"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 Ethics Subcommittee
of the Pediatric Advisory Committee
Tuesday, December 9, 2008
9:00 a.m. to 3:00 p.m.

The Legacy Hotel and Meeting Centre
1775 Rockville Pike, Rockville, MD 20852

Dr. Botkin: Good morning, everyone. We're going to go ahead and bring our meeting to order.

So, I'm Jeff Botkin. I'll be the Acting Chair for today's discussion. And my welcome to everybody here and my thanks for all of you contributing your time and expertise to what promises to be a fascinating and important discussion.

Also, my thanks to Skip Nelson and Carlos Pena for their support and expertise for helping to organize this meeting, so thank you.

Thought we would first go ahead around the table so that you have an opportunity to introduce ourselves since we'll be spending this day together. So, I'm Jeff Botkin. I'm a General Pediatrician at the University of Utah, have been doing bioethics for a number of years.

I'm the Associate VP for Research Integrity at the University. And relevant to this discussion, I'm a current member of SACARP and was on the Sub Part D, SACARP subcommittee several years ago.

Doug?

Dr. Diekema: I'm Doug Diekema. I am a

Pediatric Emergency Medicine Physician at Children's Hospital in Seattle where I also Chair the Institutional Review Board and am part of the Treuman Katz Center for Pediatric Bioethics.

Dr. Kon: I'm -- sorry. I'm Alex Kon. I'm a Pediatric Ethicist at University of California, Davis. I'm also a faculty member in Bioethics there. And work at our CTSC as the Director of Bioethics there as well. I've been involved with research ethics through that.

Dr. Link: I'm Michael Link. I'm the Pediatric Hematologist/Oncologist and Division Chief at Stanford.

Dr. O'Lonergan: I'm Terry O'Lonergan. I'm a Pediatric Research Ethicist and I'm a Clinical Researcher as well and the RSA at the Colorado Clinical Translational Research Institute.

Dr. Santana: I'm Victor Santana. I'm a Pediatric Oncologist from St. Jude Children's Research Hospital in Memphis, Tennessee. Past history, I also was an IRB Chair a couple of years ago.

Dr. Klein: I'm Harvey Klein. I'm an Adult Hematologist. I'm in the Intramural program here at the National Institutes of Health a few miles down the road. And we're responsible for providing all of the grafts that are used to transplant in the Intramural Program at NIH.

Dr. Menikoff: I'm Jerry Menikoff and the Director of the Office for Human Research Protections.

Dr. Nelson: Skip Nelson. I'm the Pediatric Ethicist with the Office of Pediatric Therapeutics and also a Pediatrician and do critical care.

Ms. Celento: Amy Celento, Patient Representative.

Dr. Hudson: Melissa Hudson, Pediatric Oncologist from St. Jude Children's Research Hospital in Memphis.

Dr. Rosenthal: Good morning. Geoff Rosenthal. I'm a Pediatric Cardiologist at the Cleveland Clinic and a member of the PAC.

Ms. Vining: Good morning. I'm Elaine Vining. I'm a member of the PAC and I'm the Consumer

Representative.

Dr. Pena: I'm Carlos Pena, Senior Science Policy Analyst in the Office of Science and Exec Sec to the Pediatric Ethics Subcommittee.

Mr. Glantz: I didn't get the briefing. I'm Leonard Glantz. I'm a Professor at the Boston University School of Public Health in the Department of Health Law, Bioethics and Human Rights.

Dr. Botkin: Alright and my thanks again to everybody for their contribution to today's work.

Dr. Menikoff has an introduction for us. Oh, sure, excuse me.

Dr. Pena: Good morning to members of the Pediatric Ethics Subcommittee, 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 being made part of the public record.

Today the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee will meet to discuss 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 of HHS. The clinical investigation is entitled "Children's Oncology Group Protocol ASCT0631: A Phase III Randomized Trial of Granulocyte Colony Stimulating Factor Stimulated Bone Marrow verses Conventional Bone Marrow as a Stem Cell Source in Matched Sibling Donor Transplantation."

Based on this limited agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that the Committee participation do not have financial interests that present a potential for conflict of interest at this meeting. In the event that the discussion involves any other products or firms, not already on the agenda for which a participant has a financial interest, the participant is asked and 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 Health Care Representative in this

Subcommittee. Ms. Elaine Vining is participating as the Consumer Representative. And Ms. Celento, Ms. Vining, Dr. Melissa Hudson and Dr. Geoff Rosenthal are all participating as members of the Parent Pediatric Advisory Committee. 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 which to comment upon.

We have an open public comment period scheduled for 11AM. I would just remind everyone to turn on your microphones when you speak so that the transcriber can pick everything up. And turn them off when you are not speaking.

I also remind all meeting attendees to please turn their blackberries and cell phones to silent mode.

Thank you.

Dr. Botkin: Dr. Menikoff, thank you.

Dr. Menikoff: Thank you, Dr. Botkin. I'd just like to thank everybody for being here. I'd particularly like to thank everybody who's made this

meeting a reality, our colleagues from the FDA, the members of Pediatrics Ethics Subcommittee, members of the Pediatric Advisory Committee.

This is a special type of meeting. 407 panels have many unique characteristics from the viewpoint of OHRP. It's an effort on our part to harmonize our thinking about the regulations together with FDA, which is, of course, an important thing.

