"Children's Oncology Group Protocol ASCT0631: A Phase III Randomized Trial of Granulocyte Colony Stimulating Factor (G-CSF) Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source in Matched Sibling Donor Transplantation."

Pediatric Advisory Committee

Tuesday, December 9, 2008

The Legacy Hotel & Meeting Centre

1775 Rockville Pike, Rockville, MD 20852

Pediatric Advisory Committee Meeting Roster:

Marsha D. Rappley, M.D., Chair, Expertise: Developmental and Behavioral Pediatrics, College of Human Medicine, Dean's Office, Michigan State University, East Lansing, Michigan

Carlos Pena, PhD., M.S., Executive Secretary, Senior Science Policy Analyst, Office of Science and Health Coordination, Rockville, Maryland

Carl D'Angio, M.D., Expertise: Pediatrics, Neonatology, Associate Professor of Pediatrics, University of Rochester, Rochester, New York

Keith Kocis, M.D., M.S., Expertise: Pediatric Critical Care, Cardiology, Professor of Pediatrics & Biomedical Engineering (Adjunct), Fellowship Director, PCCM, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Amy J. Celento, Expertise: Patient Family Representative, Nutley, New Jersey

Daniel Notterman, M.D., Expertise: Clinical Microbiology, Professor of Pediatrics, UMDNJ-RWJ Medical School, New Brunswick, New Jersey

Avital Cnaan, Ph.D., M.S., Expertise:

Statistics, Director, Multi-Center Studies Section, Center for Clinical and Community Research, Children's National Medical Center, Washington, DC

Geoffrey L. Rosenthal, M.D., Ph.D., Expertise: Pediatric Cardiology, Director of Training, Research, and Inpatient Medicine, Pediatric and Congenital Heart Center, Children's Hospital, Cleveland Clinic Foundation, Cleveland, Ohio

Brahm Goldstein, M.D., Expertise: Pediatrics, Industry Representative, Princeton, New Jersey

Melissa Maria Hudson, M.D., Expertise: Hematology/Oncology, Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee

Elaine Vining, Expertise: Consumer Representative, Silver Spring, Maryland

Also Present:

Jeffrey Botkin, M.D., M.P.H., Acting Chair, Pediatric Ethics Subcommittee

Diane Murphy, M.D.

Jerry Menikoff, M.D.

Robert M. Nelson, M.D.

P R O C E E D I N G S

[Convened at 3:35 p.m.]

Dr. Rappley: -- people would please take their seats. We'd like to get started. Thank you.

We'd like to convene the Pediatric Advisory Committee. And I would like to begin as we usually do, with introductions and say hello again to everybody we've met recently. So, thanks to everyone on the group for coming back out again for this important subject. Dr. Cnaan, would you like to start? And please tell us your name and your area of expertise.

Dr. Cnaan: Avital Cnaan, Biostatistics, Children's National Medical Center.

Dr. D'Angio: Carl D'Angio. I'm a Neonatologist at the University of Rochester.

Dr. Goldstein: Brahm Goldstein. I'm a Pediatric Critical Care Physician. I'm the pharmaceutical representative.

Dr. Kocis: Keith Kocis from the University of North Carolina on Chapel Hill. And I'm a Pediatric Cardiologist and Intensivist.

Dr. Botkin: Jeff Botkin. I'm General Pediatrician, Associate VP for Research Integrity at the University of Utah.

Dr. Rappley: Marsha Rappley. I am Chair. And my area is developmental and behavioral pediatrics.

Dr. Pena: Carlos Pena, Senior Science Policy Analyst in the Office of Science and Exec. Sec. to the Pediatric Advisory Committee.

Ms. Vining: Elaine Vining. I'm the consumer rep. for the Pediatric Advisory Committee.

Dr. Rosenthal: Geoff Rosenthal. I'm a Pediatric Cardiologist and an Epidemiologist.

Dr. Hudson: Melissa Hudson. I'm a Pediatric Oncologist at St. Jude Children's Research Hospital.

Ms. Celento: Amy Celento, Patient Representative to Pediatric Advisory Committee.

Dr. Nelson: Skip Nelson. I'm the Pediatric Ethicist with the Office of Pediatric Therapeutics.

Dr. Menikoff: Jerry Menikoff, Director of

Office for Human Research Protections.

Dr. Murphy: Diane Murphy, Pediatrician, and Director of the Office of Pediatric Therapeutics at the FDA.

Dr. Rappley: And Dr. Pena?

Dr. Pena: Good afternoon to members of the Pediatric Advisory Committee, members of the public, and FDA staff. Welcome to this meeting. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made part of the public record.

Today the Pediatric Advisory Committee will hear and discuss the recommendation of the Pediatric Ethics Subcommittee from its meeting today, December 9, 2008, regarding a referral by an institutional review board of a clinical investigation that involves both an FDA-regulated product and research involving children as subjects that is supported by HHS.

The clinical investigation is entitled "Children's Oncology Group Protocol ASCT0631: A Phase III Randomized Trial of Granulocyte Colony

Stimulating Factor (G-CSF) Stimulated Bone Marrow versus Conventional Bone Marrow as a Stem Cell Source in Matched Sibling Donor Transplantation." Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that committee participants do not have financial interests that represent a potential for conflict of interest at this meeting.

In the event that discussions involve any other products or firms not already on the agenda for which a participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

We note that Ms. Amy Celento is participating as the Pediatric Healthcare Representative; Ms. Elaine Vining is participating as the Consumer Representative; and Dr. Brahm Goldstein is participating as the non-voting industry representative acting on behalf of regulated industry. With respect to all other participants, we

ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they wish to comment upon.

We have an open public comment period scheduled for 4:00 p.m. today. I would just remind everyone to turn on your microphones when you speak so that they -- that the transcriber can pick everything up, and turn them off when you're not speaking. I'd also ask all attendees to turn their phones to silent mode and Blackberries to silent mode. Thank you.

Dr. Rappley: Dr. Nelson.

Dr. Nelson: Yeah. I'd like to just put up one slide that I used for the Ethics Subcommittee Meeting, and then I'll --

So, first of all, about the process, I might say, this is the fourth one of these reviews that had been done since the Pediatric Advisory Committee was chartered for this purpose. And I'm not going to show you the charter; you can see that on the website. I will say, though, this is the very first one where we've done both meetings in one day.

And I appreciate everyone's willingness to come in. Having had the prior meeting set up for tomorrow and the next day, that's the reason we linked it to that meeting so that we could get you here a little bit early to then consider this protocol.

I mention that as well since you'll see the report of the Ethics Subcommittee findings, and as you can imagine, the PowerPoint slides are not the usual -- I mean, they're excellent given Ed Bartlett's work on them as we were talking, but they're not the usual, sort of, polished style you might see from a federal government product. But it'll be pretty good for basically 20 minutes of work.

So let me talk briefly about the process. I mean, the particular protocol that you are discussing and that the Ethics Subcommittee discussed at more length during the course of the day, is both HHS funded and FDA regulated and is such is being conducted under a joint review process. And this slide, which actually is courtesy of Kevin Prohaska, formally of OHRP and now at FDA, but not involved in

the process, he sent me this process slide which I dressed up, shows you where the Ethics Subcommittee and the Advisory Committee sit. So as you look there, you see the Expert Panel Ethics Subcommittee with public comment. There is also public comment period now. Goes to the Advisory Committee. The Advisory Committee basically attaches its assessment to the Ethics Subcommittee Report, which then goes with our office's assessment to the Commissioner. That packet then goes to OHRP, again, via our office. OHRP then takes those three documents, adds a fourth document -- their assessment -- which then goes to the Secretary who makes a decision, hopefully in a timely manner. And then that comes back to OHRP who then works with the funding agency, in this case, NCI. The IRB is involved as well as the principle investigators and grantees that are involved in this protocol. So that's the overall process.

So we here are to look at the Ethics Subcommittee recommendations to discuss them. The Advisory Committee is certainly able to make any additions or suggestions or deletions to those

recommendations, and then hopefully by the end of today we'll have a game plan for moving forward.

I'm happy to entertain any questions before Jeff comes up to gives slides he's never seen before. So --

Dr. Murphy: Skip, you might just say to them what you said to the Peds Ethics Committee, though. I know that there were more people from IRBs there that might have been tempted --

Dr. Nelson: Oh, no. Yeah. You're not an IRB. You're making recommendations to the Commissioner and to the Secretary, which is part of your charter. But the hope is to stay -- if there's something important, get it on the table, but if it's just sort of nickel and diming consent form language, we'll rely on the individuals who are capable of doing that as well as we are to take care of those kinds of details. Okay.

Dr. Rappley: Thank you very much. And now, Dr. Jeffrey Botkin is Chair of the Pediatrics Ethics Subcommittee, and he will present to us a summary of their deliberations this morning

(inaudible).

Dr. Botkin: I'm sure they'll be terrific. Now, my understanding is that folks have basically the same background that our Ethics Subcommittee had in terms of all the materials, and folks are familiar with the protocol under the discussion, et cetera, because we're not going to be talking about that. We did have a nice opportunity to hear from a number of experts in the field about some of the background science involved as well as an opportunity to ask questions about risks associated with the protocol benefits, et cetera.

So, let's see what this slide that's remarkably wordy says. So, discuss a general question of the ethics of sibling bone marrow donation in a clinical setting. So these are kids who, of course, have been enrolled by virtue of clinical indication for bone marrow transplant for a sibling, and the research intervention is the G-CSF administration to those children with the hope that that'll enhance the quality of the bone marrow that's being acquired for transplantation.

So among the issues considered: (1) whether or not a third party should be involved and advocate for the potential donor; (2) whether justification for parental discretion and the decision to permit bone marrow donation from one sibling to another is based on any purported benefit whether considered direct or indirect to the donor, or on the absence of significant risk or serious harm.

The Ethics Subcommittee also touched on a question of precedent and the relationship of recommendations made during the course of the deliberations today and future protocols involving healthy siblings as bone marrow donors. So I think one of the things we were cognizant of as we had, what I think was a terrific discussion, is the fact that there haven't been very many 407 procedures and so relatively few opportunities to work through these issues in this kind of context and provide opinions from our group, and then subsequently your group, that might provide guidance to investigators out there as they struggle with the same kinds of definitions that we were looking at today, things

like conditions and direct benefit, et cetera.

So much of our discussion was focused on issues that, to some extent, became moot. So we decided fairly quickly, for example, that the donors did not have a condition. Nevertheless, we went on to discuss the other criteria under 406 as a way of trying to develop our own knowledge in these areas as well as potentially advance the field somewhat by providing some public discussion about these concepts.

So 405 issues, first of all I would say that we had some very preliminary discussion about all of the groups that were participating in the research protocol. So you'd have the recipient groups, those who were receiving bone marrow that had been stimulated with G-CSF, and those who receive bone marrow without that stimulation. Everyone is comfortable with the fact that those children were approvable under a 405 category of research.

The two groups of children who were donors -- one group who received the G-CSF stimulation, and one group who did not -- the group who did not

receive that stimulation was also approvable, we thought, probably under a 404 criteria since basically they didn't have any significant intervention beyond clinical tracking, longitudinally over time. So it was really the bone marrow donor group who received the G-CSF that raised the problematic issues that we were focusing on here; and the research intervention not being the bone marrow donation itself, but the G-CSF administration in order to enhance the bone marrow. So tried to focus our discussion on that as the research intervention.

So, prospect of direct benefit generated quite a bit of discussion. Direct benefits are those that accrue directly in a proximate manner to the donor subject or result of research participation. Focus of the research hypothesis is the effect of G-CSF on the recipient. And this is something that is being used in clinical practice now; direct benefit argument has been used. And we understood from Dr. Grupp who was participating with us today, that the group who developed the protocol had been thinking of

this as one in which it could be approved as a direct benefit to the donors as well as to the recipients. There was also some -- and that direct benefit would be hypothesized to be the improved survival of a sibling and that that would return as benefit to the donor. And the possibility of a lower bone marrow volume potentially being harvested was raised, but that's a benefit that pertains to future donors.

I'm not sure where these slides go. But I think our group then decided that direct benefit --

Dr. Nelson: At the very end there is a list of what you decided. So -- but --

Dr. Botkin: Okay.

Dr. Nelson: When you get there you may have already said everything else.

Dr. Botkin: All right. Our group did decide that this was not a context of direct benefit to the donor children, and therefore was not approvable under 405. Nevertheless, those are the considerations.

We subsequently then decided whether -- however the benefits are construed in this context,

whether they're construed as direct benefit or indirect benefit, did the benefits justify the risk. And again, did the benefits to the donor children justify the risks associated with the G-CSF administration? Lively discussion about this, no consensus. Certainly some of our committee members were quite concerned that there -- were quite uncertain as to whether the benefits would justify the risks associated with the G-CSF. So, intervention donors would not be approvable under 405 because of the lack of direct benefit.

406 issues. And I think -- I'm not sure whether the slides go here, but we also decided fairly early on that the 404 was not an acceptable or appropriate criterion either, that this administration of G-CSF to the donor kids was more than minimal risk. So we moved beyond that criterion fairly quickly.

All right. 406. This of course is the criterion in which the children have a condition but the risk is only a minor increase over minimal risk, and the information is of vital importance.

We also decided relatively quickly that the risks associated with G-CSF administration were more than a minor increase over minimal risk. That of course took 406 off the table fairly quickly. Nevertheless, we had some ongoing discussion about the other criteria necessary under the 406 category.

