Bleeding Disorder Collaborative
June 15, 2016

Donna Sullivan: So Valarie, Susan, those at the Center, whoever is doing the presentation go ahead and I guess present the dress report.

Dr. Ray: I'm sorry. I was not under the impression that I was presenting anything. I was just requested to be available on the call. I'm sorry for the confusion. I was unaware that that was required.

Woman: I'm with you on that. I didn't know that…

Donna Sullivan: So…

Woman: Has that document changed a lot since we looked at it before?

Ryan Pistoresi: Just to clarify, so this is a different guideline than what we originally saw back in March. With March we had a review by med on different areas that we were looking to conduct the clinical trial on. This is a new report that is actually reviewing evidence-based guidelines from around the world to see how the level of evidence and hemophilia treatment compares. And so this is a different report than the one that we saw in March.

Rebecca Kruse-Jarres: As you can tell I have not seen this before.

Ryan Pistoresi: Okay.

Rebecca Kruse-Jarres: I can't discuss it.

Ryan Pistoresi: Okay. Well, we do…

Valarie: We were not asked to do a formal report, but I'm wondering if Mora Ray might just go through the few key findings from the actual report to bring everybody up to speed. I don't think we need to do more than that.

Mora Ray: Sorry. I'm in an in-patient service right now. So that's going to take me a few minutes to get this up in front of me. I'm also sitting in front of a computer that's not really opening anything. So that's another small problem here.

Woman: It's coming to your email. Just to set the background here, the whole goal, I think as Ryan alluded to of this particular report was to identify clinical practice guidelines on drug type interventions for both hemophilia A and B and to look for estimates on the cost and cost effectiveness of those interventions from the literature to inform your process in the bleeding disorder collaborative. So in terms of things that we found with this report, with clinical practice guidelines, we really identified four relevant documents and these were the Australian Hemophilia Center Director's organization guideline. That was from this year, published in 2016. The Nordic Hemophilia Council's guideline published in 2015. The United Kingdom's Hemophilia Center Doctor's Organization guidance published in 2013 and the World Federation of Hemophilia document published, again, in 2013. Three of these were of very poor methodologic quality and that was particularly for absence of clearly defined evidence process, absence or not description of methods for translating the evidence to the recommendations, and editorial independence or lack of commercial interest.

The Australian Hemophilia Center Director's Organization Guideline was fair methodologic quality. It did rely heavily on the World Federation Guideline for Evidence, but they did have fair quality methods for translating the evidence to recommendations and reporting on conflicts of interest.

In terms of some of their clinical recommendations, the United Kingdom, Nordic and Australian guidelines all recommended recombinant factors over plasma-derived factor. The World Federation recommends both viral eradicated plasma-derived and recombinant factors. All of the guidelines, all four of them, recommended prophylaxis and that prophylactic regimen should begin by age 3 and, this is an important and, and, the second clinical bleeding episode. The four guidelines were consistent in terms of giving an array of options for prophylaxis regimens and stating that both of those regimens and the protocols could vary

within and across countries. All of the identified guidelines supported the use of particular products for bleeding episodes in patients with inhibitors.

And then we turn to the section of the key points from the section of the report that dealt with costs and cost-effectiveness. We did not, in the evidence search, identify any estimates of cost or outcomes comparing specific factor preparations. The estimates of cost and cost effectiveness for prophylaxis compared to on-demand therapy varied very widely and depended upon the methods used in the analysis that generated those estimates.

We did find one fair quality methodologic systematic review on economic analyses that analyzed the use of bypass agents, i.e. things to treat folks with inhibitors. To treat either mild or moderate bleeding episodes in those populations and the estimates of total direct costs to treat a single mild to moderate bleeding episode in a patient with hemophilia complicated by inhibitors typically the assumption was that they were treated in the home setting ranged from a little over $11,000 to a little under $50,000 for APCC and $9,000 to a little over $49,000 for RF7A and those were using 2010 US dollars. The estimates of efficacy in those cost analyses were based on industry-funded studies and those studies typically used higher efficacy estimates and lower doses for their products. So that it biased them toward greater cost effectiveness. Typically those estimates came out of single-arm clinical trials. The findings that we identified from head-to-head trials did actually not support superior efficacy for either product and the authors of this particular review called for additional head-to-head clinical trials for both agents to elucidate the ideal dosing regimen, clinical efficacy, cost effectiveness and the potential that the medications might actually be synergistic or have differences in treatment effects among subgroups of the population of patients.

So those were really the main points of the review. Mora, is there anything that you would like to add to that?

Mora Ray: The only thing worth noting is that what we didn't find. So we found cost estimates around the use of bypass agents for patients with inhibitors.

But we really… the search… the evidence search didn't identify any estimates on costs or cost outcomes with specific different clotting factor preparations like [inaudible] factor versus human versus recombinant and those types of studies we did not identify.

Woman: Yeah. There was a mark for a really important and expensive area of healthcare. There was really nothing.