In terms of the specifics of this particular study that's being evaluated today, we have a number of unique circumstances. The relatively unique circumstance of dealing with the health and well being of a child who is being asked to undergo research risks on behalf of another person, which certainly raised a host of issues from FDA and OHRP viewpoints. And even beyond that in terms of how our society deals with that in various legal circumstances.

The other interesting circumstance is that the way this is going to be analyzed through our federal regulations is that we actually have some interesting and unresolved interpretive questions in

terms of a number of provisions of those regulations. So it is a lot on the plate for everybody here. And again, we're very grateful for this meeting taking place and to hear the results of it.

Thank you.

Dr. Botkin: Thank you. Skip?

Dr. Nelson: Now it is.

Well it's been over two years since we've had such a panel. And so I thought it would be useful to set the table.

So the first set of slides is going to be an overview of the process. Why are you here? Who are you? How does it fit into this process?

And then I'll lay out, briefly, the what we call, Sub Part D, the Federal Research Protections for Children categories.

And then lay out a series of questions that I think this panel needs to address over the courses of its deliberations before you actually get into the more substantive questions that the following presentations and your discussion will entail.

So first let me start with the overview. And that was the wrong -- so today's focus as Carlos mentioned is a referred protocol by the Children's Oncology Group, protocol ASCT0631. I won't read the entire title. And the referring IRB is the Nemours Oncology Institutional Review Board.

Now IRB referrals under Sub Part D occur if an IRB does not believe that research, and in the brackets is the FDA language. Clinical investigation involving children as subjects meets the requirements of one of the three categories that a local IRB may use. And there is the regulatory citations that these clinical investigations may only proceed if that IRB finds and documents that the research presents a reasonable opportunity to further understanding, prevention or alleviation of a serious problem affecting the health or welfare of children.

And then the Secretary and/or the Commissioner of Food and Drugs, depending upon the particular research and the jurisdiction that's involved, after consultation with the panel of experts, you, and

following opportunity for public review and comment, determines that the research can either proceed under one of those three categories. Or under the fourth category which is this panel's sole determination. So I'm going to basically talk about this process.

Now the Pediatric Advisory Committee is chartered to make recommendations to the Commissioner involving research under 50.54, as well as to the Secretary for research under 46.407. Those are the two categories that constitute this panel.

Now to do this there is a permanent Pediatric Ethics Subcommittee, which is this Committee. Which requires there to be at least two or more members of the Advisory Committee present in order for us to have a meeting. Which is why it's important not only for continuity, but also for participation and a quorum to have members of the Pediatric Advisory Committee here as well.

And this process today is going to be this Committee meeting. And then a report to a

subsequent, two-hour meeting of the Advisory Committee, basically since Advisory Committees are the ones that are authorized to advise the Commissioner. So that's the process.

Now there are two guidances that go through this process that are effectively harmonize since they were developed with collaboration between the two organizations, one, for the Food and Drug Administration and the other for the Office of Human Research Protections. And I've given you the URLs to obtain these on the Internet.

Now protocols meeting the conditions of 45 CFR 46.407 also may be subject to FDA regulations under 21 CFR 50.54 if the protocols involve a clinical investigation of an FDA regulated product. And in this case then there's a joint FDA OHRP review. And I might point out that the idea of being an FDA regulated product is independent of whether or not it would be done under an investigation of new drug or investigational device exemption. And G-CFS is in fact an FDA regulated product.

Here's a brief statement about that joint

review process. Basically we issue our notice and put together the Committee. In cooperation with OHRP we convene the Ethics Subcommittee to review the protocol. They'll be then a report that goes to the Pediatric Advisory Committee, certainly a draft of which we'll try to put together during this meeting and in the 30 minutes between the two meetings.

And then the final recommendations of the Advisory Committee will be transmitted to the FDA Commissioner through the Office of Pediatric Therapeutics. And then this package will be forwarded to OHRP who will then add their assessment and interpretation of these documents. And then this entire package goes to the Secretary for the final determination by the Secretary about whether it can proceed.

Here's a slide that shows you this process basically that I've just described. And as you can see we're the expert panel Pediatric Ethics Subcommittee. The next step would be the FDA.

The dotted line to OHRP indicates the flow of

information. The solid line is the flow of documents basically. And then goes to the Secretary back to OHRP who then communicates to the funding agency, in this case, NIH, the IRB and then the PI and the grantee.

So that's basically the overall process and our place today in that process. So let me -- Jeff?

Dr. Botkin: Skip, do we want to stop for just any questions and clarifications?

Dr. Nelson: Yeah, if there's any questions I'm happy to address about the process.

[No response.]

Dr. Nelson: Ok. So what I would like to do is now move briefly to just an overview of Sub Part D and questions for the panel. And I'm going to start by just walking through the Sub Part D categories.

So the IRB referral focused on the question of the risk of administration of G-CFS to the matched sibling donors. And the options available under Sub Part D are these first three categories for the local IRB, minimal risk, minor increase over minimal risk or greater than a minor increase over minimal

risk with the possibility of direct benefit or referral for a federal panel review. Those are the four options.

Now minimal risk is defined as any clinical investigation basically in which no greater than minimal risk to children is present may involve children as subjects only if the IRB finds and documents adequate provisions for assent and permission. This is how the regulations read. So effectively there -- that risk determination pretty much establishes that category.