Our determination about whether the minor increase over minimal risk was due to some information about deaths associated with -- from ARDS associated with the administration of G-CSF. I understand from Dr. Grupp that that may not be accurate information, so we may wish, as part of your conversation, to clarify exactly what the data show with respect to the incidents, or at least circumstances of ARDS with G-CSF administration in the past.

Commonly, there are side effects associated with the condition with bone pain, fever, diarrhea, et cetera. Probability of serious side effects is unknown, probably small. But I think given the lack of good information about the risks associated with G-CSF, the consensus of the group was clearly that

this was more than a minor increase over minimal risk.

Was this a condition? Lots of good discussion here. The consensus was this was not a condition or a disorder, at least in the context of this particular protocol. The outcomes for the children, or the administration issues there, were not really addressed in the hypothesis generated for the study, per sé. HLA type not a condition, per sé. That point being raised. So just the fact that the kids are in a clinical circumstance does not in and of itself give them a condition for the purposes of a 406 determination.

And the other points here, again, I thought an appropriate point, meeting and inclusion criteria characteristic doesn't mean a child now has a condition. From my personal perspective, I felt that the protocol was one in which the status of the child as a donor was assigned to them by virtue of others, so it was a socially determined attribute that they had that wasn't their own choice, wasn't by virtue of a negative characteristic of their health in some

fashion, but was a status assigned by others, which, to me, was an important aspect of not being comfortable with assigning such as a condition.

Were the experiences reasonably commensurate with the interventions and experiences that the kids would have or could anticipate by virtue of their situation? Experience includes experience with both the procedures as well as potentially the side effects. Main side effects are bone pain and myalgia. G-CSF administration does not increase time in the hospital, was the observation. We really came to no clear consensus about whether the administration of G-CSF was a reasonably commensurate experience with the experience of children who were otherwise receiving a bone marrow donation procedure.

Vitally important knowledge. No. And again, this is wrapped up with the condition determination in that it couldn't be vitally important to their condition since we don't perceive them as having a condition. So, 406, we thought was not an appropriate set of approval criteria for this

protocol.

So, 407, is this a reasonable opportunity for generalizable knowledge in accord with sound ethical principles? The general decision was, yes, with some -- a few votes to the contrary. In general, of course, the consensus was that this research should go forward with some stipulations that we outlined. And that's our ultimate determinations.

So here were a list of our determinations. I'll try to run through those quickly. The research risks that should be considered when evaluating the inclusion of healthy sibling donors is the incremental risk of the G-CSF administration, as we try to avoid the consideration of the donation procedures themselves since the kids were going to get that anyhow.

Risks to the G-CSF administration are more than a minor increase over minimal risk, as discussed. Thus, the protocol can't be improved using 50.51, 404 or 406. There are benefits to the donor, although some panel members thought these

benefits were speculative and there's not a lot of good research on exactly what the benefits are. A lot of focus on the fact that we presume that kids will be benefited by the longer survival, for example, of the sibling or fewer side effects from chronic graft-versus-host disease, et cetera. But those experiences have not been well validated by studies.

But in any case, these are indirect benefits that require a positive effect on the bone marrow recipient. Thus, the protocol cannot be approved under 405. Donors do not have a condition, as mentioned with respect to the protocol, so, in addition to the risks of G-CSF administration, the lack of a condition means that the inclusion of healthy sibling donors cannot be approved under 406.

Again, the research represents a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting health, welfare of children. Emphasize that this is a potentially life-saving intervention for the recipients. May decrease mortality, it may substantially decrease morbidity

for those children. So it's an important health problem.

Research can be conducted in accord with sound ethical principles. With one dissenting vote assuming the following changes, as stipulated in the minute, are made to the protocol and inclusion of healthy sibling donors. And this research protocol can be approved under 407.

So, here were our stipulations. And unfortunately we didn't have a great deal of time to discuss these, and so I think obviously we'd benefit from additional discussion with this committee as well as the other findings. All donors with an increased risk of bone marrow donation, not simply high risk should be excluded. There's language in the inclusion criteria that says kids who are at high risk for complications of the G-CSF will be excluded; we thought children who are at any level of increased risk should be excluded, such as any uncontrolled infection is an exclusion criteria.

Second, each research site should appoint an independent person to function as an advocate for

the potential sibling donor. Increasingly, institutions are adopting participant advocate positions to work with research participants to help them make a decision about participation as well as to troubleshoot during the conduct of the research, and we thought someone who was focused specifically on the donor to make sure that there wasn't an inordinate balance of attention being exerted or being directed towards the recipient of the transplant, would be beneficial in this context.

There was some recommendation or stipulation made that parental informed permission, that it should clearly indicate that there is a potential life-threatening complications of the intervention. And the question was raised about ARDS, and certainly the question has been discussed extensively this morning about whether there is or is not any increased risk of leukemia from the short-term administration of G-CSF.

All things being equal was another stipulation. Preference should go to an older sibling donor. So if you had a 17-year-old sibling

and a 6-year-old sibling, each of whom were comparable matches, that the older sibling should be the preferred donor and research participant. No recommendations.

So, our vote, not in favor of the motion with all of the stipulations that I had mentioned. There were two no votes, and we had bundled together the stipulations with the general 407 approval, so we got two no votes to that. One of the no votes, the subject advocate -- the feeling was that that should not be a stipulation. That they felt that 407 was -- that it was approvable under 407, but just not with the subject advocate inclusion. And the second no vote, the committee member was not certain that the research in general was in accord with sound ethical principles, and so, voted no to an overall 407 recommendation for this protocol.

All right. Time for questions for me, or --

Dr. Rappley: So, at this point, we would open to questions for you, Dr. Botkin. And if others are experiencing this as I am, they're sort of -- we

did have all this preparation in our -- and the materials provided to us, but we're hitting your recommendations a little bit cold. So I wonder if you might allow me to repeat what I think I heard you say.

Dr. Botkin: Please. That would be great.

Dr. Rappley: And then if you can correct it as I go. And I think it's probably not possible to put them all up on the screen at the same time, so then we'll -- after we summarize them, then we'll go back and we'll take them one at a time for questions. Does that make sense to people? That way you have something visually to refer to.

Okay. So what I heard in your summary is that it was -- your group decided that there was no direct benefit to the donor to participate as a donor in this protocol, the donor who receives the G-CSF, which was always our point of question here. And that the benefit did not outweigh the risk because there was no direct benefit. But there was not consensus about those two items; is that correct?

Dr. Botkin: I would say there was

consensus that the -- whatever benefits might accrue to the donors by virtue of their receiving G-CSF was indirect, and therefore did not constitute direct benefit. Whether the benefits that those children receive, whether we considered them direct or indirect, were justified by the risks or whether the risks were justified by those benefits was a matter of much discussion and no consensus.

Dr. Rappley: A third point is that there is more than a minor increase above minimal risk in this procedure for the donor, and there was consensus on this.

Dr. Botkin: Yes. That's correct.

Dr. Rappley: Fourth is that the donors do not have a condition or a disorder which would -- by definition they do not have a condition or a disorder.

Dr. Botkin: That's right.

Dr. Rappley: Okay. And there was consensus on that.

Dr. Botkin: There was consensus, yes.

Dr. Rappley: The fifth is that the

experience of donating and receiving the G-CSF and donating the bone marrow was reasonably commensurate with other experiences in the life of a child. And there was no consensus about this.

Dr. Botkin: It would be reasonably commensurate with children who are otherwise similarly situated, would be the question. And I don't believe we came to any consensus about whether the G-CSF administration was reasonably commensurate with the experiences that the kids would otherwise get as bone marrow donors.

Dr. Rappley: So the question was, do -- there are two categories of donors. There are those who receive the G-CSF and those who don't. And so when we make a decision about is the experience reasonably commensurate, we're saying, are the two experiences for both donor groups reasonably commensurate. Is that the question, or is that the frame for the question?

Dr. Botkin: Yeah. I guess I would say the question would be framed -- and this may be the same -- as to say, does the administration of the G-CSF

itself, is that reasonably commensurate with the other experiences that kids are going to get anyhow by virtue of being bone marrow donors. And --

Dr. Rappley: Okay.

Dr. Botkin: -- I think that the -- we heard from Dr. Grupp, who felt that -- if I'm characterizing correctly -- that they were commensurate. I think others on the committee were less certain. And given the fact that this point became moot by virtue of other criteria under 406, we didn't press that conversation.

Dr. Rappley: Okay. The sixth point is that there is not vitally important knowledge to the condition of the donor obtained by virtue of participation because they don't have a condition.

Dr. Botkin: That's correct.

Dr. Rappley: A seventh point is that this is -- this research protocol is a reasonable opportunity for generalizable knowledge, and the research should go forward. And that was voted as a nine in favor and two against.

Dr. Botkin: That's correct. And with one

of those two against being based on one of the stipulations that was included as opposed to the general sense that this was approvable research that should go forward under 407. We really only had one vote that raised concerns about the approvability of the protocol itself under 407.

Dr. Rappley: So it's your interpretation of one of those no votes that it was rather about whether one of the items called a stipulation should actually belong in the recommendation category and not --

Dr. Botkin: That's correct.

Dr. Rappley: -- not a no vote to the question itself.

Dr. Botkin: Yes. That's -- and that specifically was the stipulation they were concerned about. They thought that requiring a participant advocate as part of the protocol was excessive and that that would be better made as a recommendation rather than a requirement.

Dr. Rappley: And then lastly, that the research can be conducted with sound ethical

principles. That was ten in favor and one not in favor.

Dr. Botkin: Well, we didn't take the vote quite in that sense, but we got the nine to two vote, and with --

Dr. Rappley: Nine to two.

Dr. Botkin: -- one of the two votes being yes for the 407 in general but without that one stipulation. So I think it's fair to conclude that ten participants thought that this was ethically appropriate to approve under 407.

Dr. Rappley: Okay. So that's the end of my summary. Would you say that was fairly accurate? Simplistic, and doesn't reflect all the work that went into that, I realize.

I think it's maybe worth saying as Dr. Pena reminded me, the difference between a stipulation and a recommendation. So when you all put these things in the category of stipulation, it means that each one of those has to be met in order for the research protocol to be approved. And instead of if it was a recommendation, there would be -- yes, Skip?

Dr. Nelson: I might say, since you're actually making a recommendation about a stipulation, all it is is a really, really, really, really strong recommendation. But your whole determination is a recommendation to the Commissioner, strictly speaking.

Dr. Rappley: So the role of the committee is always to make recommendations. But it is your conclusion that there are a set of stipulations that must be met in order for these to be considered approvable, in order for this protocol to be approved. That's the recommendation that you would ask us as the Pediatric Advisory Committee to take to the agency; am I correct?

Dr. Botkin: Yes.

Dr. Rappley: Okay. So given that summary, let's open for questions. Yes, Dr. Goldstein.

Dr. Goldstein: I have a few comments and then one that may be more for Dr. Grupp than for this, but then one question for the committee.

My first comment is that you had mentioned that there may need to be further study on whether

there are direct or indirect benefits to siblings who act as donors. And somehow I find that -- silly is the wrong word, but almost as strong -- and I wonder if we actually do need to study whether a sibling who has an opportunity to save another sibling's life gets benefit from that. Or the obverse, if that opportunity is taken away from them and the sibling dies, how do they react to that. Some things I wonder if we actually do need to study or not, that's just a personal comment.

My two issues, maybe for Dr. Grupp and the group, in terms of the study protocol, are that I noticed that in the safety reports for G-CSF that there is a -- again, a very rare but small incidence of splenic ruptures and also the ARDS, which I'll be interested in hearing more about if that happens, later. Because it wasn't clear to me whether or not the patients who developed ARDS were actually really, completely healthy or if they had underlying problems.

In any event, it occurred to me that when I was looking at the donor exclusion criteria that

either splenomegaly on physical examination or a history of splenic injury might be something to consider as an exclusion criteria. And similarly, assuming ARDS is actually a real complication, history of lung disease may be another one.

And then, finally, I think -- which is what I want to address, get some input from the committee -- is that as I read through the protocol and as we're -- as the stipulation recommendation is for a patient advocate outside of -- a donor advocate outside of the parent and outside of the investigator, is I don't see any mention of a DSMB or a Data Safety Monitoring Board for the recipients. And I guess my consideration would be, should there be a DSMB not just for the recipients, but should there be a separate DSMB in this case given the unknown prevalence of the complications of G-CSF in this population for the donors themselves, and should there be written stopping rules for -- if a particular complication occurs, that this study would be stopped and we would know this ahead of time. I think this is fairly commonplace in the

pharmaceutical industry and in early phase -- or all phases of research, and I wonder if that would be translatable to this protocol. I'll stop.

Dr. Rappley: Please respond.

Dr. Botkin: Quick comment about your initial concern. And I don't have any professional --

Dr. Goldstein: That was more of a personal opinion. I really don't need a --

Dr. Botkin: I'm sorry?

Dr. Goldstein: The sibling thing was sort of a personal opinion.

Dr. Botkin: Well, and I just want to reflect on it because I think it was a subject with a fair amount of discussion for us. So just to tell you where are group was coming from on that issue is, first of all, the donors are kids who are six months through 18 years or so, and so the psychological benefits from improved outcome for a sibling would obviously be potentially relevant to the older kids, less relent or entirely irrelevant to the youngest kids, perhaps until they got to an age until the

recognize the contributions they had made to a sibling.

But the other issue was folks who have more knowledge in this area presented the fact that when things don't go well for the recipient that there are adverse effects for the donors. They may feel responsible for the graft-versus-host disease and responsible for the fact that perhaps a transplant didn't go well and a sibling dies. And so, you know, there may well be benefits but there may well be significant and complicated harms associated with that whole procedure as well. And so I think a lack of a good, thorough understanding of exactly what that spectrum looks like, I think was the uncertainty that our group was feeling.