Rebecca Kruse-Jarres: I would add to that that is kind of important, you know, you make the point here that the guidelines are mainly recommending recombinant factor over plasma-derived. That is very much in question right now since the results of the SIPIT(?) study, which was a randomized phase 3 clinical trial that was just published in the New England Journal of Medicine about two weeks ago. So obviously there is new data that is going to factor into this.

Mora Ray: It's interesting because I think most of the wording in those practice guidelines around that recommendation stem from the risk of spreading infection and that that's really what their motivation is. It's hard to get that, but in reading kind of the [inaudible] that you can tell it sounds like… in those countries they feel like, particularly Australia, that they have these available, these should be the standards of care because of this potential risk of any infection from a plasma-direct product.

Rebecca Kruse-Jarres: Right. And to be noted that there has not been an infection in a plasma-derived… [inaudible] in decades.

Mora Ray: Right. Yeah.

Ryan Pistoresi: Do any of the other members have any other comments for MED regarding their report? Okay. I see no further questions so we thank you for your time. We appreciate you providing us with this report.

Woman: Lovely. Thank you very much and let us know if there is anything else you need.

Ryan Pistoresi: Have a good day.

Woman: Okay. You too. Bye.

Ryan Pistoresi: To further explain, this report is going to be used when writing the legislative report, which I'm currently doing and that's one of the topics that we'll be discussing a little bit further on this summer once I have a draft and we'll be sending that out. We'll try to incorporate some of the findings of this report into that legislative report. So with that said I realize we haven't done introductions yet. So could we actually go around the room and each introduce yourself and where you're from? Just a reminder, when speaking, we are recording this so can you just say your name to help the transcriber identify you as you speak?

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

Sarah Roberge: I'm Sarah Roberge with Blood Works Northwest.

Rebecca Kruse-Jarres: I'm Rebecca Kruse-Jarres. I'm with the Washington Center of Bleeding Disorders also Blood Works Northwest.

Mike Birmingham: I'm Mike Birmingham, Bleeding Disorder Foundation of Washington.

Amanda Blair: I'm Amanda Blair with Seattle Children's.

Ryan Pistoresi: I'm Ryan Pistoresi with Health Care Authority.

Donna Sullivan: Donna Sullivan with Health Care Authority.

Leta Evaskus: Leta Evaskus with Health Care Authority.

Ryan Pistoresi: With that we are ready to move on to the next item of our agenda, which is on the protocol. So we probably will need to call in other members. So we will need to actually wait and hold off on voting until 1:45 if that's all right with the members.

Rebecca Kruse-Jarres: Yep, I think that's okay.

Ryan Pistoresi: Okay. So on the protocol I did not receive any public comments in the time allotted. So there has been no revisions or no request for questions or anything regarding to the protocol as it currently stands. Do the stakeholders in the audience have any comments? Or should I check the sign-in sheet?

Donna Sullivan: Can you… just come sit at the table across from us at the microphone and… so we can get your comments on the recording. Thank you. Yes, that's fine.

Lynda Finch: Just one quick question on the MED report because I just saw it for the first time today, as well. Just to note that it doesn't include any of the extended half-life products. So just to make that note. And then in the study protocol on… in the intention to treat section. So this is on page 4 it states that if a participant experiences a 10% or greater change in BMI between the first and second dose the participant will be included in the analysis, and I'm wondering if that's correct? Should it be "will not be included in the analysis"? Am I misreading that? If they experience a 10% or greater change in BMI you're going to include them in the analysis.

Donna Sullivan: It's my understanding intention to treat is you include them in the analysis.

Lynda Finch: Okay.

Rebecca Kruse-Jarres: That was discussed during our talks about the protocol and the question was, you know, should that happen? What are we going to do with it? Yes, generally we would say should maybe not be included, but since it is an intention to treat analysis it should be included.

Lynda Finch: Will those patients be excluded in a separate category? Would you look at them separately?

Rebecca Kruse-Jarres: No, we wouldn't. You're really basing them on the weight they have that day. So it's going to be… even if they have now… are, you know, 10% more we're still going to calculate their dose on their either actual body

weight that day or their ideal body weight that day. So it shouldn't really… it's not like we're taking the weight from the very first day.

Lynda Finch: Okay. Thank you.

Ryan Pistoresi: Thank you. So with that are there any other comments or amendments or any other questions on the [inaudible] cause as it currently stands? Okay. So in order to vote for a quorum we'll need to wait for Heidi so that way we have enough members to vote on it.

Stephanie Simpson: Mike said his meeting is at 4:30.

Ryan Pistoresi: At 4:30.

Rebecca Kruse-Jarres: Did you make contact with him?

Stephanie Simpson: East Coast time.

Ryan Pistoresi: Okay. So 1:30 Pacific.

Rebecca Kruse-Jarres: Does he know we're trying to vote?

Stephanie Simpson: Yeah.

Ryan Pistoresi: I appreciate that. Thank you. We will need to have the phone on for Mike to call in and for Heidi to call in. I guess we will vote on it when we have all the members.

Donna Sullivan: Do we want to take a break and come back at 1:30? Or review some of these other documents?