Now as a -- this is the definition of minimal risk. The probability and magnitude of harm or discomfort anticipated in the research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. That's the definition.

Now as a reminder, even though there's not much to the Sub Part D category, other than the determination of minimal risk. There are some general criteria for IRB approval of research that

must be satisfied for all of these particular categories. And this is a reminder of what those requirements are found in 21 CFR 56 and 45 CFR 46. For those in the audience 21 is the FDA, 45 is HHS. I've given both of those regulations so people can look them up at their leisure.

But basically risks to subjects must be minimized by using procedures consistent with sound research design and which do not unnecessarily expose subjects to risk or when appropriate by using procedures that are already being performed for diagnostic or treatment purposes. `The risks to subjects are reasonable in relationship to anticipated benefits of any of the subjects and the importance of the knowledge. Selection of the subjects is equitable.

Informed consent will be sought and appropriately documented in this case parental permission and child assent, if appropriate that there's adequate provisions for monitoring the data to ensure safety and then adequate provisions for privacy and confidentiality. All of those would

apply to any of these particular categories. But just as a reminder that those are some of the general IRB approval criteria.

Now the second category within Sub Part D is this category of minor increase over minimal risk. And these are the determinations that would need to be made under this particular category. Any clinical investigation in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit to the individual subject may enroll children as subjects only if the risk represents a minor increase over minimal risk.

That this intervention or procedure presents experiences to subjects that are reasonably commiserate with those inherent in their actual or expected medical, psychological or social situations. A couple of other categories I eliminated there mainly to make the slide fit, likely to yield generalizable knowledge about the subject's disorder or condition that is of vital importance for understanding or amelioration of that

disorder or condition and then again, adequate provisions for assent and permission. So that's the second category, 50.53 or 46.406.

Now as you can see in that particular category implicit is the notion that the subjects have a disorder or condition. Now the regulations offer no definition of what a disorder or condition is. And there, at this point, is no policy by either FDA or OHRP which establishes a definition. Although there's some recommendations I believe SACARP has made at this point.

This is language taken from the Institute of Medicine recommendation which is similar I believe to the SACARP recommendation which defines condition with three particular sets.

First of all there are some specific or set of specific physical, psychological, neurodevelopmental or social characteristics. That there's some evidence to establish that either scientifically or clinically and that this has been shown to negatively affect children's health and well being or to increase their risk of developing a health

problem in the future. One of the issues before the panel is going to be potentially the interpretation of disorder or condition.

Now the third category is greater than minimal risk. And this is defined as any clinical investigation these are the determinations that would need to be made in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit. So one of the questions will be whether there is such a prospect of direct benefit. Or the individual subject may involve children only if the risk is justified by the anticipated benefit to the subjects, the relationship of this anticipated benefit to the risk is at least favorable as available alternatives, then again, adequate provisions for assent and permission.

So these categories, if you will, set up a structure where we can ask a number of questions about this particular protocol. And what I'm going to run through is those questions that, over the course of the day, the panel will need to address.

The first question is what are the risks of G-CFS administration? Now if these risks are appropriately considered to be minimal risk, have the general criteria for IRB approval been met. And if not, are there additional stipulations that the panel would recommend?

Now if the risks of G-CFS administration to the sibling donors are more than minimal risk does the intervention offer the prospect of direct benefit to the sibling donors? Now in answering this question you should consider the range of potential benefits to the sibling donors including contributing to the improved health of the recipient. You should also consider whether any potential benefits are the direct result of the research intervention.

However, if the G-CFS administration does not hold out the prospect of direct benefit to the sibling donors, the question is then are the risks of G-CFS administration appropriately considered to be no more than a minor increase over minimal risk?

If you go that direction there's two other questions that should be asked.

Is the intervention likely to yield generalizable knowledge about the sibling donors' disorder or condition that is of vital importance for understanding or ameliorating that disorder or condition?

And does the intervention present experiences to the sibling donors that are reasonably commiserate with those inherent in their actual or expected medical, psychological, or social situations?

To those that haven't recognized the pattern, effectively we're walking through the categories to eventually ask the questions relative to the assignment of this particular protocol to one or more of those categories.

Finally if the G-CFS administration does hold out a prospect of direct benefit to the sibling donors, are the risks of G-CFS administration justified by this anticipated direct benefit? And is the relationship of this anticipated benefit to the risk at least as favorable to the sibling donors as that presented by available alternative

approaches? Now, if after working through those questions you find that none of the conditions of 404.50/51, 405.52 or 406.53, in other words, none of those conditions apply. You then have the fourth category which is the only category that this panel in fact -- well, that this panel can put the research into any one of those three categories.

This 50.54/407, if not available to the local IRB, it is available to you. So that the conditions where one might then say that this research fits under that category, is that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children. The research will be conducted in accordance with sound ethical principles and then again adequate provisions for assent and permission.

So that then leads to the final set of questions. That if you feel the research does not satisfy the conditions of either of these other three categories. Does the research in fact present such a reasonable opportunity? Will it be conducted

in accord with sound ethical principles? And then are there adequate provisions for soliciting the assent of children and permission of their parents and guardians?

So in effect you'll be walking through these questions in trying to formulate how this research would or would not fit in any of those four categories. A summary of the key questions:

What is the risk of G-CSF administration?