Dr. Rappley: And, Dr. Grupp, did you wish to -- are you in the audience? Yeah. Would you like to step to the microphone here and speak to the questions about ARDS and splenic rupture?

Dr. Grupp: Okay. My name is Steve Grupp. I am the Study Chair of this protocol, and I am also the Head of Stem Cell Transplantation for the

Children's Oncology Group. I'm a pediatric transplanter by trade.

So to briefly discuss your very useful questions, the incidents of splenic rupture is thought to be on the order of 1 to 10,000 in adult patients -- not patients -- in adult donors of peripheral blood stem cells. This has never been reported in pediatrics so we are unable to estimate any incidents in pediatrics.

Certainly, excluding patients with clear splenomegaly on physical exam or a prior history of splenic injury would be not inconsistent with maximizing donor safety on the protocol, isn't something that came up in our discussions but it's a very reasonable discussion.

The issue of the acute or adult respiratory distress syndrome associated with GSCF, this has been reported in a wide variety of patient populations. And there are two patients in the literature that came up in the discussion of the risks of G-CSF in the earlier meeting, and those two patients were reported in 2001 in the journal CHEST. And one of

these individuals is a 72-year-old who received G-CSF by mistake rather than receiving erythropoietin for his anemia. He developed ARDS and subsequently died. He was not a donor of either peripheral blood stem cells or marrow. So that was characterized in the meeting, I believe, incorrectly. That patient clearly had a medical condition. That patient would not have been eligible to donate peripheral blood stem cells because the maximum age for that is age 60. So I don't believe his experience is directly relevant to the risk.

The second patient who received G-CSF who experienced ARDS was a 38-year-old who was a donor of granulocytes, not of peripheral blood stem cells, so I don't see that as being a significant difference because both are for apheresis procedures, and that patient simultaneously resolved. So we're really dealing with one case, non-fatal of ARDS in an analogous, although not exactly the same, clinical situation.

So ARDS is disclosed in the current consent form. One of the stipulations is to -- of the prior

meeting, was to -- or the strong recommendations from the prior meeting was to include the statement that ARDS can be fatal, which is certainly a correct statement and we, you know, in my own mind, didn't have a problem -- I didn't have a problem with that recommendation or stipulation, of course.

Dr. Goldstein: Could you address the -- I -- the issue within the protocol or within COG about Data Safety Monitoring Boards?

Dr. Botkin: Yes. So that's a very important question. And the answer is there is a Data Safety Monitoring Board for all Phase III trials within the Children's Oncology Group. And so that board is responsible for the monitoring of both the recipient safety and severe adverse events, and the donor safety and severe adverse events on this trial. There is not a separate DSMB for the recipients. As a matter of fact, that data -- DSMB is charged with all the Children's Oncology Group Phase III trials.

Now, your comment about stopping rules I think is very well taken, but it is an enormous challenge for us in trying to figure out how to do

this. So we had a number of discussions about how you write a stopping rule on a 400-patient study for a risk that is in the, you know, 1 to 10,000 range. And we had a back and forth with the Data Safety Monitoring Board on that particular issue. And our decision was to have expedited reporting of all levels of adverse events that occur after donation for the donors on the study, whether they're on the experimental arm or on the standard arm, and that these would be reported to the DSMB and that they would have to make a decision as to the significance of these reports. Because, really, if you're talking about splenic rupture, 1 in 10,000, one event is unacceptable. So with that understanding, we decided on that process for the monitoring of donor safety.

So actually our reporting threshold for the donor events is much lower than the reporting threshold for the recipient events who are undergoing a bone marrow transplant and generally have cancer.

Dr. Goldstein: But with expedited reporting, what timeframe are you referring to? So, in other words, is there a risk that if splenic

rupture or ARDS or even a death occurs in the donor population, that somebody else could then receive G-CSF while this report was being generated?

Dr. Botkin: I would have to look at the COG process and answer that question. I would be speculating if I answered that right now.

Dr. Rappley: Dr. Cnaan.

Dr. Cnaan: So to answer the last -- the very last question, section 10.3.3.4.2 of the protocol says that -- sorry about that, it's not very far to go -- says that if there is one death in the donor population, the study is suspended and waits for the DSMB. It doesn't talk about the splenic rupture, but it does expressively talk about death. So there is already something in place.

What I wanted to ask, it seemed to me that what the donors are more at risk for, from what I read from all these materials, is a future leukemia. Because by the very nature of there being sibs, they are already, per the literature, at a somewhat higher risk for leukemia, who knows how many years later. And the question is, does the G-CSF make it worse or

not? And there were very nice numbers provided in the review materials that said that in order to detect a tenfold increase, it would take 2,000 patients over the next ten years. And this study is of the order of -- magnitude of, I think, 400; 500 patients. So I accept that we cannot answer with certainty that question.

What I would ask is, it looks like the total duration of this study, recruitment plus follow-up, gets to about six years. I wonder whether it would make sense to follow the donors even longer than that since it is done through COG, maybe to ten years out. I realize there isn't the power, but even from an exploratory standpoint, I think it'll give additional information on the G-CSF exposure. So that was my only suggestion.

Dr. Rappley: Other questions? Yes, Dr. Notterman.

Dr. Notterman: I wanted to just turn for a second to the issue of the patient advocate, because I think that it's a very useful construction. I'm concerned that the parent who is asked to give

consent is obviously and manifestly in a necessarily conflicted position vis-à-vis judging the risks and benefits to his and her two children. And therefore, I think it's quite unlikely that a parent could make a decision regarding the donor that's solely in the best interest of that child. Therefore, while I support the concept of an advocate, I would like to know if there is a possibility of better delineating the process and procedures by which an advocate is selected, and with particular reference to the qualifications of a potential advocate and to their powers with respect to providing or withholding consent.

Dr. Rappley: Dr. Hudson, can you speak to that?

Dr. Hudson: We addressed this at the earlier meeting, as well. The patient advocacy varies across institutions. We have an ombudsman, sometimes it's a social work position, sometimes it's somebody that's affiliated with IRB. But most institutions have that type of personnel in place, although they may not -- they may have a different

designation within the institution to serve as a purpose of being an independent person who is on the -- who is evaluating things from a perspective that is not affiliated with the patient or the primary -- you know, the parent.

Dr. Rappley: So do we interpret then that if this is adopted as a stipulation that every time a child would be enrolled in this protocol as a donor, the on-site advocate would be activated and be meeting with the parent to discuss this decision, or how does that work?

Dr. Hudson: If it's a stipulation of the protocol, it will have to be monitored by the protocol and there will have to be some validation in the record that this communication has occurred. And, you know, at least at our institution, it's not as formalized. That resource is available, there's this independent group that is charged with evaluating the donor medically, as well as psychosocially and emotionally.

But I think it would vary per institution, so I'm not really sure how that would be received

through COG. But, I mean, if it's mandated, it will be written in the protocol and it will be monitored and audited when they come and audit the study.

Dr. Rappley: Dr. Rosenthal.

Dr. Rosenthal: So I would say that the nuances of the role of the advocate weren't really defined in the Subcommittee meeting. But the importance of a person in such a role was agreed upon if the protocol were to move forward because of the recognition that parents are in a particularly -- parents and siblings are in a particularly leveraged position at times like this.

Dr. Rappley: Yeah.

Dr. Goldstein: If I could add to Dr. Rosenthal's comment. It's not only parents and siblings who are really necessarily conflicted here, but also the healthcare team and the physicians involved.

And so my concern is that without a fairly rigorous statement as to what we expect from an advocate, it will be a recommendation or a -- a recommendation for a stipulation with no meaning.

Because I agree with Dr. Hudson that in my experience the rigor with which these advocates or advocacy arrangements are pursued varies widely at institutions, from hospital to hospital and school to school and department to department.

So I would like to see some flesh added to this, so to speak, so that I at least am comfortable that decisions are being made at least -- not contrary to the best interest of the donor.

Dr. Rappley: Are there other questions before we move into the open hearing and further discussion? Yes, Dr. Carl.

Dr. D'Angio: Maybe this is more for the discussion, but I was interested in a little bit more of the reasoning behind the determination that these subjects didn't have a condition. It -- I don't want to quibble, but it sounds like the entire discussion pivots around a verbal quibble about what a condition is. Something is going to happen to these people -- and I'm not suggesting that this is a 406 protocol -- but something is going to happen to these people who are going to be research subjects, and the study

would allow the researchers to gain knowledge about what happened to people like them. I don't know whether that's -- it's not a disorder, I agree with that. It is a situation, whether a situation is a condition, I don't know and I'm wondering how that discussion went.

Dr. Rappley: Dr. Botkin.

Dr. Botkin: Well, it was a matter that -- first I would say, achieved relatively early consensus, much to my surprise. I thought this was going to be a long and detailed discussion about this particular issue, but it turned out not to be so. And I think the sense of -- that I had from the group was that these were healthy, average kids who happen to find themselves in a situation mostly decided by others that place them as donors. And that while you could stretch the concept of condition to cover that situation, that seemed to us to be broad a stretch. And that particularly as you looked at the other stipulations under 406 that require the research to be a valuable opportunity to ameliorate or address the condition, it's clear that the original drafters

of the regulations, as far as we were concerned, were thinking about a condition as something that negatively impacted kids' lives and that the research was designed to help address, to help rescue those kids from an unfortunate situation, as opposed to this circumstance in which their status as donors is a socially applied status, and thus not a health condition or a psychosocial condition the way we more typically think of in this context, in a research context.

Dr. D'Angio: I think -- I'm -- I'd like to hear more about that and talk more about that, but none of it's a question, so I'll wait until our discussion.

Dr. Rappley: Further questions from the committee? We had no one sign up for the open hearing segment. Is there anyone now who would like to come to the mic and give us either question or statement? So there is no one interested in speaking at the open hearing, and so we'll move on then with the discussion.

Again, given my role as the grand

summarizer here, I'm going to speak to what I heard come up in the questions, and then, of course, there are other things that you might want to bring to the discussion as well. One is that somehow either in stipulation or recommendation we suggest or recommend that in the exclusion criteria there be a specific reference to splenic problems, splenomegaly or lung disease.

The question was raised about the DSMB, and the answer was that it already follows the donors. So whether or not that needs further discussion is up to the committee.

The question of the risk of subsequent leukemia was raised, and it was recommended that the children be followed for -- the donors be followed for at least ten years.

There was suggestion and discussion about bringing more substance to the role of the advocate -- or more clarity to what the role of the advocate would be.

And then further discussion about the notion whether or not the donors have a condition.

And certainly feel free to raise other things that haven't yet been raised. So, I'd like to begin the discussion. Dr. D'Angio.

Dr. D'Angio: Okay. So I won't let go yet. I don't -- again, I don't -- I think that there are good reasons why this isn't a -- why this might not be approvable under 406, so I don't want to -- I don't want to disagree with that decision. But I worry a little bit about the precedent that since there aren't -- haven't been many 407 committee meetings as of yet, I worry a little bit about the precedent being set by saying that someone who is undergoing a medical procedure, for whatever reason they're undergoing the medical procedure, doesn't fit -- but de facto, doesn't fit 406.

And I can't -- I'm not sure I can manufacture another situation exactly like this, but here's one that has some holes in it. Somebody has a condition, a hernia, for which they're going to undergo a medical procedure that requires a certain sort of anesthesia. The anesthesia is incidental to their condition. They're undergoing the anesthesia

because they're undergoing anesthesia; you want to study what happens under that anesthesia. If the anesthesia itself isn't what we can study, but under 406, I worry that people who are being -- who are undergoing a medical procedure wouldn't fit into 406 under the definition of condition that you're describing -- that the committee described. And it -- we don't actually have to make a decision about this because this isn't a 406, but I do worry about that precedent.

Dr. Rappley: So you're worried about a precedent being set --

Dr. D'Angio: Yeah.

Dr. Rappley: -- with this as a stipulation.

Dr. D'Angio: Well, I worry about the -- I'm sure that this wasn't glossed over, but I worry about the apparent impression that could be left that undergoing a medical procedure that has risks is not itself -- that doesn't fit into he category of 406. It isn't a disorder, that's okay, but it isn't a condition -- that a situation isn't a condition. And

I'm beginning to sound like one of our former presidents, but I will stop at that point.

Dr. Rappley: Dr. Nelson.

Dr. Nelson: I guess I would say that your interpretation of -- Jeff can speak for the Subcommittee as well -- is not the way that the framing of the condition was put as a more general definition. So I wouldn't personally fear that your definition of condition was in fact the one that they were operating with. And I wouldn't necessarily fear that that would find its way in as precedent, partly because there is in fact no mechanism for any precedent being set by these as they're basically protocol-specific.

Dr. D'Angio: Okay.

Dr. Rappley: Dr. Botkin.

Dr. Botkin: Yeah, I would agree. I think that -- I think we wanted to think of the term, condition, in the context of a particular protocol. Now, I'll speak to my own opinion about this. And it seems to me you can have a circumstance in which you'd have children who were bone marrow donors.

And we can imagine that there is some negative outcome associated with having been a bone marrow donor, hypothetically. And they were going to run a research protocol that might entail more than minimal risk, but no prospect of benefit, would they have a condition in that context? I think you'd say, yeah. They had a significant medical procedure that's associated with some negative outcome; we're trying to improve that negative outcome so that it's a condition in that context.