Ryan Pistoresi: We also have the eligibility form. We have these other additional documents. That's all we really have today. It's a real light day. The main idea was to really focus and get the protocol approved so that way we can move forward and get the research started as soon as we can.

So the next item on the agenda is the eligibility form, which is the last page in your binder. Let's pull that up. So the eligibility form I took in all

your comments from the last Bleeding Disorder Collaborative webinar that we had and I incorporated all your comments into this. This was also sent out for public comment and we did not receive any public comment via email. I will open it up for stakeholders in the audience to comment if they wish. We only had you sign up so I wasn't sure if it was for the protocol or for this. Okay. So let the records reflect that no stakeholders commented for the eligibility form. Do any of the other members have any comments, questions, revisions?

Rebecca Kruse-Jarres: I just wanted to thank you for doing a great job. It looks great.

Ryan Pistoresi: Thank you. So then we will also hold off on this until we have Mike and/or Heidi on the line. So we also received three additional documents that are not in your binder, but are actually located beneath your binder and those are the Subject Information Form, the Factor Dosing Form, so the PK Testing Form, and then we also have the Adverse Event Form. And so these documents are fresh. We haven't reviewed these yet. And so we can open it up to the members to (1) select which document you would like to review first, and (2) how you would like to go through it. If you'd like me to read it, I can pull it up on the screen and we can edit it. I will open it up and allow you to decide.

Rebecca Kruse-Jarres: I guess we can just start with the Subject Information Form. This really is more for people to have at the site to keep track. This is not a form that's going to be going to us or to Sarah to collect because this is going to have both the subject ID and the subject name. So this is just to make sure that we have contact information on that patient in case we need to get ahold of them during the study and to document that we actually did the consent and that questions were asked that the HIPAA was signed, just to make sure we have all the documents.

Ryan Pistoresi: Thank you.

Rebecca Kruse-Jarres: Amanda, do you think we are missing anything from that?

Amanda Blair: I think it looks really complete.

Donna Sullivan: I have a comment. Different documents we have different… we're calling this study different things. So we're calling it either ideal versus actual and we use the word body weight-based factor dosing. On the protocol we have comparison of ideal versus actual weight-based factor dosing. So I think we should make sure that we title these all the same.

Rebecca Kruse-Jarres: I completely agree with you. I think we should just call it whatever we have on the protocol. Ryan, if you could help us make all these documents look a little uniform since you did such a great job on that one.

Ryan Pistoresi: Thank you. Yeah, I can take care of that probably offline before the next meeting next Wednesday.

Donna Sullivan: I would just recommend, Rebecca, that we add on the protocol… we have comparison of ideal versus actual weight-based factor dosing. I recommend we add in hemophilia A.

Ryan Pistoresi: Is it weight-based factor dosing or weight-base factor dosing?

Rebecca Kruse-Jarres: Weight-based.

Ryan Pistoresi: Okay. Thank you. So I'll change that in the protocol as well.

Rebecca Kruse-Jarres: And on the eligibility form.

Ryan Pistoresi: Thank you.

Rebecca Kruse-Jarres: Are there any other questions on the subject information form? Should we move to the next one? Ryan, are you ready?

Ryan Pistoresi: Let me just finish editing it.

Rebecca Kruse-Jarres: We have plenty of time.

Ryan Pistoresi: Yeah, we have plenty of time. So the next form would you want to do the testing form?

Rebecca Kruse-Jarres: Sure. The testing form then is going to identify whether this is… and we were discussing whether we should have two different forms, one for PK1. So for the ideal body weight and one for the actual body weight or should we just have it all in one form that we use? We decided to go with one, but we're happy to do it either way. So this way you would identify whether this is PK1 or PK2 depending on what they were randomized to first, the date, receiving… what they are receiving this time, whether it's the actual body weight or the ideal body weight dosing, the age, the weight that day, the factor product, and whether that is standard half-life or extended half-life. And then show the calculations either on the actual body or in the ideal body weight. And on the ideal body weight we just wrote in there to see protocol because that's kind of a complicated thing. We didn't want to put on the form… the actual form here, because it's different for adults and kids. So then the actual dose given, the infusion time started, the infusion time ended, and then a table for the PK results and there are, you know, how they were done. Whether that's one stage clotting [inaudible] or chromogenic, what the activity level was, the name of the lab where it was performed, and then with the asterisk there you see on the longer half-life they have two extra PKs.

Amanda Blair: On the 30 plus or minus minutes is that supposed to be 10 minutes or…

Rebecca Kruse-Jarres: That's right. I think in the protocol it says 10. Let me make sure that we are consistent. Yep. So we can add that to it.

Ryan Pistoresi: Should I also add the plus or minus 20% to the 50 IU per kilogram since that was also one of the changes we made in the protocol recently?

Rebecca Kruse-Jarres: Where do me… the actual… we don't need it there because this is the actual dose given. Where do you want to put this? The actual body weight is the dose calculation. I'm taking that persons weight and I'm calculating it times 50. So that is not a plus/minus. This is what I'm… the calculated dose. Then I'm going to write down under actual dose what dose I actually gave. In the end that needs to be within the 10%.