Does the administration of G-CSF to the sibling donors offer a prospect of direct benefit?

And do sibling donors have a disorder or condition?

As not a complete statement of the various questions you'll have to explore, but some of the key questions that need to be addressed as one looks at this particular protocol.

Now as you go through your discussion you should determine whether or not the research is approvable with or without modifications under a Sub Part D category. So at the end of the day we should have a clear idea of where you all think it fits.

The panel should provide reasons for this determination, ideally since as Jerry mentioned there are some important interpretive issues that exist in evaluating this particular protocol.

I might remind you that you're not functioning as an IRB. So I would hope you don't get into the nickel and diming the consent form language, for example. I mean, you're not an IRB. So please, keep your eye on the ball.

But you're to provide a recommendation to the Commissioner of the FDA and the Secretary of HHS. I mean we can fix some of the consent language if you want to, through other mechanisms. And then if you think there are important modifications that should be made, I would appreciate dividing those clearly between what would be stipulations.

In other words, if this is not done it should not go forward verses something that would just simply be a recommendation which would we think this would be better if you did it this way. But we wouldn't make that a requirement for moving forward. So if you have any modifications, if you will, to

the protocol and how this is approached, it would be helpful if you very clearly, state your wishes around that modification because both FDA and OHRP will need to move forward with those recommendations. And clarity will be helpful in guiding us in how to frame your opinion to both the Commissioner and to the Secretary.

So with that, I know that's a rather fast walk through. And I've got some time left for questions. So if people want to ask questions or we can get about your work a few minutes early as well.

Dr. Botkin: Any questions for Dr. Nelson? These should be largely ones of sort of clarification of those points. Obviously we'll have lots of time to talk about more specific details.

Elaine?

Ms. Vining: Just one question about this Subcommittee. Is this the first time this Subcommittee has been used to answer a question of this nature?

Dr. Nelson: No, this is the fourth time that this process has been used. After the charter of

the Ethics Subcommittee and the Advisory Committee, this is the first protocol that's asked this particular question. But there's been three others that have gone through this process in '04 and '05. This is the first in two years.

Prior to that there were a number of referrals which were dealt with through a more ad hoc process since the Advisory Committee was not put into place until after I think, the 2002 BPCA legislation. So there was no Advisory Committee at that point. It was included in the charter. So this is number four for this process.

Mr. Glantz: So the Ethics Committee is advising the, what is it called, PAS? I'm trying to decide. Are there two committees in the room right now?

Dr. Nelson: Well, basically our regulations stipulate that an Advisory Committee can only advise the Commissioner. And so we've designed a two step process which can be a little cumbersome. But where there's a standing Ethics Subcommittee for the purpose of this review and for the more general

discussions as we had in June.

And then that report goes to the parent Advisory Committee for endorsement and modifications as they see fit. That's the process we used for the other three. This is the first time we've done both meetings in one day mainly because the parent Pediatric Advisory Committee is involved in meetings tomorrow and the next day which is why we were able to put this together in relatively short notice for a federal agency.

Mr. Glantz: But the meeting has -- I mean the Committee has five members on it? `

Dr. Nelson: There's four members of the Pediatric Advisory Committee --

Mr. Glantz: Right.

Dr. Nelson: -- That are present. We needed two for a quorum.

Mr. Glantz: Ok.

Dr. Santana: Two questions. What happens in terms of timelines based on the recommendations of this Committee in terms of getting this issue resolved so that the protocol can or cannot be

carried forward based on past experience? And then secondly, this protocol has been reviewed by other IRBs, improved under other than non 407 categories. So what does the recommendation of this Committee for the Commissioner or HHS do to those approvals that have already occurred?

Dr. Nelson: Well, two comments. And I'll see if Jerry wants to comment on the second. The timeline for some of the other determinations has been variable. But I think there's certainly a hope that it could be late winter or early spring. We're talking next February, March, April at the latest to work through the process. At times it has taken up to seven to nine months to do that.

I don't want to put a particular timeline on our ability to work through the process that I showed you. But it's certainly my desire to try and do that as expeditiously as possible. Precisely for the second point which is at the time of this referral NCI decided after being informed of the referral by OHRP to suspend the conduct of this trial.

So I'm cognizant that there's some need to try to be as expeditious as possible. I would not presume to guess what NCI might decide to do after consultation with OHRP. Based simply upon the discussion that happens today independent of what the Commissioner and the Secretary decide. Ultimately I think that would be much too speculative.

Dr. Menikoff: I don't know that I would have a lot to add to that assuming the result of today after it's gone through FDA and OHRP is that it is approval under one of the categories. And again, we have a number of categories there. Presumably then the study would then proceed.

If there was a determination it was not approvable under 404, 405, 406 or 407, that would obviously be a more complicated issue.

Dr. Botkin: Alright. Thank you very much. We now have the opportunity to hear from a number of experts and individuals who've been involved in this process to date or in clinical questions relevant to the study under our evaluation today.

And I would say just from my perspective, I want to thank everybody who's been part of this process so far, contributed to our background materials. I think the Children's Oncology Group Committees and scholars have done an outstanding job as has the Nemours IRB looking at these issues, albeit different conclusions. And we may come to our own set of conclusions about this. But that doesn't take away from the expertise and the thoughtfulness that those folks have brought to this debate.

