't it?

Rebecca Kruse-Jarres: You're right.

Woman: It's still a calculation.

Man: It's still a calculation based on total units per kilo.

Woman: But I think we should try and aim at that to keep it as consistent as possible. 10%? 15%? I'm okay either way because I have some people that go just outside out that and I don't want to waste any factor that's not that important. Even if I do something on an 80% corrective dose I'm still going to get the data I need.

Woman: I would say plus or minute 15% and I would say every effort should be made to give… use the same vial size as end dose for each of the two PK studies.

Rebecca Kruse-Jarres: I like that.

Woman: We're using their home factor?

Rebecca Kruse-Jarres: Because they are going to be getting it anyway, right, if they are on prophy? The question is, what about people who are not only prophy?

Amanda Blair: What if they don't have vial sizes you need to make up the two different doses. The assumption is that everybody has multiple vial sizes at home.

Rebecca Kruse-Jarres: Right. Because some people are not on 100% corrective dose.

Man: That's a good point.

Rebecca Kruse-Jarres: That's a really good point. The thing is, I mean… and so I do PK testing on people all the time or I give 100% corrective dose because I want to know what does it really do in their system and I, you know, bill normal billing for it.

Man: You just bill [inaudible] dose [inaudible].

Rebecca Kruse-Jarres: I think it is clinical care that I do a PK study on somebody that I know where they really are. I might not put them on 100 unit pre [inaudible] or 100% corrective dose in the end, but that's what I need to really know what's going on in this patient. So it's clinical care.

Woman: At Children's we don't have access to… I mean do we have every product that all of our patients are on?

Woman: No, we don't, not on the formulary. I mean practically speaking most of these people who are going to want to participate are going to be on prophy or fairly… or on frequent on-demand. You know? The people who are 10% are probably not going to be as interested unless they have a procedure or something coming up. So, I mean…

Rebecca Kruse-Jarres: And everybody should have 100% corrective dose at home for a bleeding episode. Even if their prophy dose might be 50% corrective dose over the 75, but usually… and that's why I think, "Well, we need to be really soft with the over and under," because I don't want to change their dosing completely. Right?

Man: Yes.

Rebecca Kruse-Jarres: So… even 20% then? Plus/minus 20% of the 100% corrective dose?

Woman: Again, we're going to do the math and if you say that and you make every effort to have it be the same, vial size and the same lot, we're going to find out what we want to find out.

Rebecca Kruse-Jarres: Right. I agree.

Donna Sullivan: Because I'm not familiar with it, are we saying it is 50 units per kilogram plus or minute 20%? Okay. So 50 units per kilogram is the… what we're calling a 100% curative or corrective dose? Okay. So then is the rationale to have the same size vial and the same lot numbers are to try to get... make sure that the second dose is the same dose? So do we want to just say that instead of… I mean the lot number, I don't know how much that is going to… or are we figuring out that the vial itself might have 10% more than the 50 mL that it says it has on it. That's what we're trying to figure out is that we assume that each lot would be the same.

Man: That's why I said lot number.

Donna Sullivan: Okay. Got it.

Man: Because the number of units in each vial will be the same.

Donna Sullivan: So we do want to be that specific as opposed to saying the same dose?

Rebecca Kruse-Jarres: I'm making every effort. That doesn't mean that if they don't have the same lot number and the doses close enough that we should exclude these patients, but I think it's a much cleaner study if we can have the same lot number; especially if we're starting to use… if there is anybody on, I don't know, a [inaudible] containing product because you're going to have to… they are going to be different from lot to lot.

Man: [inaudible]

Man: We should record if someone is on plasma.

Rebecca Kruse-Jarres: Yeah, I mean I think… yeah. And then somewhere in there we need to say recovery should be measured… never mind. We don't need to do that. So… okay, I think we're good with that and then we have the hemophilia A, hemophilia B. You can scratch all the hemophilia B because we eliminated that.

Mike Recht: So the only recommendations I would make for the [inaudible] every single person. [inaudible] primary end point.

Woman: That's really type…

Mike Recht: Let's pick one time.

Woman: I think plus or minus five minutes I think is really tight. I mean I could… I might do 60 plus or minute 10 or something or 30 plus. I just think we need a little… I mean have you never failed on the first poke on a 10-year-old?

Man: Without question. A standard and the [inaudible] pivotal trials is always 30 minutes plus or minus 5. That doesn't mean that's what we have to do here, but that's what the FDA wants.