Ryan Pistoresi: Okay. I was looking back at the protocol and one of the lines was participants will be randomized to receive 50 U… per kilogram plus or minus 20% of the factor product. So that's where I had that.

Rebecca Kruse-Jarres: Right. It's a legitimate question. We can certainly put in there what those ranges would be to make sure that we're actually within those 10% if we need that.

Ryan Pistoresi: It is certainly up to you. I just thought that since it was in the protocol I wasn't sure if we wanted to keep that over here as well or not.

Amanda Blair: It seems like what you're trying to record here is the actual dose of factor they got. Right? Yeah? I mean it's going to be whatever random number of units based on the vial size.

Rebecca Kruse-Jarres: The vial size needs to be within those plus/minus 10. So it's a legitimate point to bring up. Do we need to record that somewhere that yes, we're actually falling within that window.

Amanda Blair: You say 10%, but in the protocol it says 20%.

Rebecca Kruse-Jarres: 20%. Yeah, sorry.

Ryan Pistoresi: So for my understanding so that you'll actually have the dose calculation by the 50 IU per kilogram in this line, which is an exact 50 and then the actual dose given is within that 20%. So I wasn't sure, you know, if that needed to be somewhere or not. But as long as it is clear to who is dosing it then I think that should be all right.

Rebecca Kruse-Jarres: That might have to be a reminder for people that, yes, actually it is within those plus/minus 20%. So I'm not opposed to put that on the… either we can put the range that's allowed plus/minus 20, you know, if we calculate that or after the actual dose given we can say this dose is within 20% of…

Ryan Pistoresi: I agree. I think we can put the range as a reminder after this actual dose given. So that way you can look back and make sure that is within that 20%.

Donna Sullivan: I have a question. I was a little confused. So the dose calculation, and it says actual body weight in parentheses is 50 IU per kilogram. The dose calculation ideal body weight it says see protocol. Aren't we dosing them at 50 IU per kilogram whether we use actual versus ideal body weight? Is that not correct?

Rebecca Kruse-Jarres: Their ideal body weight. So it's different. It's not just their actual kilogram today. Because here you're recording their kilogram up there. Right? So that's their weight… it's very easy… it's 50 IU per kilogram, whatever kilograms we have there. But our kilograms are going to be different based on the calculation off the ideal body weight. So it's a longer algorithm to get to that.

Donna Sullivan: This is what I'm trying to figure out is are we really asking them to calculate what their ideal body weight is in this question versus the dose?

Rebecca Kruse-Jarres: The dose.

Donna Sullivan: But we also need to… I think what we need is a…

Rebecca Kruse-Jarres: Ideal body weight.

Donna Sullivan: Somewhere for the ideal body weight, because that's where I think the C protocol is.

Rebecca Kruse-Jarres: You're absolutely right. Yes, so that's…

Ryan Pistoresi: Correct me if I'm wrong, but is the ideal body weight going to be calculated by Sarah and then reported back? So then should that be right next to the current weight? So an actual body weight and then a separate line, which then is reported by Sarah?

Rebecca Kruse-Jarres: You can have… where it says weight in kilogram we can call this actual weight in kilogram. There you go. And then maybe right after that calculated ideal body weight. Sarah?

Sarah Roberge: I'm just wondering how the timing is going to work out. I mean are these going to be calculations that I can do beforehand, before someone needs

them? Because we talked about it before I would do it and then Rebecca would check it. So it's not going to be the type of thing where someone can just call me and say, "I need you to do it right now." Because I might not be available for one, or two Rebecca won't be able to check it.

Ryan Pistoresi: That's a great question, Sarah. Thanks for bringing that up. I suppose one thing that we should really consider is the actual flow for this protocol. So when a patient is recruited, when a patient gives the okay to be in this study and then you fill out the paperwork, do patients always get a dose when they come in? Do patients come in for other reasons than to receive a dose? Or are you expecting a patient would receive a dose on one day, then be recruited, and then at that next future prophylactic dose or any future prophylactic dose say a month from now or two months.

Rebecca Kruse-Jarres: So if we want to do it based on the weight of that day then this all needs to happen on that same day.

Amanda Blair: Would it be possible to have it designed so that you had a double check at your own location? You just needed yourself and someone else to do the calc… like to verify your calculation. That way it's not having to go to…

Rebecca Kruse-Jarres: Right. So I think… I think we can allow… because it's simple enough to do for everybody to do the calculation, but I think centrally we should double check and make sure that that calculation was actually done right.

Ryan Pistoresi: A proposed way of doing this would be to have the site calculate the ideal body weight and have it checked and then report back to Sarah for Sarah to do one final check or…

Donna Sullivan: When we're talking process, too, I'm just reading about the randomization. So it says the participant has completed the consent and eligibility forms and is able to be enrolled and the participating center will contact WCBD to receive subject ID and treatment arm assignment. So based on what Sarah just said it sounds like you're not going to necessary be able… if somebody is in for their regular appointment and needs

factor it doesn't sound like you're going to be able to enroll them and get them… and use that visit as their first PK.