We now have three presentations for us to augment our background for our discussion. Dr. Santana will talk to us about the use of G-CSF in stem cell transplants. We'll then hear from Dr. Grupp who will be talking about this particular protocol. And then from Dr. Wysocki from Nemours IRB, who initiated this Committee analysis of this particular protocol.

So, Dr. Santana, thanks so much.

Dr. Santana: Good morning. So my charge is to give you a general review of some of the biologic

effects of G-CSF, current indications and side effect profiles. And then delve a little bit into a little bit more detail on the issue surrounding G-CSF use in different pediatric and adult disorders and the risks that have been identified so far with particular attention, obviously, to children. And then provide some summary comments.

So what are the biologic effects of G-CSF? G-CSF is a naturally occurring cytokine, hematopoietic cytokine, normally produced in all of us by monocytes, fibroblasts and endothelial cells. And this cytokine maintains a normal, steady status of poiesis by regulating the production, the differentiation and also very importantly, the functional activation of nutrafils. Back in the late 80s, early 90s, clinical studies were done with G-CSF at pharmalogic doses that obviously led to approval by the Agency at various indications I will review in a minute.

This recombinant G-CSF when it's given at pharmalogic doses then augments this response that stimulates the development of both committed and

progenitor stem cells and causes also the release of some of these progenitors from the bone marrow into the peripheral blood. And that's been exploited in the past couple of years with the use of peripheral stem cell harvest. And then there are a number of these subsets of progenitors that have been identified that become the target of the aphoresis procedures or the bone marrow procedures.

G-CSF also has some other effects that are biologically and functionally important. It increases the regulation of other cytokines like TNF receptors, etcetera, etcetera. Some of the side effects may be related to those secondary effects on other cytokines.

When you give a patient a pharmacologic dose of G-CSF at pharmacokinetics are pretty standard both in adults and in children in the half life in terms of what we can measure in serum is very short in the order of three and a half hours. But the biologic effects in terms of the binding of the cytokines to the receptors is a much more prolonged effect. The current indications for the use of this compound, G-

CSF, the primary indication that was approved back in the early 1990s was to decrease the duration and the severity of chemotherapy, induce neutropenia in both adults and in children.

The American Society for Clinical Oncology, ASCO, had some guidelines that were published a number of years ago in terms of when G-CSF should be used in terms of prophylaxis of patients that are likely to have neutropenia associated with chemotherapy. And the general consensus there is that if there's an expectation of an incidence of neutropenic greater than 40 percent it should be used in a prophylactic setting. The guideline states that pediatric patients should be treated with the above recommendation which is I note, based on adult data because pediatric data really, in general, has been very limited, has been not studied as rigorous in terms of perspective clinical research as has been done in the adult setting.

There are some other indications. There are a number of hematologic disorders that have to do with the production and function in pediatrics. One of

them is congenital, neutropenia in childhood and another one is cyclical neutropenia. And in both of those settings G-CSF has been used quite effectively.

As I mentioned to you it's also been used in the autologous, peripheral, blood stem cell donors for patients that are undergoing autologous, stem cell transplantation. And this applies to both adults and children. So these are primarily, for example adults with solid tumors that require consolidation with high dose chemotherapy or radiation. And G-CSF is used to mobilize their own stem cells into the periphery so those patients can undergo aphoresis harvest.

It's also been used as you'll see in a minute in a healthy adult for peripheral blood stem cell donors and in bone marrow donors for adult bone marrow donors for stem cell mobilization. It's been used in individuals that give granulocyte transfusions. It's also been used in allogeneic stem cell donors.

And there are a number of reports of physicians

using them off label in patients that have acute sepsis syndromes in which patients are very ill. But that is an off label indication. And not widely accepted as something that is routinely done.

There's a lot of experience with the side effect profile of G-CSF. Most of this data that I'm presenting in this table really is derived from patients that either have hemonologic or other cancer disorders for the primary indication that I mentioned which is the prophylaxis of febrile neutropenia in patients undergoing cancer chemotherapy. Very common side effects in arbitrary definition, common means that greater than 20 percent of subjects of patients may have this particular side effect.

Bone pain is very common. And it makes a lot of sense in a very simplistic way because you're rapidly expanding the marrow space. And patients do complain of bone pain and general malaise. Reports of headache and myalgia are fairly common.

Less common side effects are nausea, vomiting, diarrhea. G-CSF is usually administered

subcutaneously, although it can also be given intravenously. When it's given subcutaneously, patients can develop some erythema at the injection site.

Very rare side effects and by rare means a rate less than five percent, included splenic rupture. Remember the spleen is part of the metapoetic endothelial system. And in particularly in children it's a very active organ.

And there have never been, to my knowledge in the literature, any reports of splenic rupture in children. Most of them have been in adults. But children can get splenomegaly, usually very transient, associated with hyperleucocytosis when they get G-CSF.

There's some rare reports of acceleration of autoimmune disease. Which makes a lot of sense given the fact that G-CSF has some secondary effects on augmentation of other cytokines. As this is a recombinant protein product, so allergic reactions can occur and then there's some been, some rare events reported of vascular problems in some

patients and particularly in adults.