Amanda Blair: Are we going to make stipulations they all have to be peripheral sticks?

Woman: That was my next question.

Man: Yeah.

Rebecca Kruse-Jarres: Thoughts?

Woman: They should be.

Man: Yeah, they can't be gone through the same catheter where we [inaudible] administered. So if we're putting in an IV you can use your IV for your blood draws, but you can't… but then you'd have to do a purple stick for the factor. If they have a port it can be either infused or

have their blood drawn through the port, but it shouldn't be used for the PK.

Rebecca Kruse-Jarres: I agree. I mean this is… we're trying to determine PKs here and that needs to be really [inaudible]. Now that's really, really tough in an obese person.

Woman: If they don't have a line.

Woman: So your obese adults have ports?

Rebecca Kruse-Jarres: But getting access in them, getting them once is hard enough.

Woman: But they are doing frequent dosing most of them, aren't they?

Woman: Some of them do and some of them don't.

Rebecca Kruse-Jarres: Is there any study that ever showed that coagulation studies are affected by lines?

Dana Mathews: I actually looked at the data once because I have this great belief that having an IV in a vein over time can muck up your studies, because the tip if sitting there in the vein irritating [inaudible] and activating, and I always used to say… I never liked placing IVs for serial blood draws for coax purposes. So I actually went out once and I said, "Is there any data for my strongly held conviction?" And I actually found no data to support that it mucked it up and I did find data to say it didn't. But I don't recall looking at, you know, whether or not you could give a factor dose through an IV and flush it a lot. Ports I don't like because there's just too much room in that little chamber. So I would not want to give a dose of factor 8 into a port and then come back despite a big wastage of blood I would not want to count on a 30-minute yield. That's our primary endpoint.

Woman: Can we do a, you know, give the dose and then… so we can get the pre-level and give the dose [inaudible] through the same IV and then we just need a second stick for the… so the recovery study has to be drawn through a different… just differently from…

Man: All the PK [inaudible] points. It could not be drawn [inaudible] the factor is given. [inaudible]

Woman: So then would you allow prefactor 8 to be drawn from a port in someone who's on [inaudible] through a port? The sticky details.

Man: I think I need to think about this. In the iterations let's… go back and look at some of the [inaudible] trials that have PKs in it.

Rebecca Kruse-Jarres: Donna, for all four of us plus/minus Judy to go back and look at the literature and then during the next conference call to discuss what we should put in the final protocol. Because that's really, really important that we get that right.

Donna Sullivan: Have we landed on baseline plus 30 minutes plus or minus 5 or are we still deliberating that?

Rebecca Kruse-Jarres: [inaudible] has not landed there, but…

Woman: We'll bow to the majority.

Woman: I'm optimistic. I mean I think if we're going to have somebody in clinic we're going to have a nurse who is dedicated to doing these… the PK study. So, you know, if they have to stay there for 20 minutes and draw the lab… I think for four patients it's [inaudible].

Rebecca Kruse-Jarres: So you would propose 30 minutes plus/minus 5 or 10 or…

Woman: No. I think if the 30 minutes plus or minus 5 is what…

Man: If they are trying [inaudible] 25.

Woman: Let's just play this out then. So you put… you use a butterfly to draw the pre and give the dose. You pull the butterfly out. So then at that moment you're going to start mucking around to get the quick path in for the 30-minute draw? Or you wait until 25 minutes and then you start?

Man: We would start at 25 minutes.

Woman: And if it takes more than 10 minutes to get that needle in?

Man: Then you get the lab and you do it [inaudible].

Woman: Okay. I'm just going to push back a little bit. This is not a PUP trial.

Man: Correct, but it's our primary endpoint.

Woman: Okay. And what do we know about the difference between a 20-minute and a 40-minute lab?

Woman: We don't.

Man: It's lower at 40 minutes.

Woman: Thank you. But we don't know by how much?

Man: Nope.

Woman: And do we really know that?

Donna Sullivan: What you… you said something that if it took more than 10 minutes that you would something.

Woman: A protocol deviation. So does that mean that that patient's not included or…

Rebecca Kruse-Jarres: No. They are still included, but we just write that this was a deviation from the actual protocol.

Woman: [inaudible] not part of the primary endpoint analysis.