Rebecca Kruse-Jarres: We talked about this yesterday, too. If we know that somebody is coming in to a clinic visit, you know, for a comprehensive visit, we know that they are coming. We kind of know that they are overweight to begin with, so they are going to be on our radar where we can say or give Sarah a heads up and say, you know, Sarah there is somebody coming in who possibly is eligible. Are you available to give us a study number and randomization? We would like to dose them that day.

Donna Sullivan: Do you have their… I mean if you have their medication record can you calculate their ideal body weight before they come in? It's not like you have to wait. If you're actually calculating ideal body weight you don't need them there if you already have their height.

Rebecca Kruse-Jarres: The weight may have changed.

Donna Sullivan: But you don't use actual weight to calculate ideal body weight, do you?

Rebecca Kruse-Jarres: You're right. We just need their height. But, you know, especially in younger patients that are still growing that is something that is also a moving target.

Donna Sullivan: I was thinking more of an adult that wouldn't be…

Rebecca Kruse-Jarres: We certainly could do that ahead of time and double check with Sarah and say this is what it is and then come up with a number and then double check so we can do the check before.

Mike Recht: I just called in.

Ryan Pistoresi: Good afternoon, Mike. We're glad you could join.

Mike Recht: Great.

Ryan Pistoresi: So Mike just to review and catch you up, we finished the review of the MED report and had one question for MED and we did have stakeholder

comment. We then went on to the protocol. There were no stakeholder comments, I believe. And we moved on from that when we were waiting for the quorum to be able to vote on it.

Donna Sullivan: We still don't have a quorum.

Ryan Pistoresi: Yeah, we're still waiting on Heidi who will be on in about five minutes. And we are looking at additional documents, which unfortunately have not been sent out to the members yet. They were printed out for the meeting in person. So…

Donna Sullivan: I'm sorry. I'm counting bodies in the room.

Ryan Pistoresi: We should be good to vote now, but Heidi will be joining us in five minutes. So we can wait for Heidi. We'll have seven members then and that will be enough.

Rebecca Kruse-Jarres: Mike, is that okay?

Mike Recht: Yeah.

Ryan Pistoresi: So Mike we will be sending out the updated version of the documents that we're currently working on and you'll be able to review them before our next meeting, which will be next Wednesday.

Mike Recht: Super.

Ryan Pistoresi: Mike, did you have any comments regarding some of the previous items either on the MED report, on the protocol or on the eligibility form?

Mike Recht: Nope, I'm good.

Ryan Pistoresi: Thank you. So I can turn it back to you, Rebecca, I believe you were making a comment on the…

Rebecca Kruse-Jarres: What was I commenting on?

Ryan Pistoresi: So we were…

Rebecca Kruse-Jarres: The ideal body weight. So we're not talking about a huge amount of patients and usually we know that those patients… there is somebody who is coming in who might be eligible and because they are coming from far away we can set things up and then approach them and give Sarah a heads up and say, "Hey there might be somebody we're going to call you about. This is typically what we do for studies anyway. Does that work for you, Sarah?

Sarah Roberge: Yeah. And so then the plan is still that you're going to double check me?

Rebecca Kruse-Jarres: Yep.

Sarah Roberge: Okay.

Donna Sullivan: So then getting back to my point though was that regardless of if you're using actual body weight or ideal body weight the dose is 50 units per kilogram.

Rebecca Kruse-Jarres: Right.

Donna Sullivan: So we don't need to put see protocol. It would be 50 units per kilogram.

Rebecca Kruse-Jarres: If we put the actual body weight like you just did, so now we have actual body weight, ideal body weight, then we can just say dose calculated. Because further up there we say whether he's receiving actual or ideal body weight.

Ryan Pistoresi: I noticed that there is a difference. Up here it says IU per kilogram and down here it says U.

Rebecca Kruse-Jarres: You can use either. I would go probably with IU because most people do and just make it consistent throughout.

Ryan Pistoresi: I think in the protocol we just used, yeah, we just U per kilogram. We can change those all to IUs. Yes.

Rebecca Kruse-Jarres: Thank you.

Amanda Blair: And then at the bottom under assay is that supposed to be OSCA instead of OCSA?

Rebecca Kruse-Jarres: OSCA.

Ryan Pistoresi: Thanks.

Rebecca Kruse-Jarres: On that form we also need some place where it is signed… or initials of who filled this out.

Woman: For the people who are going to use extended half-life products are we going to mandate that they get chromogenic assays or are we going to accept one stage for them?

Rebecca Kruse-Jarres: The problem is that, I think it's not going to be feasible to demand chromogenic because most outside labs are not going to be able to do that. So even though I would prefer that and would love that. That was the whole discussion behind initially about doing central lab testing, but that got so far away from reality that we decided we're just going to do it by… the baseline needs to be done. The baseline and the 30 minutes and hopefully the five to seven hours needs to be done locally or, you know, at the center and everything else we said can be done somewhere else.

Donna Sullivan: I think also in the PK results we should put a column for the date, as well as the time since we do expand over 24 hours.

Rebecca Kruse-Jarres: I agree.