I mentioned to you specifically that these rare events with the exception of allergic reactions are very rare in children. Most of these reports are really in adults. Where as the common effects that you'll see in a minute of bone pain and myalgia and general malaise are commonly seen in children just like in adults. And then there's this hypothetical risk that we'll talk about in a little bit more detail in a few minutes about development of mild myeloplastic syndrome or AML because obviously G-CSF by its nature can affect hematopoiesis related to myelogenous leukemia and to MDS syndromes.

So that's kind of the introduction of some of the setting of the background. Now I want to spend a little bit more time trying to dissect this issue of G-CSF and risk in different populations and looking at some of the in vitro and VIDO data, looking at some of these hemonologic disorders, looking at some experience in children with cancer and then focusing at the end of studies in stem cell donors both in adults and in children. And I

mentioned that all the data that I'm presenting to you is published data. So it's not personal communication or anything like that. It's -- a lot of the data that you had in your package.

Before we get into some of this in vitro and VIDO data, I want to spend one or two slides doing biology 101 because this issue of allelic replication will come up in a manuscript that I'm going to discuss with you. Remember during normal DNA replication during the S phase, normally two alleles are present. And how both of these alleles are replicated temporally is very important.

And most of the time the two alleles are replicated synchronously. They both are replicated at the same time. And obviously that allows important biologic express genes to be transcribed and expressed concommently with both alleles replicated at the same time.

However there could be asynchronous replication. And like the word says, asynchronous is that one allele is replicated temporally earlier than the other or one allele is not expressed at

all. So there's monoallelic expression. And you've heard about silencing x and activation and exclusion is normal biologic processes in which one monoallelic expression does occur.

And this monoallelic expression is very common. It's not an abnormal finding. It does occur for example, in the regulation of T and B cell antigen specific receptors.

However, when there is a cell that has a transition from synchronous to asynchronous mode of replication, this is commonly seen in cancer associated phenomena. There are many reports, for example on prostate cancer and breast cancer and other cancers where this asynchronous replication is a hallmark of the phenotype of that particular cancer. But it's not disease specific in the sense that it defines a specific disease. But it's a very general epigenetic effect that's seen sometimes in various cancers.

For those of you that are a little bit more visual. I thought I'd present this little cartoon. If you focus on the B panel, these are obviously two

alleles. Right. And if they undergo synchronous replication you get the effect that you see in panel C, where you see then a duplate of the alleles that have been replicated.

On the other hand on panel A, you have one allele that has gone synchronous replication and now has two dots and the other one has not replicated yet. So this is an example of an asynchronous replication of the pair of alleles. And this panel A is what I'm referring to which is commonly seen in some cancer disorders.

Why is this important? This is important because in 2004 there was a report that created a lot of interest related to what G-CSF does to normal volunteer donors in terms of generating epigenetic and genetic alterations. And this is a very small report.

It was only 18 healthy adult allogeneic stem cell donors that were treated as part of a donor protocol with G-CSF at 10 micrograms per kilo per day. And these investigators obviously did a lot of in vitro work looking at the lymphocytes of these

normal donors. And they did notice an increase in this asynchronous allelic replication.

However, it should be noted that this is a transient phenomenon. It was not permanent and lasted approximately 140 days. However they did see that there were other genetic alterations, particularly aneuploidy. Remember aneuploidy is a mis-segregation of chromosomes that results in a cell that does not have the normal 46 compliment of chromosomes. And this aneuploidy was persistent in some donors.

Now what are the implications of this observation? Obviously it's a very small subset. But what are the theoretical implications?

Well one of the implications is if you have monoallelic expression and this is a mutated gene. And that gene potentially could then be transcribed and express. It could result obviously in the unmasking of something that otherwise would have been recessive condition and then the vulnerability issue of a second hit that people already have one monoallelic gene and potentially if that gene gets a

second hit than you may produce a cancer phenotype.

I mention to you and I stress to you that these are theoretical implications. They're not implications that have been seen clinically. There have been other studies looking a little bit more specifically at the changes in gene expression in subjects that have received G-CSF in terms of healthy donors.

And there's two publications. I think these are part of your packets also that address this information. So these were adults treated with G-CSF for four days as part of a typical donor protocol.

And these investigators did some affymetrix gene array studies. Just very broadly looked at hundreds of genes and which genes were up regulated and which genes were down regulated. And basically they noticed, this would be expected that some of the target genes that are related to hematopoiesis would be up regulated and others were down regulated.

But when they looked at these subjects again

over a period of time all of these changes normalized over a six month period. So they were not permanent changes in gene expression that were produced by the use of G-CSF. And a lot of the interpretation of this data which is that G-CSF obviously causes the expression of these genes that are very early in hematopoietic development. Which would be expected or maybe that what we're really seeing with these gene array chip studies is because these are highly sensitive studies that you're just picking up on those very rare, mobilized cells that have that signature imprint that's of interest. So it doesn't really represent the whole experience but represents really a signature of one or two cells that you've picked up by these very sensitive methods.

So I think there is some data that gene expression patterns change. But most of these become counter balanced in the bigger picture. And most of these are really transient phenomena that are not long standing.

Now one of the issues that this raises is

whether any of these colony stimulating factors have anything to do with leukemogenesis, which obviously would be a significant risk if that were the case. So if you look at colony stimulating factors there may very different mechanisms of why leukemogenesis could be an issue. One is that these growth factors could induce clonal proliferation of the malignant clone. And either accelerate or inherently produce hemonologic malignancy.