I think in this particular context -- or in the example you used, if somebody's getting anesthesia for an appendectomy and the condition is appendicitis or something related to their -- so, in that context, I'm less concerned about this as that would -- that being a concern. I think the fact that these kids come into the protocol that includes the research intervention as well as the clinical intervention and they're being assigned a status -- healthy kids being assigned a status as a donor -- and then saying, well, now that you're a donor you have a condition, and since you have a condition we

can exert more than minimal risk. So it's kind of a double jeopardy circumstance for those kids.

Dr. D'Angio: I guess my only response to that is that they -- these children, by virtue of what is a socially-assigned situation, are going to undergo some risk. One could -- and again, this isn't the right protocol to make this argument about, but one could make the argument that these -- that we could learn about ways that would require -- ways to use G-CSF that would require fewer children to need priming for peripheral blood -- for peripheral stem cell collection, and that that might be a benefit that would eventually accrue to that class of people who are exposed to this risk.

If the risk of G-CSF itself were indeed a minor increased over -- increase over minimal risk, I would think that that would probably, in my mind, fit a 406. There are a couple things here that disqualified it, so it -- so the discussion is moot here. But I think that -- I could twist this protocol into that if the risks were a little bit different.

Dr. Rappley: Further discussion. So it is now the committee's step then to approve, modify, or delete this set of -- this one recommendation to adopt these stipulations.

So we have heard some suggestions, is there more discussion about the things that you have suggested? Dr. Notterman.

Dr. Notterman: Well, perhaps Dr. Nelson can help us get our arms around the concept of an advocate, which is a specific word. There are other words that could be used.

There are contexts in which in the course of granting consent for research, and advocate is used, or even a court-appointed guardian in some cases. Not that I'm suggesting that this be referred for adjudication. And I'd like to know if you have any thoughts, Skip, about what kind of process could be used if we decided to recommend that that would be reasonably consistent from institution to institution, and reasonably rigorous in the sense of actually forestalling this conflict that occurs in the parents desire to help one child by enrolling

another child in a research project.

Dr. Nelson: I mean, I guess I would agree that without trying to identify what you would think would be essential criteria for what someone functioning as an independent advocate ought to do, that the manner in which advocacy would be interpreted in any given context could potentially render it non-functional. Part of the difficulty is the ability to predict over what could ultimately be 70 institutions spread among 50 states, each with their own laws specific to bone marrow donation. I mean, some states -- Wisconsin, for example, has a specific law that says 12 and up you can consent for yourself, below that you need an independent advocate, which is defined as someone doing a psychological evaluation separately from that process. So, you know, I guess I'm hedging a little bit because it's a little hard, when you said that's the same across all institutions. To say it ought to be independent of the transplant team is one thing. I would be a little hesitant to say it has to go outside the institution in any kind of official, sort

of, legal advocacy venue, which would be a very strong position, because I think most of us would want to feel parents are making reasonable decisions as they try and balance this.

The other thing that's also important is that the transplant itself is really standard of care. It's the G-CSF that's kind of being added onto it. So it's not as if you had an advocate for the protocol and then someone said, well, don't go in the protocol, and that was the advocate decision. The decision to be a donor may well still stand. You know, so I think it's complex and I'd be interested in Jeff's thoughts. But I think because of that complexity, the Subcommittee hesitated to try and be more directive beyond saying that we want everybody to do this.

Dr. Botkin: I think there is not a great deal of experience, at least that I would have, and I would say others on the Ethics Subcommittee had with exactly what the functions of these type of folks are. I think the -- I can't probably speak beyond the general sense of the Subcommittee to say that

given the fact that this is an emerging and relatively common position at many institutions these days, that given the complexities of this protocol and the real need to try to support the donor side of the research enterprise with its protocol that this would be an important one to bolster the ethics of the child by including such an individual that we weren't able to get into the -- any details about exactly what the job of that person would be and other aspects of how they would relate with the family. And so I think there's a -- that's pretty non-specific and frustrating outcome, but --

Dr. Notterman: Would it make sense to -- and again, I'm -- these are questions for you folks who have thought more about this. Would it make sense to include in the recommendation that the advocate be able to participate in a meaningful way in the decision, or some such locution?

I agree that it would be burdensome to specify a specific detail process, and it would be probably burdensome to require that it be outside of the institution or that the usual process of court

appointing a guardian be used. I think that would be excessive. But we could ask that people do their best to make sure that the advocate participates in a meaningful way in the decision. And then perhaps allowing the individual institutions to decide for themselves what constitutes meaningful participation.

Dr. Goldstein: And, Dan, what about a generic comment to the effect that the advocate would act in the best interest of the donor?

Dr. Notterman: All right. That makes sense to me without thinking through all of the complexities that best interest means.

Dr. Rappley: Yes, go ahead. Can you introduce yourself, and then --

Ms. O'Lonergan: Yes. I'm Terri O'Lonergan, and I am a Research Subject Advocate. I'm actually the founding President for the Society of Research Subject Advocates. The position was generated in 2001 by NCRR as a requirement for all GCRCs. Now most of us are CTSAs. We have developed standards of practice. We've developed different guidances for our Research Subject Advocates. There

are about 125 in the United States now. They're all associated with either GCRCs or CTSAs, so there is some regional accessibility to RSAs. And our society -- I'm still on the executive board of our society -- anybody could contact us and we could find someone who would act as a Research Subject Advocate. And we could also guide them in the correct -- or the proper way to go about advocacy. And most Pediatric Research Subject Advocates see themselves as both advocates for research, given the state of pediatric research, and the family, and then the particular child. So if that's helpful.

Dr. Rappley: Thank you. Any discussion from Ms. Celento and Ms. Vining?

Ms. Vining: I think that what we've been -- I think it's been captured pretty fully with the discussions, the comments by Dr. Botkin and Dr. Skip Nelson. I don't have anything to add.

Dr. Rappley: Thanks. Just wanted to make sure.

Ms. Celento: I don't have anything additional either.

Dr. Rappley: Dr. Grupp, would you like to add something?

Dr. Grupp: So I would just like to -- I personally don't have an issue with the discussion on the use of a patient advocate in this situation.

I'd just like to offer two observations. The first is that the research on the protocol, of course, has been very clearly pointed out, is the application or non-application of G-CSF to the patient. The -- I would say if now speaking not as the Study Chair of the protocol but as a pediatric transplanter, that the significant decision before the family is to un -- is for their other child, the donor sibling, to undergo the donor procedure. And that, truly, the -- if we look at the entire package, the risk, to the extent there is any risk -- and there is a small risk associated with bone marrow donation; that's indisputable -- and the discomfort associated with the procedure, are really all loaded on the standard of care part of this and not on the research part of this.

So, you know, when I'm called upon to

operationalize the patient advocate, I have to keep in my own mind this distinction between the research, where really I feel that the potential for coercion is extraordinarily small, especially since the finding of the prior committee was that there was no potential for direct benefit to the donor.

So I think the issue is really for the -- in front of the parents is the issue to proceed with the transplant. And having done these informed consent discussions, the reality is that although we discuss this issue, we don't spend all of our time talking about five shots of G-CSF, we really talk about the issue of transplantation, both from the going to the O.R. for the donor, and for of course the very significant experience that the recipient goes through. So just sort of trying to separate that in our own mind.

And then the other issue in terms of operationalizing this is that, you know, as a physician, what I actually see the area where I potentially conflicted, is in medical clearance of the donor, because of course, I want the procedure to

proceed because I'm an advocate for the recipient. And so the way a lot of institutions have operationalized that is to have a physician outside the transplant team do the medical clearance of the donor. And so that's just -- I just want to offer that as another potential area where -- that we might be able to do that.

Dr. Rappley: Thank you. Okay. Dr. Notterman and then Dr. D'Angio.

Dr. Notterman: And just with reference to the preceding comment by Dr. Grupp, I do want to point out that although -- that it's the purview of this committee, or the reason for this discussion, has to do specifically with G-CSF, and so that's the precedent that we're setting, taking into account your comments and acknowledging your comments that the more important aspect of the decision that the parents may be facing is the decision to have the sibling participate in the donor process at all. I understand that. But what this committee has to -- has been asked to look at is the issue of G-CSF and the possible minimal risk associated with that and

the precedents that flow from that. And so that's the reason that I have brought up the issue of enhancing or specifying the role of the advocate, even though, in this particular case, it may be a very small role.

Dr. Rappley: Dr. D'Angio.

Dr. D'Angio: I just wanted to -- it struck me as Dr. Grupp was speaking, that he makes a very good argument for the research -- for the subject advocate because there is a risk that in the hurly-burly of all of the big decisions, that the specific research decision would end up being subsumed as, oh, yeah, well we'll do that, too, without it necessarily having a lot of independent thought because there are so many other very big decisions that are being made at this same time. So I think that's actually a very strong argument for having someone whose job it is is to think about this little sliver of what's going on.

Dr. Rappley: Dr. Nelson.

Dr. Nelson: A question about the recommendation of extending the follow-up from six to ten years; I know you haven't decided whether you'll

follow that or not, but a factual question, in the prior meeting we heard about the linking of donor follow up to a program called RDSafe, which was funded through the -- going to be done through the National Bone Marrow Donor Registry. And I'm just wondering what the length of follow-up for that program is. Is it six years or is it longer?

Dr. Rappley: Dr. Grupp, you can speak to that.

Dr. Grupp: So the proposal is ten years. Now, that is a separate study, and the patients must consent to the separate study. And even in the context of our study, they must consent to follow-up within the context of our study. So they can opt out of this. But it is true that within our protocol we had proposed five years of follow-up, and RDSafe, which has now been funded by the NIH, proposes ten.

Dr. Rappley: Thank you. Dr. Cnaan.

Dr. Cnaan: So that's actually great additional information. Just for clarity, I think six years is the total duration of this study. So the first patient will indeed be followed for -- or

first donor -- will indeed be followed for six years. But according to the projections, the last donor will only be followed for two years. And we can all calculate that probably the mean follow up would be somewhere in the three-and-a-half years range.

Dr. Nelson: The reason I asked the question is I didn't know it was ten, but I knew it was longer than that, and so given the linkage between this study with RDSafe with the consent -- which, I think we would probably argue is important -- that I think the follow-up does end up being ten years outside of this study since everyone who is donating will be offered that follow up.

Dr. Rappley: So on the screen then are the four stipulations. We can move to accept that as a recommendation to the agency, unmodified. And then we can list again our three additional recommendations, and we can see if you -- if we agree on that. Is there a consensus about these four stipulations? Dr. Notterman.

Dr. Notterman: If I could ask -- just ask, Dr. Rappley. So agreeing to the second stipulation

with respect to the individual -- independent person would not preclude our further discussing enhancing that in a few minutes.

Dr. Rappley: We could right now -- I mean, I would accept your comment then as a suggestion to modify the second stipulation and to provide some language -- something to the effect that the advocate should participate in the decision in a meaningful way, acting on behalf of the donor.

Dr. Notterman: And would it be possible or appropriate to reference perhaps documents that this organization of RSAs has promulgated that we heard about. I'm not familiar with them, and so -- and I don't know if any of the FDA staff is familiar with them, but it would be nice to actually include a reference that would help the individual hospitals and investigators make an appropriate referral.

Dr. Rappley: Dr. Cnaan wanted to speak to that specifically, and then Dr. Nelson.

Dr. Cnaan: The RSAs is a wonderful organization, having been involved in both GCRC and CTSA. However, they are limited to institutions that

have a GCRC, which are being phased out, or a CTSA. Maybe Dr. Grupp could tell us whether all of the participating institutions have that or not. But if not, we'd be creating a sort of impossible situation.

Dr. Rappley: Yes, please.

Ms. O'Lonergan: The standard operating procedures are available through the SRA -- SRSA website. So that could be one easy access. And all the members are listed, and all their contact information are listed. And many of the RSAs fulfill their role outside of the CTRC, as well, especially in the CTSA as we're trying to sort of spread ourselves further out in the institution. So those are a couple contacts.

Dr. Rappley: So we could -- oh, Dr. Nelson.

Dr. Nelson: I was just going to say, there was some discussion at the Ethics Subcommittee about alternative mechanisms that may exist in institutions that don't have subject advocates. And I might point out that the way the subject advocate role has been institutionalized in different settings has not been

consistent. So you're not getting a consistent product to say that the research subject advocate should be involved in all institutions. So I wouldn't want you to labor under that misimpression.

Dr. Rappley: Dr. Grupp, did you have something to add?

Dr. Grupp: Yeah. I just wanted to answer Dr. Cnaan's question. So there are 80 transplant institutions within the Children's Oncology Group, and although each of them is capable of reading the SOPs, there's no question about that, that there is not a CTSA or a GCRC at each of those institutions.

Dr. Rappley: Thank you. So currently then, do we have the four stipulations and one suggested modification to the second bullet? Is there any further discussion about that modification? Is there anyone who would object to that modification? You want me to read it again? Okay.

So the stipulation as it is stated on the screen: Each research site should appoint an independent person to function as an advocate for the potential sibling donor. The advocate should

participate in the decision in a meaningful way on acting in behalf of the donor -- on behalf of the donor.

Dr. Notterman: We might want to add, just to address some of the concerns Dr. Grupp mentioned, that the participation of the advocate is with respect to the research questions, not the standard of care. So in this case, the participation of the advocate would be with respect to the use of G-CSF.

Dr. Rappley: So I will state the sentence again then. That the advocate should participate in the research decision in a meaningful way acting on behalf of the donor. Got that, Dr. Pena?

Dr. Pena: (Speaking off microphone).

Dr. Rappley: Okay. And so is there anyone who would object to adopting that modification of the second stipulation? Are there suggestions for the other three? Dr. Nelson.