Donna Sullivan: And then… you already have the lab name so never mind.

Ryan Pistoresi: Is it okay to put the date and time in the same column or would you like them in separate columns?

Rebecca Kruse-Jarres: Be in the same.

Ryan Pistoresi: Thank you.

Donna Sullivan: I have a question. When we have the patient here, and this is just to throw it out there, so we know when these are supposed to occur based on when the infusion finishes. Is there any… are we going to do something and give to the patient to say for those ones that can be done anywhere that you need to go and get it on this date, this date, this date at this time to give to the patient to remind them. So I'm wondering if it would help to actually put those dates and times in this table when they should occur and then write down when they actually occur. Or is that just getting too complicated?

Rebecca Kruse-Jarres: I think this is an excellent point. I think that we can come up with another form… another form to… to give to the patient and say this is the time range. This is the date for PK and whatever hour, and the next one and the next one, so the patient knows when they are expected to go back to the lab and we can document that we actually asked them to do that.

Ryan Pistoresi: So it's just a reminder?

Rebecca Kruse-Jarres: Yeah. Reminders are good.

Woman: We'll have to be careful with that form because we can't put their subject number on it.

Rebecca Kruse-Jarres: Right. So this is just for the…

Woman: What we give to them.

Rebecca Kruse-Jarres: Exactly.

Donna Sullivan: It's a reminder and I guess in a lab order, I mean, because I'm assuming if they walk into a lab they're going to need a doctor's order. So maybe it's a lab order with the dates and times on it that they can just give to the lab so that they can get their blood drawn.

Man: [inaudible]

Rebecca Kruse-Jarres: The subject information form is just for us to keep track. It's very important to know how we can contact a patient if we see the labs were not drawn to remind them. This is not going to be sent centrally because it has both the patient information and the subject ID and really… centrally we're blinded. We're just getting a number, so we're not going to know the patient's name from the site.

Mike Birmingham: Sorry.

Rebecca Kruse-Jarres: On that form… somewhere at the bottom we have to say form filled out by, and a date. Got it. Yeah, I would put it at the bottom. This is going to be filled out at different stages. One of them when the patient is coming in, when the dose is calculated, but then obviously we're going to fill in the PK results and that's not going to happen on the same day.

Ryan Pistoresi: You mentioned that this form will be completed at multiple dates. How many columns of initials do you think we would need? Just two? Or do you think one per form would be appropriate? Is it one per entry or one per protocol? Or dosing strategy, sorry.

Rebecca Kruse-Jarres: I'm thinking here right now because I think all of the labs are going to come in. There's somebody who is going to be giving the drug and then there's going to be somebody who is going to collect all the labs, the lab results and the end is going to put it in. So it's not like every single lab report is going to go in there separately or it needs a different date of entry. I think we can just do that as they are coming in.

Donna Sullivan: So it's possible that somebody… it will be a different person completing the table at the bottom with the PK results than the person that collected the information about it. So maybe put, you know, an initials for who collected the information above, calculated the dose, they initial and then maybe in the table we put a column for initial that whoever writes in that result initials that result.

Stephanie Simpson: Heidi is on the call now.

Heidi Forrester: Hi. Sorry.

Ryan Pistoresi: Hi Heidi. Welcome. To catch you up what we've done is we've reviewed the MED report, which we had a few questions and some stakeholder input. Then we went over the protocol. We had one stakeholder comment. And then we went over to the eligibility form, which we had no stakeholder comments and no discussion on. So we weren't able to vote on them because we did not have a quorum, but with you on we do have a quorum so we are able to vote on the protocol and the eligibility forms. Right now we are currently working on some additional documents that were sent yesterday and today. So I did not have the opportunity to send them out to members yet, but we will be likely reviewing them at our next meeting. So I will be able to send them out after today for you and other members to review.

Heidi Forrester: Okay. Thank you.

Ryan Pistoresi: So should we move back to the research protocol and… okay.

Rebecca Kruse-Jarres: We can vote on that and…

Ryan Pistoresi: Okay.

Rebecca Kruse-Jarres: Get the people on the phone off the phone.

Ryan Pistoresi: Right.

Heidi Forrester: Uh huh.

Donna Sullivan: I move to accept the protocol as drafted and amended.

Rebecca Kruse-Jarres: I second that.

Donna Sullivan: Everybody… any questions or comments? Okay. So everybody in favor say aye.

Group: Aye.

Donna Sullivan: Those opposed, same sign. So the motion passes.

Ryan Pistoresi: Thank you. So then we can move on to the eligibility form. So there were no changes to that. Do we have a motion to accept it as is?

Rebecca Kruse-Jarres: Motion to accept as is.

Ryan Pistoresi: Second?

Donna Sullivan: I'll second.

Ryan Pistoresi: Any further discussion? Okay.

Donna Sullivan: All in favor say aye.

Group: Aye.

Rebecca Kruse-Jarres: Anybody opposed?