Man: I don't know if that's true or not. I think we'd have to talk to the statistician about that. If you're outside that… so whether that 30 minutes plus or 5 is aspirational and you're excluded…

Woman: I'm happy to aspire to it.

Man: Yeah, yeah.

Woman: Why don't we aspire to plus/minus 5 and make plus/minus 10 a reality?

Woman: I think it would be interesting to talk to the statistician. I don't know if the statistician… I don't know this person. I don't know what their experience is and these are kind of subtle and somewhat high level, you know, the pharma world lives and breathes this stuff. It is, you know, clinically I… if someone has a 30-minute versus a 60-minute level I'm okay. I think those are clinical meaningful to me. So I think we need to be thoughtful about this. We want to be… again, we're not looking for 3% differences, we're looking for…

Man: [inaudible]

Woman: Right. So let's not shoot ourselves in the foot. I mean I don't want us to be open to criticism so that everybody can throw it out because they say, oh my God, that lab draw was drawn at 37 minutes. But I'm just pushing back a little bit because I don't want to lose the valuable data.

Man: The other [inaudible] we don't have like research nurses who are in the trenches doing this and how often are they deviating this first time point?

Donna Sullivan: I'm going to let Lisa jump in here because she actually is.

Lisa Humphrey: In my prior life before state service I was a clinical research nurse in oncology. And so you are correct, if it is stated specifically in the protocol and we're anywhere outside that window protocol deviation is filed whether or not those clients… or those subjects are included in the study report, that I'm not sure of, because we would report it, you know, to the larger center and they would go from there. But anything outside of what is explicitly written in the protocol is written up as a deviation.

Woman: [inaudible]

Rebecca Kruse-Jarres: Yes, they do.

Lisa Humphrey: As far as timing goes, granted these were oncology studies, but as the research nurse I sat with the patient. So I knew if I had to do a PK draw within an hour we kept them in clinic, sat there and went back and forth.

Man: That's how we do it [inaudible].

Dana Mathews: I don't have any problem with that. I just worry a little bit about what happens if we can't get the needle in the vein for an overweight 40-year-old or an overweight 13-year-old. That's all.

Man: I hear you.

Woman: Then also the question, what if you can't get it in at all? Do you then get a second trial to get the data? On PK 1 we run into trouble and we can't get that second, you know, the time point, which is important. Can they then come back in a week and try again? I think they should.

Man: Yeah.

Rebecca Kruse-Jarres: I will talk to the [inaudible] statistician to see if that's a protocol deviation for a primary endpoint. Will that data then be excluded from analysis? Right? And if it is do we then broaden the inclusion to plus/minus 10? And otherwise we leave it at plus/minus 5.

Dana Mathews: I think I have made my preferences clear. I will totally defer to the majority. I have not done a bunch of PK studies and I don't know what Amanda wants to do because it's going to be her patients.

Man: Let me reach out to some of the clinical trialists at the companies and see what they do for this. Not to say that's what we have to do… right. Just to get what their experience is.

Woman: That sounds great.

Man: Yeah.

Woman: And if that's what we want to do, that's fine, but we don't necessarily… we're not looking for FDA approval.

Man: You're exactly right. So I very much appreciate your keeping us grounded and this is supposed to be real-life experience.

Woman: What do you think?

Woman: I agree. Uh huh. I see it both ways.

Donna Sullivan: I just want to kind of summarize what I think I heard. That is if we miss the timing and we can't get the second draw within whatever time period we decide upon, that particular draw is a protocol deviation, but the patient is still alive in the study and can… we can dose them again with the second dose at their next scheduled dosing and then try it again?

Rebecca Kruse-Jarres: If they come in for the first dose and we do not get that 30-minute level then that gets completely scratched and they get another run on that first PK trial.

Donna Sullivan: Okay. And then on the second attempt; like we're dosing them now with the alternative dosing schedule. If you don't get that one within the 30 minutes then they can have another attempt as long as they meet that two-month window that we set before.

Rebecca Kruse-Jarres: Exactly.

Donna Sullivan: Okay.

Rebecca Kruse-Jarres: Because we cannot have patients in the trial that do not get that 30-minute… that's our primary outcome.

Man: I concur.

Rebecca Kruse-Jarres: So glad.

Man: [inaudible]

Woman: So in terms of like the protocol deviation is totally true, but it's going to depend on which IRB is used, if they would be out of the project. Like we use WERB and WERB would be totally fine as long as you're writing all of this in the protocol right now, then they wouldn't be out of the project. But some other IRBs are different and…

Rebecca Kruse-Jarres: The three of us or two centers are you going to use WERB? Do you accept WERB too?