Dr. Nelson: Just for clarity. There was one that's consistent with the first stipulation that was brought up earlier relative to the issue of splenomegaly and splenic injury and history of lung

injury. So my question is whether to that first stipulation you would want to provide that modification or not.

Dr. Rappley: Right. We could modify that first bullet; we could provide it as a separate bullet. It would make sense, I think, because we're talking about risk in that bullet. I think that's a point well-taken. Dr. Notterman.

Dr. Notterman: Just in terms of the language, we should probably refer to active or recent pulmonary condition, cover things like asthma, lung infections. I wouldn't limit it because we don't really understand the antecedents to the risk for lung injury.

Dr. Rappley: So that statement then, the first stipulation, could be modified: any increased risk for participation in this research, including splenic injury, splenomegaly, active or current lung --

Dr. Notterman: Active or recent.

Dr. Rappley: -- active or recent lung condition.

Dr. Notterman: Pulmonary condition.

Dr. Rappley: Pulmonary condition. I'd like to raise a question then as from my previous life as a general pediatrician. Lots of kids have asthma, lots of kids carry a diagnosis of asthma that may or not be accurate. It seems to me that we would be pretty close to excluding 10 percent of the possible donor pool, or greater, if we aren't careful in how we word this. Other thoughts about that? Dr. Cnaan.

Dr. Cnaan: You would be excluding them from this study; you're still not excluding them from being a donor.

Dr. Rappley: Dr. Kocis.

Dr. Kocis: You know, as I sit here and try to bundle a couple things -- and hopefully this will be helpful and not more confusing -- but there was some discussion about having a pediatrician outside the transplant team being involved, focus like a laser on the donor child, and to be able to make that assessment of increased risk, you know, I think to spell out everything, we'll probably leave out some

things and overstate other aspects. But I think if we could have that first stipulation be by a physician -- and now maybe that physician could be an advocate -- and I'm not -- I don't want to necessarily require for point number two that that independent person be an independent physician, but in fact that could be the case. And it may be convenient to do that.

Dr. Rappley: But I'm not sure -- to me that kind of confuses medical clearance and advocacy. They seem like two different roles. But I do see how, perhaps in the first bullet, we might suggest, recommend, or require that the decision about exclusion be made by a physician who is outside of the research protocol.

Dr. Kocis: And I would simply say -- and I don't want to say that that independent person would be a physician, but they could be a physician. And I would say that certainly as a pediatrician, that's a large part of what we do for advocacy. So I wouldn't negate that as being a possibility.

And then just two other things that come up

with more later, I'm not sure where they fit into the stipulations and stuff, but the DSMB, I'd like to know more about that, when they're convening. And this sense of two DSMBs is important to me, not that it couldn't be done by one independent committee, but the typical, obviously, fatal outcomes or serious outcomes will be evaluated in a timely fashion. Generally, DSMBs convene at enrollment numbers, more driven by statistical time points or what -- and I think for the DSMB for the donor, I would like that to function under its own timeframe. And in fact, it may be -- and I don't know if this is logistically possible, you know, on a case-by-case basis, to then role -- to allow the next donor to enroll. I want to think a little bit more about that. I don't know the criteria for convening the DSMB for the recipient.

But -- and then the death criteria as the only criteria for stopping, seemed to be also limited. And I think if we have a good DSMB, then that would -- should be fine for stopping.

Dr. Rappley: Dr. Goldstein.

Dr. Goldstein: I think as Dr. Cnaan

pointed out earlier, I think the last two comments you were making about the DSMB, I think actually are adequately addressed in 10.3.3.4.

And in terms of your prior comment, I think there's two different functions. One is comments on the exclusion criteria, which are different than medical -- than providing medical clearance. Somebody who provides medical clearance is judging whether or not the inclusion and exclusion criteria have been met. We're talk -- we're -- that's separate from stating what they actually ought to be, which is what this recommendation is.

And I would -- I don't vote, but I would agree with Dr. Rappley's comments that it would just be easier to expand the first bullet point. And medical clearance is really a separate issue.

Dr. Rappley: Yes, Dr. Botkin.

Dr. Botkin: Just a quick comment. I think (inaudible) that instigated this first bullet, it's on page 22 of the protocol, and basically it's about donor exclusion criteria. It's 3.2.5.3: donors who are found to be high risk for bone marrow donation

due to pre-existing medical condition. So, obviously the concern was the, you know, why just high risk? So this is intended to address that. And I don't think we thought through the complexities of kids who might be a conceivable risk but yet there is no data to -- for example, asthma. Does asthma create risk? If -- you know, if the answer is, we don't know, I don't think we intended to say all those kids have to be excluded. So there may be some language issues here that need massaging.

Dr. Rappley: Dr. Notterman.

Dr. Notterman: I think your comment, and also yours, Dr. Rappley, are correct. We don't want to draw the exclusions potentially so broadly that at different institutions we are preventing meaningful participation, even in the small research aspect of this. So I like the idea of just parsing that under the idea of having a physician outside of the study designate this individual as having minimal risk, based on his or her professional judgment, taking into account the available literature.

Dr. Rappley: So would then a modification

-- the first sentence of the first bullet: All donors with any increased risks for bone marrow donation not simply high risk should be excluded as determined by a physician who is not a member of the protocol or transplantation team.

Dr. Notterman: And I would add, it's perhaps unnecessary taking into account the current medical literature.

Dr. Botkin: Perhaps a saying --

Dr. Rappley: We hope they would do that, right?

Dr. Notterman: We hope they would, but --

Dr. Botkin: Any known risk of -- yeah.

Dr. Rappley: Further discussion? Dr. D'Angio?

Dr. D'Angio: Something about the first bullet just hit me. I wonder whether we're -- we would be guilty ourselves of the mix-up that we have been worried about with the study itself. The risk that we're concerned about is not the -- is not somebody who is an increased risk from bone marrow donation -- which may be a very reasonable exclusion

criterion for other reasons -- but the risk of G-CSF.

Dr. Rappley: Right. Right.

Dr. D'Angio: And I wonder whether --

Dr. Rappley: We should maybe specify that. So --

Dr. D'Angio: -- that -- whether this bullet should talk about that rather than about risk -- increased risk for bone marrow donation. That's not a research risk in this case unless --

Dr. Rappley: So --

Dr. D'Angio: -- the investigators could tell us that G-CSF would increase the bone marrow donation risk itself.

Dr. Rappley: So it could be modified to: All donors with any increased risk for bone marrow donation and stimulation with G-CSF as determined by a physician who is not part of the research protocol.

Dr. D'Angio: Bone marrow donation following stimulation with G-CSF. Not and; it's not and. It's the G-CSF that I think is the issue, maybe I'm wrong. Maybe I'm misinterpreting.

Dr. Botkin: Well, I think part of the

problem is in the protocol, half the kids will be randomized to a no-G-CSF group. And would we be comfortable saying that it's okay for them to be at high risk of -- or moderate risk of adverse outcomes from bone marrow transplant.

Dr. D'Angio: I'm not sure that -- yeah, I'm not sure that's the same question. The investigators are excluding subjects who are at high risk from the bone marrow donation. Donating your bone marrow isn't part of this protocol. It is part of this protocol, but it's not the experimental question in this protocol. The experimental question in this protocol is getting the G-CSF. So unless you're at increased -- unless being in the study increases your risk, there's not -- I'm not sure there's a reason to exclude someone.

Dr. Rappley: So you would just like to be certain that the stipulation applies to the research arm of this, which is stimulation with G-CSF.

Dr. D'Angio: Right. Right.

Dr. Rappley: Okay.

Dr. D'Angio: And, yes, half the people

won't be at that risk, but that's what we're trying to protect them against. Not the risk of bone marrow donation, that's a separate thing --

Dr. Rappley: Because that's a broader decision that's made before even --

Dr. D'Angio: Yes.

Dr. Rappley: -- the decision about G-CSF.

Dr. D'Angio: That decision is already made by the time.

Dr. Rappley: Dr. Goldstein.

Dr. Goldstein: Well, I agree and I disagree. There already are donor exclusion criteria on page 22 of the protocol. What we're suggesting is to add additional specific exclusion criteria for G-CSF stimulated donors.

Dr. Rappley: Correct.

Dr. D'Angio: And we're saying the same thing.

Unknown: Right.

Dr. Rappley: Dr. Nelson.

Dr. Nelson: I think in the discussion of the Ethics Subcommittee, perhaps by putting these two

together we did confuse a little bit of those issues between the risk of bone marrow donation, per sé, and then the increased risk relative to G-CSF administration, because the second point is clearly related to the theoretical discussion of ARDS, which is the whole reason the discussion of pulmonary infection -- which actually is -- that would be redundant if you generalized that to other recent conditions.

But I will say, I don't think it would be entirely accurate to say that the Ethics Subcommittee didn't think that children at high risk for bone marrow donation independent of the G-CSF shouldn't all -- that that might be too high a bar for the exclusion from transplantation. But, I mean, I'd be interested in Jeff's thoughts about whether that was parsed out as cleanly and as clearly as it could be.

Dr. Nelson: No, it wasn't by the committee. So I'm only probably representing what my thinking was as we discussed this. And I guess the kids are recruited into the study and then randomized, and kids in the study will include

children who don't get the G-CSF. And I would say that it would be not adequately protective of the human subjects to allow that -- to kids to be randomized to even the non-G-CSF arm who are at high risk for bone marrow transplantation. Even though they're not getting the experimental intervention, they're still in the study. And so I think it protects those kids simply just to include --for all of the children enrolled in the study to say if they're at high risk for adverse impacts, then that would -- that language should be changed.

Dr. Goldstein: They actually are not in the study. They are screened and they're excluded already. So we're suggesting just adding additional exclusion criteria to screen and exclude G-CSF-stimulated -- patients who may receive G-CSF-stimulated bone marrow.

Dr. Botkin: That's correct. The kids who are at high risk are excluded. I think what we're concerned about is kids, say, that are at moderate risk. And should they continue on in this study and be randomized to either receive G-CSF -- and I think

the Ethics Subcommittee wanted to say, no, those kids ought to be excluded, too. Now, would we be in a position to exclude them from the clinical intervention? No. But in terms of inclusion in this study as part of the randomized group that's going to be followed longitudinally, perhaps, yes.

Dr. Rappley: Dr. Notterman then Dr. D'Angio.

Dr. Notterman: So just to make sure I understand this. I'm referring now to section 3.2.5, donor exclusion criteria. Dr. Botkin drew our attention to this. This pertains to donors in their -- to all donors -- and it makes no reference to specific issues pertaining to G-CSF. There's no mention, as you said, of splenic injury, of previous lung injury. There's no section in this protocol that particularly pertains to G-CSF.

Unknown Male: Right.

Dr. Notterman: I'm correct in that. To excluding patients, I mean, for G-CSF. So I agree that this first stipulation then becomes a bit ambiguous, and perhaps we're even over-reaching into

standard of care territory and not limiting our comments to the research question.

Now, you know, perhaps we want to do that explicitly and say, well, by virtue of presenting this protocol for review, we are going to reach into what could arguably be standard of care. And that argument is sometimes made that we owe more to research subjects by virtue of their presentation, but I think we should be explicit about that if we're going to do it. Otherwise we should just stipulate that the G-CSF -- I think we should just limit our comments, our stipulations to the use of G-CSF, in my opinion.

Dr. Rappley: Dr. D'Angio then Dr. Cnaan.

Dr. D'Angio: All right. I promise this is the last time I'll weigh in on this. I agree with Dr. Notterman that -- I'm not -- the other piece of that is I'm not sure that even if you said that anyone who is at any increased risk for bone marrow shouldn't be in the protocol, that we've actually improved the protection of anyone from risk, because those people will go on and donate bone marrow

exactly the same way that they would have if they could be included in the protocol.

So I'm not sure that setting the bar to be in the research lower for the -- to setting the qualifications for bone marrow donation lower improves anybody's safety because those kids are going to go on and donate bone marrow anyhow.

What we, I think, need to be concerned with beyond what the investigators already have in the protocol, is their exclusion for donating bone marrow, is that we need to ask them to be specific about whether anybody needs to be excluded on the basis of donating bone marrow after G-CSF.

Dr. Rappley: Dr. Cnaan.

Dr. Cnaan: I agree with Dr. D'Angio. I think we are doing almost exactly what Dr. Nelson warned us not to do. I think we are being -- maybe we're not becoming the IRB but we are becoming the protocol committee some couple of years later, and I don't think that's our charge. In looking how clear section 3.2.5 is, I would second, or third, I guess, the suggestion that in the stipulation we restrict

our comments to adding inclusion criteria that relate to the G-CSF and not go back to the exclusion criteria of the bone marrow.

Dr. Rappley: Dr. Nelson.

Dr. Nelson: Just let me ask a question of clarification. If one divided that first stipulation into two sentences and took away the, for example, which implies the second part is related to the first part -- which may or may not be true -- the second part was proposed as much as a specific issue relative to the complications of G-CSF. So if you did that and then you added to it the splenomegaly and splenic injury, and then the active or recent pulmonary infection all related to G-CSF, my question is -- not that that's what you're going to do, but if you did that -- what would that do to that first sentence? And -- which then still stands alone, and was in fact in the context, I think, influenced a bit by the overall risk benefit of going into being a bone marrow donor. Do you want to simply resolve that procedurally with this independent physician and be done with it, or would you do anything else around

that language of increased -- any increased risk versus high risk?

Dr. Rappley: Dr. Hudson.

Dr. Hudson: Well, my -- you want to clarify that they are at increased risk for adverse reaction to G-CSF? You want to be more specific with the statement?