There could be altered tumor cell differentiation if these colonies stimulating factors somehow caused differentiation of cells and stimulation of tumor cells. They could inhibit apoptosis or they could enhance leukemogenic effects of other secondary factors. So this issue of leukemogenesis with the use of colony stimulating factors has always been in our mind in those of us that practice pediatric oncology.

And there is some data that suggests that this does happen. But it does happen in patients that obviously have a condition in which one would theoretically expect that this could be a

possibility. And so there are two reports.

One is this report from Rosenberg looking at patients with hemonologic condition which is congenital neutropenia. And you see the number of patients in this report. And these patients obviously are treated with G-CSF to augment their neutrophil counts and the neutrophil function cause many of these patients have inherently disorders that result in difficult infections to treat and complications from their dysfunction on neutrophils.

And as you can see the cumulative incidence of developing AML or MDS in this patient population is fairly high. It's in the order of 36 percent at 12 years. And also this report indicated that there may be some dose effect. And that is that patients that get a higher dose of G-CSF have a higher fold increase in the probability of developing a secondary ML or myelodysplastic syndrome.

So in these conditions, once again these are hemonologic conditions. These are not normal patients. There is evidence to suggest that the use of G-CSF does increase the risk of secondary AML and

MDS in these patients.

These patients inherently have a risk of developing AML and MDS. So it's not a zero risk that gets converted into a higher risk with the use of these factors. But there is a background risk that obviously increases with the use of G-CSF in this setting.

The other question is how about children with acute lymphoblastic leukemia which is a fairly common hemonologic malignancy seen in childhood. And Mary Relling at St. Jude back in 2003 published our experience with two leukemia trials that total 13 A and B studies. These studies obviously are multiage chemotherapy that include topoisomerase 2 inhibitors and alkylating agents which we know can produce secondary AML and MDS by themselves.

And in this particular study patients were randomized to receive G-CSF or placebo for 15 days in order to increase their neutrophil recovery, post remission induction. And as you can see there were a number of patients, there were 20 patients in this study that developed a treatment related myeloid

leukemia, 16 AML, 3 MDS and 1 CML. And there was a higher incidence of these secondary hemonologic problems in patients that received G-CSF compared to those that received a placebo.

So I think there is data to suggest that in patients in children with leukemia the use of G-CSF may increase the risk of those patients going on to develop a secondary MDS or a secondary AML. Once again, with the caveat that these patients were also getting additional therapy that, by themselves, that additional therapy is also associated with the development of these secondary problems. So those are children that have a condition that we know may predispose them to developing AML or MDS.

How about healthy donors? So here we have to turn to the adult experience and looking at studies in healthy donors that have received G-CSF as part of various procedures. And there are a number of data out there.

One is from the MD Anderson Group that looked at 281 peripheral blood donors. Once again, these were all adult patients with a median follow-up of a

little bit under three and a half years. They have reported no cases of hemonologic malignancies.

The National Bone Marrow Transplant Registry here in the United States has also looked at that data both in subjects that are peripheral blood donors or subjects that are marrow donors. Over 4,000 patients that are peripheral blood donors with follow-up up to nine years, they have reported no cases on hemonologic malignancies. Similarly in the marrow donors over 1,000 of patients or subjects with a follow-up of three years, there have been no case reports of hemonologic malignancies in these adult, healthy donors that have received G-CSF as part of mobilization procedures.

There's some data from the Japanese Registry, over 3,000 experiences there. The publications did not provide a follow-up of those patients. They do describe one case of AML that developed in their registry.

This was a donor who had donated peripheral blood with G-CSF stimulation for a sibling who had multiple myeloma. That's important to note because

one of the things that we have to remember is that there's a sibling effect in terms that there's always a higher risk of an individual developing a hemonologic malignancy if they have a sibling that has a hemonologic malignancy. And obviously it's going to vary depending on the malignancy that you're talking about.

The German Bone Marrow Donor Center also, very large group of patients of subjects, have looked at their experience. Over 7,000 peripheral blood donors with five years of median follow-up, they reported one case of Hodgkin's disease. And in their marrow donors, over 3,700 cases, here the contact has been periodic. It hasn't been as rigorous as some of the other registries. They reported one case of chronic lymphocytic leukemia and one case of acute myeloid leukemia.

And then Cavallaro looked at 101 patients that were peripheral blood donors with a median follow-up of close to four years. They report no cases of hemonologic malignancies. There was one case of a patient that developed, a subject that developed a

transient lymphadenopathy of unknown cases that resolved. And then one case of breast cancer and one case of prostate cancer which would not be predicted to be a relevant in the case of G-CSF and its relationship to hemonologic malignancies.

How about the conclusion of these studies? Well it appears from this limited data, although some of these registries do have a large number of subjects of patients, that there's a low rate of hemonologic malignancy associated in these healthy adult donors. However, remember that many of these registries are retrospective reports. These are questionnaires or things that are done afterwards.

Many of these registries have relatively short periods of follow-up. When we tend to see treatment related AML in children for example, usually we see it between three and eight years after the primary exposure. So you have to kind of keep that time set in mind when you look at these registry data in terms of the median follow-up of these subjects.