Man: Judy does WERB, we do not.

Rebecca Kruse-Jarres: Okay.

Man: I know. It's too bad.

Rebecca Kruse-Jarres: That would make it great because then we only need one approval for the three sites.

Woman: And as long as you write it all out like this it will probably be fine. Like they wouldn't get excluded from the study.

Woman: Is there a difference between whether a patient is excluded from the study… continued participation in the study versus whether or not their data is used in the analysis. Is there a difference there? And is the IRB in charge of whether or not the data is included in the analysis or is that the biostatistician?

Woman: The statistician.

Woman: Okay.

Rebecca Kruse-Jarres: So then who is allowed to run those essays? What essays do we use and how much time do we have?

Donna Sullivan: It is 10 to 3 right now so we've been going on for almost two hours. Do we want to take an 8 minute break? Okay. Let's do that and we'll reconvene at 3:00.

Woman: Okay. Sounds good.

Donna Sullivan: I think we can resume and what I would say is let's deliberate until 3:30 and then we'll cut it off and allow for stakeholder input. Then we will figure out the next steps.

Rebecca Kruse-Jarres: Can you cut me off at 3:30ish?

Donna Sullivan: I will. The lights will go out.

Rebecca Kruse-Jarres: So I think the biggest thing left to discuss, I think, is the question around what assays to we allow. This is, again, between ideal and practical question. I just talked to Mike and one thing that came up, I mean for one it would be good to do it locally because it doesn't cost us too much. The other thing is also is this a clinical expense? I do PKs on my patients all the time and I do that as part of clinical care; especially these days. So I don't have a problem with doing that as a clinical expense rather than a study expense. And the other thing is, I think if you're doing a local lab, especially for the recovery, it absolutely needs to be the same lab that's running the PK1 and the PK2. I think that has to be demanded.

Mike just brought up it would also be really nice to do that in a central lab to just spin [inaudible], freeze them away and then batch them in the end and then maybe we can run them at our lab since that's our primary outcome. I think it would be great. It would add some expense to it and we can just see how expensive it would be. Any thoughts?

Mike Recht: For the central you're thinking just the pre and the recovery, and not the rest of the PK or the entire PK?

Rebecca Kruse-Jarres: I would just do the primary outcome. So the pre, because otherwise it gets too messy and we were also going to have to talk about the half-

life, the rest of the PK. Do we demand that people go to the same laboratory as they did for the recovery? Or can that be a different laboratory? But it needs to be the same between PK1 and PK2. Some people live pretty far away and when I do PKs I just have them come in. I do the recovery in our lab and then I do the other time points at a more local lab. To them I think that makes it easier for the patient and makes it more likely for them to enroll. But I'm open for thoughts.

Mike Recht: I think the idea of the pre and the recovery being run in the same lab is very important. We can budget out whether there's going to be enough money… running it centrally. Again, I think if we go back to what Amanda and Dana were saying about this is real life and we're not worried about a 1 or 2% difference, but we're looking for bigger differences, we're probably good.

Woman: The central lab is a cool idea, but not only does it add cost, it also adds a lot of infrastructure and hassle.

Mike Recht: And room for error.

Woman: Also true.

Mike Recht: Yeah.

Woman: I mean I think, you know, in a lot of ways we're… real life is a good goal. Real life is good and it is… as long as it's done in the same laboratory. So whatever laboratory… we're not checking from one patient to another. We're just checking within that patient. So I'm absolutely okay as long as it is the same laboratory.

Woman: I just don't have enough experience with the extended half-life. Are there assay issues for those?

Woman: There are.

Mike Recht: Not as much for the 8s as for the 9s. 9s for sure, 8s are pretty close.

Woman: Okay.

Rebecca Kruse-Jarres: But I think for those, again, if you do it in your laboratory and then you switch laboratories for the more, you know, the later time points, I'm still okay to do that because it's real life. And for some patients it's not feasible to come back at those time points to the same institution as the [inaudible] laboratory. So I think it's okay to do that. I personally have been open to your thoughts on that to allow that, but make sure that the second PK it's done exactly the same way.

Amanda Blair: In my three months of practice in the Seattle area I don't have any idea how many outside labs are actually consistent or you get reliable factor 8 levels from.