Dr. Nelson: I'm just asking what you'd like to do because that's -- that was what the Ethics Subcommittee put forward. And so in the cover letter that Dr. Rappley is going to put with the Ethics Subcommittee report, I'd just like some clarity about what would be suggested as an alternative if you're not happy with that language.

Dr. Rappley: Well, I would interpret that as a result of your long discussion and review, you feel that the first sentence there should stand. That we should not modify that first sent -- well, you -- I mean, you -- you made that -- your committee believes that should be a stipulation. We might further add as a second sentence, for those donors who are in the treatment arm to receive the G-CSF,

exclusion criteria should include splenic injury, splenomegaly, recent lung infection -- recent lung --

Dr. Nelson: Well, the realty is it's a randomized trial. I mean, you're not going to exclude people after randomization, so you can't let them go into --

Dr. Rappley: Okay.

Dr. Nelson: -- the trial and then drop them out because it's --

Dr. Rappley: Right.

Dr. Nelson: -- your intention to treat (inaudible), I presume, statisticians. So --

Dr. Rappley: So it does have to occur at the level of which they are --

Dr. Nelson: Yeah. Yeah.

Dr. Rappley: -- first randomized.

Dr. Nelson: Right. Right.

Dr. Rappley: So it's not really correct thinking that this is a second step. I mean, this is an exclusion that must occur in the first step.

Dr. Nelson: Right.

Dr. D'Angio: Just -- and to be very

specific in my answer, what would I do with the first sentence? I would remove it because I don't agree with it. I think that the investigators have established their inclusion/exclusion criteria and that the question that came to us doesn't have to do with deciding who should donate bone marrow.

Dr. Rappley: Well, but --

Dr. D'Angio: And that's my opinion.

Dr. Rappley: Well, but what I read there on that -- in that first bullet is the committee decided that the current language is high risk, and that that notion should be expanded and not applied simply to high risk but that consideration should be given to children at moderate risk.

Dr. D'Angio: Moderate risk for bone marrow donation following G-CSF, or just --

Dr. Rappley: No, I think we --

Dr. D'Angio: -- moderate risk for --

Dr. Rappley: I just heard from Dr. Nelson that that decision has to be made at the level of which the randomization occurs, therefore, it would be made without regard to G-CSF.

Dr. D'Angio: That's a little bit of a different interpretation then. They -- you need to know if someone would be at risk for -- sorry?

Dr. Goldstein: You can't know upon entry.

Dr. D'Angio: If I'm going to randomize somebody to two groups and one of the groups has a risk that has -- that -- I'm going to randomize two groups of people with asthma to two medications, and one of the medications might make somebody's asthma worse, somebody with asthma can't enter that study.

Dr. Rappley: Correct.

Dr. D'Angio: Right.

Dr. Rappley: Right.

Dr. D'Angio: But that has to do with the medication, it doesn't have to do with the asthma. In this case, bone marrow donation is the -- is -- the bone marrow donation decision is already made.

Dr. Rappley: No, I think -- I think Dr. Nelson -- I interpreted what he said as that at the point of randomization to give bone marrow.

Dr. Goldstein: -- groups, you're randomizing one group to two.

Dr. D'Angio: I understand that.

Dr. Goldstein: You're only using one group to treatment arms.

Dr. D'Angio: But the only thing that matters is whether they're at risk --

Dr. Nelson: Having created the confusion, let me see if I -- if -- you know, there is a decision that's been made that transplantation is the appropriate response to the leukemia that this particular child has in the context of receiving hemotherapy, independent of whether it's on this protocol or not on this protocol. So that's the clinical decision.

The research component of this protocol itself is the G-CSF. And all of the various issues have been raised about complications of G-CSF, is -- all of the specificities related to that. All I'm saying, and it's not that you necessarily have to agree with it, is I think on the subcommittee there was ambiguity about whether or not the intent was to take that first sentence and apply it to the entire decision or not. And if you think that it really

ought to only be applied to the research decision, meaning, you know, you've decided a transplant is appropriate, let's talk about this protocol. And it's that point at which then the issue of the risk of G-CSF, I mean, et cetera. You know, I want to get back to Dan's suggestion about an independent evaluation by a physician of that risk. That's -- that provides, in my mind, some clarity around the nature of the recommendation around risk.

All I'm saying is that the -- I don't think in the Ethics Subcommittee discussion that that was clearly teased apart. So --

Dr. Rappley: Dr. Notterman and then Dr. Kocis.

Dr. Notterman: Thank you. I'm concerned that we not intrude into -- certainly into the clinical aspects of this and the standard of care aspects, but that we also don't intrude into the conduct of this research study beyond the question we've been asked. If it turns out that by virtue of limiting our comments of risk assessment to G-CSF, it perturbs the mechanism or the interpretation of

randomization because this intrusion might occur after randomization, that's a problem for the study designers to deal with in the way they want to. It's not -- it doesn't mean that we should expand the scope of our stipulation to include bone marrow in general. So I feel we should limit our stipulation to the research question in this study, which is G-CSF, and let the study designers and the investigators handle the consequences that flow from that.

Dr. Rappley: Dr. Kocis.

Dr. Kocis: Yeah. I'm going to disagree on -- in a setting that this study, the research study to enter this protocol, it's not just a G-CSF protocol. In other words, we can develop protocols in normal, healthy children or adults and we're randomizing the received drug and drug alone. This is receiving drug followed by bone marrow transplant -- excuse me -- bone marrow donation, excuse me.

We don't know what the impact of giving G-CSF to a donor will be with its interactions with anesthesia or with the bone marrow itself, et cetera,

et cetera. To enter the protocol you have to go through both steps, and I don't think we can isolate ourself (sic) to just the aspect of the drug. As much as that's paramount, we need to look at it in the context of what will follow, and it's drug followed by a donation. And that donation, by the way, follows through standards of care to clinical practice with regards to how you are going to put that child to sleep and follow them, and et cetera, et cetera. And so I don't think you can tease those two things out.

Dr. Rappley: Dr. Cnaan.

Dr. Cnaan: I think there is a little bit -- some confusion here still. I think this is one of the first protocols, if not the first -- maybe one of the first that in a bone marrow transplant context, makes the donors subjects of the research. Mostly, it's the recipients who have been the subjects of the research. So I think at this point, the issue of who can donate bone marrow has been studied well enough to come up with this donor exclusion criteria. So I support at least the notion of we not get into this

and that we limit our additional exclusion criteria to the additional increased risk of G-CSF, that at the time the patient and family sign consent, they don't -- or assent, whatever the setup is -- they don't know whether they will receive G-CSF or not. So I think that's -- we need to limit ourselves to that. The rest of it is beyond what we were asked and I think beyond our scope.

Dr. Rappley: So what I'm not clear about then, Dr. Cnaan, is do you feel that that first bullet is beyond the scope of the committee as it is currently on the screen?

Dr. Cnaan: No, I actually -- Dr. Nelson's separation of the first bullet into two pieces really helped. I think I disagree with the first sentence, and I would like to exclude it. And I think I would take the second part and just list the couple of potential adverse outcomes of G-CSF that are right now not in the exclusion criteria. That's all.

Dr. Rappley: And then how does the committee's -- the sense that I hear from the Subcommittee that they wanted to move beyond high

risk and to capture moderate risk as well, how is that noted in a stipulation or a recommendation if we eliminate the first sentence?

Dr. Nelson: Well, I guess I would -- what I would suggest you say in your cover letter would be something along the lines of, the advisory committee felt it appropriate to limit its exclusion criteria to those issues that are specific to the research question, which is the administration of G-CSF. Now that still doesn't get at what might then be a procedural way to get both issues, which is the suggestion of -- actually raised by Dr. Grupp, of -- the issue of conflict in the investigator from the standpoint of medical clearance of the donor, which is -- was raised, and I think mentioned by others, and whether that procedural approach then gets at the first bullet point independently of changing the risk language. Because, frankly, IRBs don't know what minimal, moderate, minor, high, low might mean, and so that -- all of those terms are subject to a variety of interpretations. So I would -- even if you made that division and said we'd like to limit

our exclusion criteria to the G-CSF administration, the issue of independent assessment of medical risk for bone marrow donation is still, I think, an open question.

Dr. Murphy: And, Skip, again, when the Committee's recommendations go forward, it will include the Subcommittee's -- I know we -- that this language said delete. You're -- we would not delete anything.

Dr. Nelson: No.

Dr. Murphy: Okay.

Dr. Nelson: The Subcommittee's report stays intact.

Dr. Murphy: Yes. Yes.

Dr. Nelson: Then you write a cover letter saying, no, we'd want to modify that. So it's a separate report. And then on top of that is a third cover letter generated by us -- me. And then that goes to OHRP, which generates their own assessment, which ultimately goes to the Secretary. So the Secretary gets three to four documents.

Dr. Murphy: Yeah, the word delete is

really --

Dr. Nelson: Yeah.

Dr. Murphy: -- not appropriate.

Dr. Nelson: So -- yeah.

Dr. Murphy: Okay.

Dr. Nelson: So it'll be an independent document.

Dr. Rappley: Dr. Notterman.

Dr. Notterman: So perhaps taking all this into account we can not delete anything but have our own recommendation, which is all donors with increased risk for G-CSF administration prior to bone marrow donation as judged by an independent medical evaluation should be excluded. Potential risks currently described in the literature include splenic -- prior splenic injury or existing splenomegaly, a neoplastic disease -- right? Which I guess would get them out anyway. Recent pulmonary disease and other conditions based on the judgment of the independent observer, or independent physician -- something like that, and leave it at that.

Dr. Rappley: Okay. Then your suggestion

is that we add as a separate bullet -- I'm going to just restate what you said -- all donors for increased risk -- all donors at increased risk for receiving G-CSF as judged by an independent evaluator should be excluded for risk factors such as -- that -- such as splenic injury, recent or active pulmonary infection.

Dr. Notterman: Well, I wouldn't say pulmonary -- I'm sorry -- pulmonary infection, because --

Dr. Rappley: Condition. Right. I'm sorry.

Dr. Notterman: -- ARDS or ALI is not an infection.

Dr. Rappley: Right. Right. Condition.

Dr. Notterman: But we should really -- I like the idea of really emphasizing the independent physician's professional judgment and not being too specific with risks because I think that that's hard for IRBs and other folks to understand.

And then in our recommendation, or your cover letter, however it's put, I, after that, would

leave out stipulation -- the original stipulation, one, because I think it's no longer relevant. That whole business about bone marrow.

Dr. Rappley: Dr. Kocis.

Dr. Kocis: My only point was, he said G-CSF administration followed by bone marrow. That was excluding yours.

Dr. Rappley: So there is a suggestion then that we add that language as a bullet. It would be the second bullet then. And then there's an additional suggestion that we recommend eliminating the first bullet; is that true? Does somebody wish to make that -- I've heard at least two people suggest that, perhaps three.

Dr. D'Angio: I think we just heard that these -- that this stands, and what we say is, we as the whole Committee disagree with the first recommendation. And we -- and our recommendation would be blocked, which you've just stated, instead of that. Am I correct in --

Dr. Rappley: Right. I'm not sure --

Dr. D'Angio: -- (inaudible) --

Dr. Rappley: I'm not sure that we have to say we disagree. I mean, I think we --

Dr. D'Angio: That we --

Dr. Rappley: -- our language could be --

Dr. D'Angio: Whatever nice words --

Dr. Rappley: -- that we -- that we felt that --

Dr. Hudson: Just have it state that you -- just have it state that you suggest the statement, the first bullet, be modified so that the first bullet is going to focus on excluding individuals who are at high risk for an adverse event associated with G-CSF, not with the bone marrow procedure.

Dr. Nelson: I'm fine with the sense of what needs to be written in that cover letter, basically limit the scope with the first recommendation to the risks of G-CSF administration. I mean, it's fairly straightforward.

Dr. Notterman: That's one element, and --

Dr. Nelson: And with the independent physician assessment --

Dr. Notterman: -- the second is -- right.

Dr. Nelson: -- of that, which is fairly straightforward, secondly. I will say, I mean, when you write exclusion/inclusion criteria, you're going to have to be a little more specific than just saying whatever that physician decides. But, I mean, I think we have some general sense of how that might be framed.

Dr. Notterman: But is that our -- is it our job to delimit the --

Dr. Nelson: It might be the protocol people's job --

Dr. Notterman: Right.

Dr. Nelson: -- to (inaudible).

Dr. Notterman: Right.

Dr. Nelson: I'm not saying it's necessarily our job, and that's -- we'll try to craft language that provides appropriate direction and some flexibility.

Dr. D'Angio: Okay. And I agree with that part of it very strongly. It might not be a good idea for neonatologist to tell the oncologist how to write their protocol.

Dr. Rappley: So then we have -- we will -- so here are the suggestions as they stand. That we include language in our cover letter that says we chose our recommendation -- we suggested our recommendation should focus on those children who are in the arm to receive the G-CSF. No, no, no, take that back, take that back. Our recommendation should focus on the administration of G-CSF. We'll make it better.

That the first stipulation then will be modified by addition of the second bullet, which we read earlier, about all donors at increased risk for G-CSF followed by bone marrow donation as judged by an independent physician should be excluded. Such risk factors might include -- and then we described those, too.

We modified the language of the second bullet making it somewhat stronger by adding the language about participation in a meaningful way, which I think was already noted.

Then are we fine with keeping the last two bullets? Okay. So are people clear then about what

we just recommended? Dr. Notterman.

Dr. Notterman: Can you just say it one more time from the top?