Ryan Pistoresi: Okay. Those two documents have been accepted. So they will be posted online to the collaborative website. So we can actually go back to where we were to the [inaudible]. So that is actually it for the documents that we were voting on today. So if the members would like they can continue to stay on the phone; otherwise, if you need to, if you need to leave, you can drop off now. We appreciate you calling in to vote. Thank you.

Rebecca Kruse-Jarres: Thanks guys.

Heidi Forrester: You're welcome.

Ryan Pistoresi: Okay. So we are back to the PK testing form. So what I did…

Donna Sullivan: Is anybody going… are you guys going to be remaining on the phone? We just want to know if we can disconnect the conference line or should we keep on?

Mike Recht: I'd be happy to stay on. I can stay on for about another hour and a half.

Donna Sullivan: Okay.

Heidi Forrester: I can stay on for a little while longer, as well.

Donna Sullivan: Just let us know when you're dropping off. Thank you.

Mike Recht: Okay.

Ryan Pistoresi: So Mike and Heidi on the phone, unfortunately you don't have the documents in front of you so it may be a little hard to follow, but right now the only other things that we have are these three documents and then planning from now until future meetings. So what we would be discussing then.

Heidi Forrester: Okay. No problem.

Ryan Pistoresi: Thank you.

Rebecca Kruse-Jarres: Mike?

Mike Recht: Yes. Which Mike? Mike Recht?

Rebecca Kruse-Jarres: Yes. That's right. Stephanie is going to send you a picture of the form we're discussing right now.

Mike Recht: Great. Perfect. That will be perfect.

Rebecca Kruse-Jarres: We're just discussing the PK testing form, which is to document the calculations, the body weight, and the PK results.

Sarah Roberge: I think you should keep the form completed at the bottom because someone needs to sign off when it's actually all done. That all those columns are filled out. So maybe instead of putting… just keep that one at the bottom and then at the very top it says visit PK1 or 2 and date. You could put initials there, too, in case whoever does all that is different from people down below.

Rebecca Kruse-Jarres: I would not put it by the visit, but maybe by the dose calculation and by the factor given.

Ryan Pistoresi: Where was the factor given? The actual dose given?

Rebecca Kruse-Jarres: Actual dose given and the time. So the actual dose given, time infusion started and the… all those together should be initialed.

Donna Sullivan: I think what we could do is underneath the blank put like time and then slash initials. Under that, as well as like the dose calculation, you know, you could put weight/initials. So that on each blank whoever calculated… made the calculation initials it. Whoever calculates the dose initials it at each point in time and that way I guess you have more control over who did what.

Rebecca Kruse-Jarres: Where you are right now you can also say just dose administered by.

Ryan Pistoresi: Does that look adequate?

Rebecca Kruse-Jarres: After the calculation we still don't have initials.

Ryan Pistoresi: So you want initials after each one of these columns? So this whole section?

Rebecca Kruse-Jarres: No, just the dose calculation/initials. Exactly. Just to show who did the math.

Ryan Pistoresi: And I'll be making this look prettier before the next meeting.

Sarah Roberge: Maybe instead of having four lines for the notes down below, too, you could remove two of them to… because people like one-page forms. Otherwise if that little bit goes on the second page it might not get filled out.

Ryan Pistoresi: I agree and will do all the formatting to make sure that it is one page when I send it out for review next week. Any further discussion on this item or we can move on to the next?

Rebecca Kruse-Jarres: Then we're just left with the adverse event form. Right?

Ryan Pistoresi: That is correct.

Rebecca Kruse-Jarres: I think this is a very standard form that we see in studies all the time that Sarah was nice enough to put together. I mean that's just how it is usually reported. Any problems with that? I know that there is really not much of an intervention, but…

Sarah Roberge: I think maybe now that we've kind of agreed on the title we can just remove the bleeding disorder collaborative study part. We don't need it.

Ryan Pistoresi: Okay. That has been removed. I do have a question and that is regarding if a patient happens to have four adverse events. Would they then have just an additional form where it would have that notification?

Rebecca Kruse-Jarres: I would rather keep it going with four, five, six, seven.

Ryan Pistoresi: I am thinking that, you know, if something happens at the first time and then at an additional time.

Sarah Roberge: We can add another column there too if you want, if it fits.

Ryan Pistoresi: I think we can maybe carry this over and have this be potentially a two-sided one or because we did remove that title we can shrink this box down.

Rebecca Kruse-Jarres: You can shrink the next box down, too. That doesn't have to be a 12 point font.

Amanda Blair: Are there any guidelines about timing for adverse events? Is it going to be… just whether… in the… doing the PKs? Is that in the protocol?

Rebecca Kruse-Jarres: I don't know that we have it.

Amanda Blair: During the month between the two PK studies. And what are they supposed to call us with?

Ryan Pistoresi: So it looks like the timing was not addressed in the protocol and it was to be addressed here on this form.

Rebecca Kruse-Jarres: I think adverse events usually just get reported at… I don't even know that there is a time for that. Serious adverse events should be reported within 24 hours.

Amanda Blair: But if like they do their first PK study and then a month later they do their second one, if something happens to them in that month between are we going to have them report that? Are they going to report a bleed as an adverse event?