Rebecca Kruse-Jarres: You don't.

Woman: A whole lot of frankly more and more of the outside labs seem like they are using [inaudible] out of Sacred Heart Medical Center Lab, which is pretty good. They're not bad.

Woman: [inaudible] substance that I don't know what it is and then I don't get any factor 8 levels.

Woman: That doesn't happen to me.

Rebecca Kruse-Jarres: I'm going to send my patients to you.

Woman: I mean it's not a primary endpoint.

Rebecca Kruse-Jarres: Right. That's why I'm saying I think… again, we're comparing one patient at one time point and a second time point so I'm okay as long as those time points, PK1 and PK2 are done in the same labs.

Woman: Okay.

Donna Sullivan: I'm going to clarify. So you're saying the pre PK and the recovery draws must be done in the same lab and that's true for the first dose and the second dose. So the pre PK and the recovery for both doses should be in the same lab. Okay. Got it.

Rebecca Kruse-Jarres: And then the subsequent time points can be done somewhere else.

Donna Sullivan: I think I captured what you were saying.

Rebecca Kruse-Jarres: Right. But the PK1, wherever they were drawn, that's exactly where they need to be drawn the second time.

Donna Sullivan: Right.

Rebecca Kruse-Jarres: Okay. That's all I have. We talked about the statistics.

Donna Sullivan: What we didn't really talk about was the acute bleeding one day prior.

Rebecca Kruse-Jarres: Right. You are absolutely right. Thanks for bringing that back up. So what do we want to… that needs to be somewhere in that section.

Man: Maybe it would be [inaudible] bleeding state with 48 or 72 hours prior to the last…

Rebecca Kruse-Jarres: But what do we define as non-bleeding state?

Man: Someone telling us they're not bleeding.

Rebecca Kruse-Jarres: Well… but… so if somebody had a bleed yesterday and they are telling you today they are not bleeding anymore I don't think that's okay.

Man: Without treatment. Because we have the 48 or 72 hour from last dose.

Rebecca Kruse-Jarres: If somebody had a massive bleed two days ago then [inaudible]…

Woman: Just define it almost like by a functional status. I mean, you know, sometimes we don't even know if a bleed is a bleed.

Man: All the time.

Woman: Fair enough. The truth is somebody who had a massive bleed two days ago is probably not going to be wanting to do this. And they will certainly not meet the 48-hour criteria. If they had a massive bleed two

days ago… I actually hadn't thought about that, but I like that. The other question, well, you're going to be giving them a big dose that day. So I guess… I mean what happens if they have a bleed the day after? Then you're losing everything beyond your primary endpoint, which is not terrible.

Man: That's real life.

Woman: Yeah, that's the way it goes. So you could just actually make a comment have patient with a bleed active enough to have [inaudible] ongoing treatment will be excluded by basis of the timing criteria.

Rebecca Kruse-Jarres: Yeah. Or we can just say patients with acute bleeding… patients should not have PKs drawn during acute bleeding episodes just to make sure. Or do we just not put it in there at all?

Donna Sullivan: So we don't want to exclude them. Maybe we just want to push them further down the road and re-evaluate them at a different time. So if you're saying… if they had a bleed and they took product if 48 hours have elapsed is that enough time? Do we need to even address this if we're saying already we have 48 hours or 72 hours before the last time they had factor. Does it matter if it was because of a bleed or a prophylactic dose?

Man: Yeah. So maybe someone comes in that morning bleeding and they think, well, I'm gonna be on this trial and get a dose of factor.

Rebecca Kruse-Jarres: It will have been 48 hours, but they have an acute bleeding episode and we don't want them on the trial because their PKs are going to be [inaudible].

Donna Sullivan: So then I think what we could say is that the PK won't be measured if the patient has an active or acute bleed, but not to say that we're excluding them.

Man: We are excluding them from that day…

Donna Sullivan: From that day's… yeah. Right.

Amanda Blair: Didn't you earlier say that… I mean can't you just say that PK studies will be delayed until resolution of any acute bleeding episodes?

Rebecca Kruse-Jarres: So we said if somebody comes in for a PK study we get time .1, but we do not get time .2. They are allowed to come back and try that PK1 again or the PK2 again. How many times do we allow that? Up to three times or indefinite or…? Do we not put that in there?

Mike Recht: I wouldn't put it in.