Dr. Rappley: So we will include language in the cover letter that we feel it was our purview to focus on the donors who would be receiving G-CSF.

And then the stipulations would be that the first bullet would stand, and a second bullet would be added. And it would say: All donors at increased risk for G-CSF followed by bone marrow donation as judged by an independent physician should be excluded. Such risks might include splenic injury, splenomegaly, recent or current pulmonary condition. Dr. Cnaan.

Dr. Cnaan: Our focus is not on the donors who receive G-CSF because we don't know that up front. It goes back to the randomization. Our focus is on the risk aspects associated with the G-CSF administration in this context. That's all.

Dr. Rappley: Okay. Risk aspects associated with G-CSF. You got that? Dr. D'Angio.

Dr. D'Angio: I'm sorry. Could I ask Skip

a question? If the majority of the group doesn't -- in a nice way -- doesn't agree with the first bullet in the Subcommittee's report, Dr. Rappley is suggesting that our reporting -- that our cover letter include that, as well. I'm -- does our cover letter need to recapitulate everything that's in your report, or does our cover letter say that we suggest that the first stipulation focus on -- solely on the -- focus on G-CSF, that the second stipulation be modified to say -- does the second stipulation add da-da-da-da-da, and we accept the second and third?

Dr. Nelson: Since the number of previous protocols are three, the confidence (inaudible) around how you should proceed obviously is quite wide from a statistical perspective.

In the past, what has been done is generally the Ethics Subcommittee Report is on the order of four or five pages, it's longer because we throw a lot of stuff at the beginning. And the Advisory Committee cover letter has been on the order of two and has not -- you know, those things that you agree with -- you know, so it would be a supplement

to, it would not alter the Ethics Subcommittee Report, given the integrity of that process to maintain transparency, but would say why it is you decided to deviate from those recommendations and then how you would modify them. And then that would -- as I said, we would put a cover letter together that would then go to the Commissioner.

Dr. Rappley: I actually would not support removing that first bullet. So it wouldn't be a consensus statement. And the reason -- and I don't mean that that that should -- that my vote should count more than anybody else's. But the reason why I say that is I have serious concern about rejecting a statement that I think comes from a very long and careful process that actually says we should not limit ourselves to just considering high risk; we should also include those that -- at a lower-risk category. And I think to throw -- to eliminate that from consideration -- I would want to support that rather than eliminate that.

Dr. D'Angio: Okay. Then -- we've been talking at cross-purposes because I disagree with

that, and that's okay, I get my vote.

Dr. Nelson: Then I would suggest as you walk through these -- I mean, the Ethics Subcommittee lumped and then split, you could decide if you want to split and then lump. But however you want to go through it, it'd be appropriate to capture those differences because those differences inform our transmission of these recommendations.

Dr. Rappley: Correct. Speaking from the Office of Pediatric Therapeutics, right?

Dr. Nelson: Correct.

Dr. Rappley: Dr. Notterman.

Dr. Notterman: So I'm afraid I'm a little confused, although I've tried diligently to follow this conversation. We as -- if we present different recommendations, if our recommendations differ, particularly if they differ materially from the Subcommittee's recommendations, then that implies that we disagreed, or at least didn't want to support the Subcommittee's recommendations. So I think it's irrelevant whether you actually say that.

Now, taking that into account, however, if

as the Chair of this committee you write a letter that records what we feel, then I don't think you -- and perhaps I misunderstood you -- I don't think you can say in the -- in your role as the letter writer something different than we've actually decided.

Dr. Rappley: No, you're correct. Yeah. No, I would call for a vote on that. And would portray it then in the -- in our -- so, for example, they relayed -- the Subcommittee relayed to us that these stipulations were adopted by the Subcommittee with a vote of nine in favor and two opposed. And if we could -- if we were to say, how many people would support eliminating the first bullet, how many don't support, I mean, it might be -- I might be the only one not supporting it, and that would be reflected.

Dr. Notterman: That's fine. That's perfectly accurate then. Thank you.

Dr. Rappley: Dr. Goldstein.

Dr. Goldstein: Just pointing out from a pragmatic standpoint that there is no defined difference between increased and high, so all of this conversation when it gets down to an interpretation

probably doesn't matter.

Dr. Rappley: Well, I interpret it -- their inclusion in parentheses to make some point, and the point --

Dr. Goldstein: I --

Dr. Rappley: -- there being made is that there's just more than high risk. I --

Dr. Goldstein: -- I understand. But I understand that you can't --

Dr. Rappley: -- I don't know, maybe I didn't understand.

Dr. Goldstein: -- if you can't -- if you can't measure it, it doesn't matter.

Dr. Rappley: That's a discussion for --

Dr. Goldstein: But that's my own --

Dr. Rappley: -- those who write protocol language.

Dr. Notterman: So can I ask that we -- one more time, just summarize what we as this committee are going to recommend, and then perhaps it'll be appropriate to have a vote, if you would.

Dr. Rappley: So, yes. Chip. Sorry, Skip.

Dr. Nelson: Well I'd be happy to read what I've got just so that --

Dr. Rappley: Thank you.

Dr. Nelson: -- since this is in the computer and will become the text, with Carlos's additions and your additions. But I've got three things at this point that I've heard as what I'm interpreting as stipulations not just recommendations, meaning this is what you would recommend strongly go forward. First is a modification to that first bullet point dividing it into two with the first one being rewritten to say: All donors at increased risk for bone marrow donation following G-CSF administration as determined by an independent physician should be excluded. So, you know, what you've done is you've divided that and then limited it to G-CSF and said that that's not just a broad decision. Now, procedurally, there's a lot of institutions that have an independent process to evaluate donor medical, but I don't know if that's true universally among all institutions. Separate question.

So the second one then becomes sort of a factual question. The risks of G-CSF include, which informs the first one, the presence of an uncontrolled infection as an exclusion criteria should be (inaudible) to any child with an active infection, especially pulmonary.

And then the donor exclusion criteria relative to the risks of G-CSF administration would also include splenomegaly and a history of splenic injury, as well as an active or recent pulmonary condition. So that's then the second point.

And then the third point is modified to say, as was already read: Each research side should appoint an independent person to function as an advocate for a potential sibling donor. The advocate should participate in the research decision in a meaningful way, acting on behalf of the potential sibling donor.

And then the last two stand. So, you know, I interpret the first one as a narrowing and focusing, and the second two as certainly consistent with the other recommendations. And whether -- I

honestly don't think the Ethics Subcommittee dove down deeply enough to be able to say whether that first point is even a disagreement or not, to be honest with you. Is that fair, Jeff?

Dr. Botkin: Yeah, that's fair. This group has spent far more time than we did thinking about these particular stipulations. And so I think it's hard to say what the original Ethics Committee would -- Subcommittee would say about this discussion.

Dr. Rappley: But we started with stipulations, you ended with them, so we had more time to fiddle with them.

So what Skip just read to us, is there support for that as our set of recommendations?

Dr. Notterman: I move we adopt them.

Dr. Rappley: Okay. Second that? Or, no, we have comment. Dr. Kocis.

Dr. Kocis: I just want to add one other -- I re-read the DSMB thing, I still don't think that it's adequate for the donor arm of this. And so my only addition to that would be to strengthen the safety monitoring of the donor who may or may not be

randomized to receive G-CSF.

Dr. Rappley: So you would like to add then, a recommendation that we strengthen the monitoring and the data safety monitoring of the donor.

Dr. Kocis: Right. And that's the 10.3.3.4.1; and tied into that also ties into the follow-up duration, which, again, I'm confused. Is it two years, is it six years, is it going to be ten years? And those were just clarifying points.

Dr. Rappley: Well, I think we've gotten the information that they'll all be offered to participate in the ten-year study.

Dr. Kocis: I'm just troubled by that, though. You know, offered is different than we're mandating it and following up, because --

Dr. Rappley: I think it was clear that they can't -- that that's a research protocol itself, and people can opt to not participate.

Dr. Kocis: Right. And my point would be that I would require follow-up of significant duration. And if the standard is now ten years, I

would recommend that that -- I would advocate for ten years being the standard for this protocol, and not allowing them to opt out and potentially only be followed up for two years, if that's how the math works out.

Dr. Grupp: Just very quickly. On the DSMB thing, let me just -- since I'm actually going to have to operationalize this, is the issue speed of reporting and you want that clarified, or what exactly is the request?

Dr. Kocis: Sure. You know, certainly with fatalities, all DSMBs would be notified. I'm not worried about that. I'm worried about the language there in the 4.3, which is focusing just on pain. And I think, as we've discussed, there's a lot of other things that may play into it and I think needs to be accounted for, to be followed. And it goes back to the incremental increase in risk to future donors as they make their decisions. So, you know, while we've talked about what you know about G-CSF administration and the bone pain, et cetera, et cetera, I think that there's -- what we don't know so

well about these patients, and I think that we should learn. And that should then go and potentially be modified as future donors, as families and children are making those decisions about whether they're going to participate in that or not. I just don't think it's a strong -- and then certainly the follow-up is very important to me.

DR. GRUPP: Well, I totally agree that the follow-up is important. But I will say, in the two-and-a-half-year process of discussing this, at no point were we ever in a position to believe that it would be appropriate to coerce people to participate in a research protocol. And at every point in the discussion and at every point in the review, the clear consensus was that we had to offer the people -- folks the opportunity to opt out of follow-up.

Dr. Rappley: Okay. I think, really, that -- I mean, we can add a recommendation that we feel there should be long-term monitoring, and then that can be incorporated as appropriate to the research protocol.

Dr. Nelson: But I think it does raise

significant consent issues. So I can't imagine that one would go forward with a requirement to participate in long-term follow-up. I'm unaware of any research study that's ever had that format.

Dr. Rappley: And I'm not sure we should use the word requirement. I mean, I think --

Dr. Kocis: I guess I'm confused by this whole second follow-up mandate. I'm just simply saying, for patients in this protocol, that a two-year follow up given what has been expressed about the concern for the development of malignancies, is inadequate for this protocol. And again, I'm confused on the overlap of another protocol, and, blah, blah, blah. What I'm suggesting is that if the standard for these sorts of long-term follow ups are ten years, or whatever the standard is -- I don't for this for a living so I don't know what it is -- I'd say two years is inadequate; six years, I believe is in adequate. And based on some of the concerns about the number of patients you need to enroll over so many years, the decade issue, that number ten, to me -- and without going in to all the numbers -- seems

like a reasonable number. But that should be in this protocol and not requiring you to be part of another protocol that you have to consent to or not.

Dr. Rappley: Dr. Nelson.

Dr. Nelson: Just procedurally. At least the institutions I'm familiar with, have a bundled follow-up protocol where all of the intervention protocols often stop at two, three, four, or five years, and then everyone rolls over into that follow-up protocol. Given that, you know, you then have a single protocol that follows all of those individuals in a fairly standard way. Some of that's related to funding sources, some of that's -- a lot of complex reasons for that. So --

Dr. Rappley: But -- so we could just make a recommendation that there would be a long-term, ten year follow up --

Dr. Nelson: Right.

Dr. Rappley: -- of those donors. And --

Dr. Murphy: Yeah, I think that --

Dr. Rappley: -- then it would be up to the protocol and to the committees to decide how to do

that.

Dr. Nelson: I think you're drilling down a little bit too much into the procedural details around that. I think with the RDSafe, frankly, they've already got it. But that's, you know, a separate issue.

Dr. Murphy: I was just going to say the same thing. All you guys need to do is make a recommendation, if it's consensus, that you need longer than two-year follow up, and it needs to be offered -- the longer period needs to be offered.

Dr. Rappley: So that --`

Dr. Murphy: Which means it has to be in place to be (inaudible) offered.

Dr. Rappley: And that would be an additional bullet then to what you just read, that the committee would recommend long-term follow up for those donors.

Dr. Nelson: Well since I think that already exists, whether you -- I mean, whether it's a fact or whether it's a stipulation or recommendation, and since the RDSafe is ten years, it already exists.

It's not clear to me, unless you're just not sure is there, that --

Dr. Rappley: How about if we say we support the long-term follow ups?

Dr. Nelson: Yeah. I mean, it's --

Dr. Rappley: So then you can understand that it's --

Dr. Nelson: Yeah.

Dr. Rappley: -- important to the committee.

Dr. Nelson: Right. I'm still not clear about how one might strengthen the safety monitoring of the donor, so -- by just saying to strengthen it doesn't give us anything concrete. Is the issue that they should have other stopping rules besides death? And then what would you pick as a stopping rule?

Dr. Rappley: Dr. Cnaan.

Dr. Cnaan: I think that if we want to strengthen those, that's the only way. Just like there are several stopping rules for the recipients, we -- if we want to suggest that, we have to be just a little bit more specific. What is it about? Are

we saying that if we see one splenic event, we want to suspend just like for a death event? Is that the idea? I'm not making any particular suggestion; I'm just saying I'm agreeing with Dr. Nelson that leaving it totally vague, without specific one or two additional stopping rules doesn't help much.

Dr. Rappley: So, Dr. Nelson, actually you're suggesting that we not include that recommendation because it's adequately covered. Dr. Kocis, you're suggesting that it's not adequately covered. So we need to not complicate things further by giving a recommendation that adds to the confusion.

Dr. Nelson: Yeah, the only point is to say strength, and absent saying how is a recommendation that's unclear how one might move forward with that. So if it's, you know, around splenic rupture, which, granted if it's 1 in 10,000 at this point, would be an event that would be unpredictable since it's never been reported in pediatrics, one could make that recommendation. If there are others that one might want to put on the table, I don't have an opinion on

that, I'm just looking for guidance.