Rebecca Kruse-Jarres: I think that the only adverse events that should be reported would be during the PK. Or the washout before. So it's really for…

Donna Sullivan: Because we're not… the measure or the outcome of the study we're not looking at whether or not they… the ideal bodyweight versus actual bodyweight prevented a bleed in between. We're not powered to measure that. We could collect that information, but there's not much we could say to it as far as the subgroup analysis.

Rebecca Kruse-Jarres: I discussed that… Sarah and I discussed that yesterday, too. It would be nice information to have, but that's definitely not powered for it and it is a completely different study. So we have our primary outcome is strictly PK and not clinical. So I'm not even sure that, you know, I guess if somebody has a bleed it's going to be an adverse event, but not as particularly a category bleed. So on this adverse event form do we then have to specify serious adverse event to be reported within 24 hours or…

Ryan Pistoresi: I think it would be a good idea to have that on the form because if there is a serious adverse event and they are filling it out then that reminder would be on there for them to contact and report back.

Sarah Roberge: Should it say within 24 hours of them finding that out? Because it might not be… a patient doesn't tell them within 24 hours it's not going to be…

Rebecca Kruse-Jarres: Have patient reporting.

Donna Sullivan: I'm confused. So within 24… the adverse event happens within 24 hours of the infusion.

Rebecca Kruse-Jarres: A serious adverse event, not standard usually needs to be reported to the… centrally…

Donna Sullivan: Got it.

Rebecca Kruse-Jarres: Within 24 hours of the patient reporting it to the site. And that's only serious adverse events.

Ryan Pistoresi: Does the statement at the bottom… is that adequate? Are there any other changes or any other amendments that you want to make to this document or any of the previous three documents at this time? I think it would be good to send this out so that the members who aren't here or that currently see this will be able to review that and we can probably vote on this, you know, as early as next meeting.

Rebecca Kruse-Jarres: That would be great. If you could just make them look a little more uniform.

Ryan Pistoresi: I can certainly do that.

Rebecca Kruse-Jarres: The titles always…

Ryan Pistoresi: Yeah. Right. We want to make sure it's consistent. Okay. So with that that's actually really all that we had planned for today. The last item was to discuss what we will be doing for future meetings and so, you know, that's going to be just a very general open discussion. I actually don't think we need to have any more in-person meetings because from this point forward with the protocol we will probably just be focusing more on actually administering the research rather than trying to do this coordination. The next steps for me was I will be finishing up the draft for the legislative report and that will go out to internal review within HCA first before it goes out to external review, but in that process you'll be able to have your chance to review that report and provide any comments on it. And so that is actually going to be probably taking up some of our time in later June and early July. So just giving you a heads up for that. Otherwise, you know, the bleeding disorder collaborative

does not necessarily need to meet unless there are specific topics that members would like to discuss moving forward.

Donna Sullivan: We still will have to come up with the final guideline recommendation and implementation rollout plan for whatever we decide. So we might have future meetings, but I believe at least the August meeting will be cancelled. We will be cancelling the in-person meeting.

Rebecca Kruse-Jarres: I agree with that because I think we need to do the research first and then at that point, when we're done with it, I think it would be important to have an in-person meeting.

Ryan Pistoresi: Correct. So we'll probably look at an in-person meeting in early 2017 once everything is completed and we have all our information and we can prepare the analyses. So right now it's just going to be as needed. So there probably will be a few more meetings once we get all these forms and once everyone has coordinated and we begin enrolling patients or subjects into this study. So it's going to be a lot lighter than what it has currently been.

Donna Sullivan: And do we still need to meet weekly?

Rebecca Kruse-Jarres: I would say for right now let's keep it weekly until we see how things are going. If there are questions that arise early on in the clinical trial just to make sure we can always cancel them if we see things are running smoothly and we can say, "Well, let's skip next week."

Donna Sullivan: So Monday mornings maybe we will have Ryan send out an email to the members on Monday seeing if there is anything we need to discuss and then Tuesday we'll send out an email whether or not we'll be holding the meeting on Wednesday morning.

Rebecca Kruse-Jarres: I don't think that we're going to have to have it weekly, but let's just keep it on the schedule for now and cancel as needed.

Ryan Pistoresi: I think it's easier to have a schedule where everything is weekly and then to cancel it as needed rather than having to make an emergency meeting. So we can currently keep the structure as we recently repurposed a few

weeks ago and then just cancel the meetings if we don't have anything to discuss.

Rebecca Kruse-Jarres: I think it's going to be important in keeping us on track with making sure that we deliver this on time.

Ryan Pistoresi: I think it would be a good idea to have that consistent schedule so that way we do have a time, you know, set away that we can meet. Great. So I don't have anything else to add unless other members have, we could adjourn early.

All right. So that's it. Great. I appreciate you all coming out today. We were able to get a lot done. And we will be seeing you next Wednesday where we will be reviewing these three documents and any other items that members would like to discuss.

Mike Recht: Great. Thanks everybody. Sorry I couldn't be there.

Donna Sullivan: Bye, bye.

Ryan Pistoresi: Thank you, Mike.