Rebecca Kruse-Jarres: Okay.

Man: Unless they cross that two-month [inaudible].

Rebecca Kruse-Jarres: Right. Yeah, but I mean if they have not even had the PK1 done there is no two-month period. We can keep on going until we get them.

Man: I'm assuming the studies [inaudible].

Rebecca Kruse-Jarres: Sure. Sure. Okay.

Man: Can we go back to one thing in trial design all the way on the first page? In the second paragraph, the last line, it says ethics approval will be obtained at all locations before trial enrollment. We'll only have two IRBs involved. I think we should reword that so it says, ethics approval at each particular institution. So for example if OHSU takes a long time to approve this I don't want that to delay you guys from enrolling…

Donna Sullivan: Where is that at?

Man: The last line, second paragraph under trial design. So the way I interpret that sentence is that everybody has to have IRB approval before anybody can enroll.

Rebecca Kruse-Jarres: Yeah, that's not how it was meant. It was obviously that we don't enroll anybody.

Man: Right.

Rebecca Kruse-Jarres: Ethics approval will be obtained at all locations. Okay. Did you get that Donna? All right. Any other comments? Did we forget anything? Everybody know what they need to do?

Woman: In the statistics section I'm not really wanting to dive into it in this forum. Are we… but I just skimmed it for the first time. Are we all really comfortable with it or do we want to make sure that in our next phone call we…

Rebecca Kruse-Jarres: What I can ask is… I can ask whether she could join us for the next call.

Woman: That would be great.

Donna Sullivan: That would be fine. Yeah. We'll have to figure out when the next call will actually be.

Rebecca Kruse-Jarres: Because I mean we absolutely need that before we finalize the proposal.

Donna Sullivan: To me the proposal still needs a lot of work as far as getting it up to the research protocol quality. I think we're doing really good about agreeing on concepts, but getting it into the language that you would read in a paper, I think it does need a little bit of work, and it does need to be at that level before we officially approve it. So what is going to go to the IRB is what needs to be approved.

Rebecca Kruse-Jarres: That's why I didn't think we were going to approve it today.

Donna Sullivan: Gotcha. I just wanted to make sure. Rebecca, you said the 27th you're not available. So the next meeting would be the week of May 11th or 12th unless we try to schedule a special meeting.

[inaudible]

Donna Sullivan: Okay.

Rebecca Kruse-Jarres: You're not there the week in between. Right?

Donna Sullivan: Yeah, 3rd and 4th. The 4th I can see if… I'll talk with Ryan and see… we're going to be in Portland. So it's possible that we might just…

Rebecca Kruse-Jarres: [inaudible]

Donna Sullivan: We're actually at a conference in Portland at a meeting. So we'll have to see if logistically if we'll be able to call in at 7:00. So I'll let you know about that one. But we'll try to shoot for that.

Man: Who's in Portland? [inaudible] turn them on.

Donna Sullivan: It's more the logistics between transportation from the hotel to the conference. So we'll figure that one out.

Rebecca Kruse-Jarres: I'm happy to find… I don't think it's going to take a full hour.

Donna Sullivan: Okay.

Rebecca Kruse-Jarres: You're going to the conference when?

Donna Sullivan: May 3rd through the 5th.

Rebecca Kruse-Jarres: So that's Wednesday, Thursday. Is that right?

Donna Sullivan: Yeah.

Rebecca Kruse-Jarres: It's Tuesday, Wednesday, right?

Donna Sullivan: We would be available Tuesday morning. We just have to leave Olympia in the afternoon on Tuesday.

Rebecca Kruse-Jarres: It will work if you can set it up for then.

Donna Sullivan: For Tuesday morning? Okay. We'll have to call it a special meeting.

Rebecca Kruse-Jarres: Or even…

Donna Sullivan: If not then we'll try the 3rd.

Rebecca Kruse-Jarres: Or even 7:30, whatever it may be.

Donna Sullivan: Okay.

Woman: We're anticipating final review of the stats and of the final language or?

Rebecca Kruse-Jarres: I think we just wanted to talk to the…

Woman: [inaudible]

Rebecca Kruse-Jarres: Yeah. I mean we definitely… we just wanted to look at the statistics section and make sure that everybody understands it.

Donna Sullivan: So we're not going to address any of the other follow-up items that we talked about today?