Dr. Rappley: And what I'm -- well, Dr. D'Angio and then Dr. Kocis. But I think we do need to recognize that we can't begin, with even this amount of information given to us, list the things that we think a physician or investigator should attend to. That we have to assume that those who write the protocols and receive approval for their protocols and their research are attending to those important issues. Dr. D'Angio.

Dr. D'Angio: Could I ask one point of information, and then maybe suggest a way out of this impasse? The point of information is, I haven't -- I can't find the specific language in here. Death would cause a suspension of the protocol, which is not quite the -- which doesn't mean that it's terminated, it just means that it's suspended until the DSM -- means to me -- it's suspended until the DSMB sorts it out. Is that correct? I see heads nodding. Okay. Good.

Could we suggest in strengthening the safety monitoring, perhaps by, for instance, adding

other suspension criteria, such as splenic rupture or ARDS? Period. There are probably others, but we've asked the investigators to think about what other things would make them not want to give another donor G-CSF, and ask them to consider those two things that everybody seems to agree, at least have happened to somebody who had G-CSF, as examples of things that they would then add to their suspension criteria. It doesn't endanger the study to the point of view of having us ask them to terminate something, it just asks them to think -- it asks the DSMB to think about that if it happens. Same way that they'd think if a death occurred.

Dr. Rappley: So the recommendation is to consider other points that would suspend the study, such as.

Dr. Murphy: Yeah, and I think give those two examples.

Dr. Rappley: Dr. Notterman.

Dr. Notterman: So I can think of three things that wouldn't be show-stoppers, but would cause a pause. One would be a splenic rupture or

laceration, I would say. The second would be admitting admission to an intensive care unit for acute lung injury within, oh, 30 days of receiving the G-CSF priming. And the third would be the appearance of a malignancy in the donor within -- I don't -- I don't know the right amount to specify, we could ask another member or Dr. Hudson --

Dr. Rappley: I'm not sure that we should be writing that level of detail. I mean, I think we've indicated that we think that those who are, I would think, more informed than we are, should be identifying suspension points other than death.

Dr. Notterman: Well, I'm not sure I agree, Dr. Rappley. I think that while we may not want to get into the specific elements of what would trigger a suspension, I think there are three broad categories of adverse affect that we've considered and that the literature supports and that the study designers have presented to us. And those are the three that I've listed.

And perhaps we don't have to put a time limit on it; I was trying to circumscribe our

recommendation. And so I would say within a month of receiving would be -- we could apply that for all of them, but certainly splenic rupture, admission to an intensive care unit for acute lung injury, and the appearance of a malignancy in a donor, are reasonable, and they should cause the study to think about what they're doing and maybe proceed and decide that it was stochastic.

Dr. Rappley: Those could be included in, as such as. Further discussion? Dr. Nelson, do you want to read -- you did a good job of reading that summary.

Dr. Nelson: (Speaking off microphone).

Dr. Rappley: Right.

Dr. Nelson: That fourth one under DSMB, I just basically said to strengthen the safety monitoring for the donor, parenthesis, by adding other suspension criteria such as splenic rupture, acute lung injury, -- I'm not sure you need an IC or not, I mean, hopefully they're there, they might not be there -- or a humanological malignancy in donor. Trial is 44 months. The statistics suggest you won't

see it in that time, but if you do, I guess, then that'd be the same as a splenic injury. So -- and I would assume that a laceration is the same as a rupture, if they got -- but, yeah. So -- and I put that under stipulations and --

Dr. Rappley: Does the Committee agree with then that set of recommendations that Dr. Nelson has read? Is there any who would not support that? Yes, Dr. Rosenthal.

Dr. Rosenthal: I've been quiet as my voice seems to be going. But I just want to raise the point and help people to realize or to see that the process through the day, initially went through in great detail, the steps of determining that in this study protocol -- the specific protocol -- there is no direct benefit to the donor; there is greater than minimal increase in risk; the donor does not have a condition that's being treated; the risks and benefits are accrued to two different parties; and that both the physicians and the family are likely to be inherently conflicted. And based upon that, these -- my position -- and this isn't -- wasn't shared

with everybody on the Subcommittee, but my position was that this protocol, as it's written, may not adhere to fundamental ethical principles that are required.

And the stipulations that have been discussed in this committee, have been addressing ways to make it conform better. And I'm not sure that even with these stipulations, the fundamental issues have been adequately addressed. So I just want to raise that as a point. We've been very focused on the details of the icing, and I don't know that we've re-addressed the issues in the cake.

Dr. Rappley: So I think we could note that, that there was not support of this recommendation and we would use the language that you just said, that even with this further modification, a member of this committee felt that the ethical principles do not justify approval of the protocol. Dr. Nelson.

Dr. Nelson: I would be careful how you state that because the criteria under 50.54 for approval require that it's being conducted in accord

with sound ethical principles. So the question the Committee has to ask is whether Geoff's concern is simply his concern or anyone else's concern.

And the other question is whether all the things that he listed actually pertain to bone marrow transplantation as an enterprise, sibling to sibling, independent of the research question that's superimposed upon that context, because all of the criteria that we're given, in fact, in many ways pertain to the bone marrow transplant, per sé, independent of the research question. So you can't just -- you know, I mean, the criteria under 50.54 are that it's a reasonable opportunity and it's being conducted in accord with sound ethical principles.

Dr. Rappley: Correct. And what you presented to us is that you had nine people supporting that and two people not supporting that.

Dr. Nelson: Right. And the one person who -- since it was bundled -- would have supported it if in fact the stipulation for the independent advocate had been a recommendation and not a stipulation.

Dr. Rappley: Right.

Dr. Nelson: So -- and obviously Geoff just identified himself as the one dissenting vote. So --

Dr. Rappley: So my question then, I guess, to Diane and to Carlos, is we could do the same. We could say that among our voting members, this many supported these recommendations and one did not support them on this basis.

Dr. Nelson: Right. Absolutely. You go down and you vote on each individual point --

Dr. Pena: I should mention though that if it does come down to a vote, we'll be taking votes from Cnaan, D'Angio, Kocis, and Notterman, with the deciding vote to Marsha since Jeff, Melissa, and Amy were on the Subcommittee, and it would be sort of a double hit if they were also allowed to vote on the recommendations from the parent committee. So --

Dr. Rappley: Okay.

Dr. Pena: -- it's really the four votes here if you're going to vote on any items.

Dr. Rappley: And, Dr. Rosenthal.

Dr. Rosenthal: So I just want to clarify that if the decision is made to approve the protocol

under 407, I'm completely supportive of the stipulations. And if the vote is whether the 407 process should continue, I'm completely supportive of that.

Dr. Rappley: So -- Dr. Cnaan. So what we need to do is either support the recommendations given to us from the Subcommittee as stated or modify them. And we have made modifications. That and we don't vote on a protocol moving forward or not moving forward. And so I think of the question to us, to those of us who would then be voting, is do we then wish to accept the recommendations of the Subcommittee with the modifications that we so described?

Dr. Notterman: I'm sorry, Dr. Rappley. Can I just introduce just a small point of order?

Dr. Rappley: Yes.

Dr. Notterman: Is it the case -- I'm asking FDA Staff -- that we do not make a recommendation with respect to whether this protocol moves forward or not? I thought that the form of our recommendation would be that we recommend that it

move forward, for example --

Dr. Rappley: Can -- can you restate --

Dr. Notterman: -- with these stipulations --

Dr. Rappley: -- that question for me?

Dr. Notterman: Sure. I'm -- I thought I heard you say that we don't speak on the issue of whether the protocol should go forward. But my understanding was, in fact, that was the kernel of what we do.

Dr. Nelson: That's in fact, incorrect. Yes, you need to -- there's two issues here. One, the category under which this protocol may or may not be recommended for possible approval; and that's the 50.54. So even though we went through that quickly, yes, you need to opine on that.

And then the second is the specific stipulations, which either you can do as a group, or you can break apart. So by accepting the Ethics Subcommittee Report with these modifications to the stipulation, you are in fact endorsing that it can go forward under 50.54 or 46.407.

Dr. Notterman: So may I make a motion, Dr. Rappley? I move that we endorse the recommendation to the Subcommittee with the modified stipulations as read into the record by Dr. Nelson.

Dr. Rappley: Do we have a second?

Dr. Kocis: I second.

Dr. Rappley: Dr. Cnaan, you have a point to make?

Dr. Cnaan: Yeah, just one point. On page 67 of this document, after explaining that expedited is within five days, there is text that says: the following are of special concern in the donors receiving Filgrastim are required to be reported, and it includes thrombosis, splenic rupture, and worsening of autoimmune disease. It includes ARDS, and it includes life-threatening or incapacitating complications of BM harvest or G-CSF administration. So all of those are actually in there and go into the reporting system within five days, and, hence, to the DSMB, et cetera. So I'm not sure whether the last recommendation that we added is not mostly redundant.

Dr. Rappley: Dr. Notterman.

Dr. Notterman: Yes, except that we are adding the recommendation that -- not only that these events be taken note of, but that they require a pause in the study -- suspension of the study during review. That's the -- what we're adding.

Dr. Rappley: So the motion is --

Dr. Murphy: I just want to -- before we start voting, I think we need to lay out for the Committee, we may need to vote both ways because what we have is -- in the past we have included the members of this Committee that have been on the Subcommittee, they have been included in that final recommendation. Okay. There -- what Carlos is telling me, though, that the science board and policy have recently discussed that there are some concerns about this approach, because we're not -- we don't have any real guidance or regulation on that at this point. This is simply something new and evolving. I am suggesting that at this point, that we go ahead and take the full committee and then that will give you the -- we can always remove the Subcommittee if we have to, the sub -- I'm sorry, the members of the

full committee who were on the Subcommittee. We can always then -- if it's decided, we can always take those votes out. But I think at this point we need to gather that information, and we'll make an internal decision. We'll find out whether this is in a discussion stage or this is an implementation stage, because I'm not familiar with this.

Dr. Nelson: I would want the full vote. And I want to know the vote. And, frankly, if I knew what the policy, I might have excluded the current members of the pack from voting on the Subcommittee so they could vote at this level. So, I mean, that's a whole separate set of issues. But I want to hear the vote of everybody. And we can do that separately so that there's no contamination across old votes and new votes. So let's just keep that clear.

Dr. Rappley: Dr. Rosenthal.

Dr. Rosenthal: I want to vote again because I think we may be voting about slightly different things. The way that some of these votes may be --

Dr. Nelson: Well, you'll get your chance.

But to keep it separate --

Dr. Rappley: Yeah. Now, I think there's --

Dr. Nelson: -- because, trust me, we're going to have to answer this other people. So to keep it separate, that half of the room should vote first about everything, and then this half of the room can say what they want. All right.

Dr. Rosenthal: However you want to do it.

Dr. Nelson: Well, so we can be clear.

Dr. Rosenthal: But my point is that if the issues are different now --

Dr. Nelson: You can change your vote any time, Geoff.

Dr. Rosenthal: No --

Dr. Rappley: You know what? We need --

Dr. Nelson: You're not mandated.

Dr. Rappley: We need to move on. So, Diane, have you -- I heard you suggest -- I heard you tell us that we need to take a vote of the full committee by name, register our vote, and then at some point in the future you may only be able to

count five of those votes depending on decisions made within the --

Dr. Murphy: Correct. We need to proceed with a full vote. As Skip is saying though, just in case something comes up, we would prefer that that side of the room go first.

Dr. Rappley: Okay. Very good.

Dr. Murphy: Okay.

Dr. Rappley: Yep. Dr. -- so the motion on the table is to support the stipulations with the modifications as read to us by Dr. Nelson. And that has been seconded. Discussion's been completed. We're taking a vote. We'll start with Dr. Cnaan.

Dr. Cnaan: I support.

Dr. D'Angio: Aye.

Dr. Rappley: Dr. Kocis, you are next.

Dr. Kocis: Aye.

Dr. Notterman: Notterman. Aye.

Dr. Rappley: I only vote for a tie, but I should. Okay. I would vote in support.

Dr. Nelson: Marsha, can I ask for a clarification of your vote? Earlier you had

expressed concerns about the first --

Dr. Notterman: I have a point of order. I object to having an interrogation during the vote, please, Skip.

Dr. Nelson: All right. That's fine.

Dr. Notterman: Thank you.

Dr. Nelson: Fine.

Dr. Notterman: Thank you.

Dr. Rappley: So we have voted and we now are -- we've voted in the membership that did not participate in the Subcommittee and we are now proceeding to include the full membership. Dr. Rosenthal.

Dr. Rosenthal: I support the stipulations.

Dr. Hudson: I support.

Ms. Celento: Amy Celento. I support.

Dr. Rappley: So we have all in support of these stipulations with the modifications as read into the record.

Dr. Nelson: All right. So earlier you had expressed some reservations about the modification of the first sentence, so I just wanted to offer you an

opportunity to -- because the clarity of the recommendations that we put forward depends upon the discussion not just the vote about why you don't feel the need to break apart the stipulations and talk about them individually given the modification of the first one around the risks of bone marrow transplantation. And you could say that you just changed your mind, that's fine, too.

Dr. Rappley: I am supportive of the stipulations as you read them. I also think that my comments will be part of the minutes, that I recognize some message from the Subcommittee about not simply relying on high risk as an exclusion.

Dr. Murphy: Thank you.

Dr. Rappley: Thank you. And the meeting is adjourned. So we will see some of us bright and early tomorrow morning in the Hilton Dome; is that correct? The meeting room is in the Hilton. At 8:30.

[Whereupon, at 6:00 p.m., the meeting was adjourned.]