Rebecca Kruse-Jarres: We can still address that because… we can bring that up during that conference call as well. Right? Because we have several things that we still work on and between your notes and my notes before that we're going to incorporate a lot of what we said today and have a clean-up version of that.

Donna Sullivan: Okay. By May 3rd or that week.

Rebecca Kruse-Jarres: Right.

Donna Sullivan: Okay. So I'm thinking next week you're not available. If we have… one of the things that we could do, just to keep the ball rolling, is if we do have follow-up or feedback from a nutritionist on ideal body weight that we meet and discuss it, not make any decisions, but have that conversation knowing that you're not there and then we can catch you up to speed at the following meeting.

Rebecca Kruse-Jarres: Sounds great.

Donna Sullivan: Okay. Great.

Rebecca Kruse-Jarres: Yeah.

Woman: I have a meeting I have to go to at 7:30. So I can be there for the first half hour.

Donna Sullivan: If we don't have any feedback from the nutritionist we can cancel the meeting if there's nothing to discuss other than that. So we'll send out an email and get the logistics early, late this week or early next week to figure out if we will or will not have that meeting on the 27th.

Rebecca Kruse-Jarres: Any thoughts I have I can communicate with Mike so let's make sure that it gets brought up during the meeting.

Woman: To Ryan.

Donna Sullivan: To Ryan.

Rebecca Kruse-Jarres: Because I'm not allowed to talk to you.

Donna Sullivan: You're not allowed to talk to each other. So that's the next meeting. I do want to allow some time for the stakeholder input. We did have one stakeholder that signed in. Dr. Rosalynde Finch. Did you have testimony that you wanted to give or comments that you wanted to make? Can you walk… there's the podium up there there's a microphone or you can sit down here at the table here and speak into the microphone. Just introduce yourself and let us know where you're from and who you are representing.

Rosalynde Finch: Yeah, okay. So I'm Rosalynde Finch and I am with Biogen Medical Affairs. We did submit comments, the Briana Buckley comments that were discussed at the last meeting. That's from our group and you guys did respond to them. So I had planned to discuss some of that today, but since you already responded to it… some of the comments are moot since you're not going to be doing hemophilia B. Some of our comments on the PK and also on the lab assay and then our other comments were on the other proposal which you've moved ahead with

today as well. What I'll be doing is each it iteration of the protocol as it comes forward I'll bring it forward to our internal group. We have experts, obviously in clinical trials who do extensive PK work and some of the comments that were brought up today I can actually even ask for their feedback on in terms of how, you know, how tight do these types of measures have to be and then also if there is other feedback that they think should be brought forward in terms of some of the changes that have been made.

Just for today, a couple of the things that I noted during the discussion is… I know this is… the primary outcome is looking at recovery. But in any kind of situation where you might be changing a patient's dosing there might be safety concerns either, as you mentioned, if you increase… if you're dosing it at actual body weight there may be safety concerns from [inaudible] events, for example, or if you're dosing an ideal body weight and you're changing the dosing that a patients' been on. So my question is, what kind of clinical outcomes are you going to be collecting and how are you going to be reporting those or any adverse events and I don't see any language in the proposal as to how you're collecting and reporting out on adverse events or clinical outcomes. So that's just for today, just from the discussion, one thing that I wanted to bring forward. That's something that the IRB I'm sure is going to be asking you as well. That's all I really had for today. So thank you.

Rebecca Kruse-Jarres: That's a much appreciated comment and, yes, you're right, we're not collecting clinical outcomes on this at all. That's not the purpose of this. This would be completely clinical; a different clinical trial, but I think to have an adverse event section is more than reasonable.

Mike Recht: Have adverse events and serious adverse events [inaudible] is important.

Donna Sullivan: And serious what?

Mike Recht: Adverse event and serious adverse event and standard definitions of those two.

Donna Sullivan: We still have 30 minutes potentially in the meeting. We can either adjourn or are we finished? There's nothing else…

Rebecca Kruse-Jarres: There's nothing else we have?

Donna Sullivan: Yeah. That was it. Just one stakeholder unless, Mike, you signed up. Do you want to…

Mike Recht: I signed up as a stakeholder?

Donna Sullivan: Yeah, the sign-up sheet was just for stakeholders.

Mike Recht: I apologize for being an idiot.

Donna Sullivan: Do you want to adjourn the meeting then?

Rebecca Kruse-Jarres: I will adjourn the meeting.

Mike Recht: I move to adjourn.