And obviously because they are retrospective and they were not designed to be registries looking

at specifically the issue of under reporting has to be also considered as a caveat. And then also remember that when you do see a case of hemonologic malignancy in these adult stem cell donors, you know, many of -- all of these donors are donating, obviously, for siblings. And so these siblings have a hemonologic disorder or have a malignancy. So there's going to be this issue of the shared genetic susceptibility. So it's something that has to be considered in terms of making conclusions about the risk of developing these problems in these patients.

How about in children which is what we're really here today to talk about. So there are a couple reports. One is a Spanish cooperative group published in 2001. They looked at 61 donors less than 18 years of age, a median age of 14. Interestingly they had a patient that was only one year of age who was a donor.

They used the standard doses of G-CSF for mobilization for about five days. They reported common side effects. Bone pain occurred in over 90 percent of the patients. Headaches was also common

in about 21 percent of the patients.

They considered that these symptoms in general were mild. They were managed with minor analgesics. And none of the individuals of the children that were getting G-CSF discontinued the G-CSF because of concerns related to toxicity. However the very few donors in this registry have had a significant follow-up in four years. Less than 15 percent of these children have been contacted in terms of looking at long term issues related to the G-CSF administration.

There are two Japanese studies. One published in 1999. One published in 2002.

The first one had 19 donors that were children with a median age of six. Standard dose of G-CSF for mobilization. They reported "no side effects in donors less than ten years of age." But the older children tended to have more symptoms with mild headaches, general fatigue and required non-steroidal anti-inflamatories. There was no follow-up data provided on these subjects.

The other report was little bit larger. It had

57 donors less than 18 years of age, a median age of eight. But interestingly there was one subject that was nine months of age who was a donor. Standard doses of G-CSF administration.

They reported that the older patients/subjects tended to have more symptoms in terms of bone pain, mild headaches. But they responded fairly well to non-steroidal anti-inflamatories. They did have some follow-up data in 40 of the 56 donors at a median of 25 months. They performed blood counts and medical examinations on these subjects and reported no significant findings at follow-up.

And then lastly there has been some experience published here in the United States. In 2005 looking at over 201 donors less than 18 years of age with a median age close to 12 years of age. A standard dose of G-CSF administration for approximately four to five days.

Once again, common side effects of the bone pain and myalgia seen in these normal, healthy children, some of them required minor analgesic treatment for these side effects. And one older

child required an oral narcotic for a very brief period of time. Unfortunately no long term follow-up data was reported in this U.S. experience. But Stephan during his presentation may have a little bit more follow-up on this experience, if he wishes to comment.

So I think in summary to conclude my charge. In terms of the use of G-CSF in normal, healthy adults and children, I think we can say that there are common, acute, mild side effects that are observed in these healthy individuals. Both in vitro and VIDO studies suggests some genomic changes. However these genomic changes appear to be transient and are present at very low levels. And presently their clinical significance is really unknown. It's just a theoretical risk.

And then lastly the adult experience is certainly a much larger than what we have in pediatric. But the adult experience suggests that there is no increased risk of using G-CSF in normal, healthy adult donors in relation to the development of hemonologic malignancies. But unfortunately we

don't have a lot of data in children to be able to reach any conclusions at present.

So I think with that I'll finish. And I'd be happy to address any questions now or later. Thank you.

Dr. Botkin: Excellent. Thank you. We will be loading Dr. Grupp's slides for a minute or two so we do have several minutes for questions for Dr. Santana.

Dr. Klein?

Dr. Klein: I think that was a wonderful presentation. Just a couple of questions on the in vitro studies, you know, the ones with the gene array studies. What cells were studied? Were they mononuclear cells, were they lymphocytes, you know, or staton CD34 positive cells. What did they look at?

Dr. Santana: They were mononuclear cells of which a large component were lymphocytes. In the other study with the asynchronous allelic replication --

Dr. Klein: Yeah, those were --

Dr. Santana: -- Those were lymphocytes that were obviously --

Dr. Link: Well, not lymphocytes. They're T-cells that PHA stimulated.

Dr. Santana: Right, right.

Dr. Link: So our question is what relevance does that have to anything in the --

Dr. Santana: Your point is well taken. I think I stressed that, you know, all that data is kind of has to be considered in terms of its context that these are really studies that, you know, mainly hypothetical.

Dr. Botkin: Dr. Kon?

Dr. Kon: Thanks very much for that presentation. I was just wondering if you could comment there were there's been a number of case reports although no studies are on G-CSF causing ARDS in normal, healthy individuals which is certainly something we need to consider given the relatively high mortality rate of ARDS. I was wondering if you could comment on that.

Dr. Santana: Well I didn't specifically

comment on that because I try to focus primarily on published studies that have large numbers of patients. My recollection of the data is that they're very small case reports. They're small series.

And I think it's an important issue. And certainly we've seen in the oncology field in patients that have, you know, pneumonia or you know, neutropenia, that certainly that when they're given G-CSF either as part of prophylaxis or as part of the treatment of the neutropenia that there is a very large inflammatory response once the neutropo recovery occurs on those patients. So I think it's a very relevant observation. But in terms of normal, healthy people --

Dr. Botkin: Excuse me, Dr. Santana. I apologize. Not all of our participants have medical background. So I wonder if you could take a second to interpret this question and concern.

Dr. Santana: So I think what the question is there's been a couple of case reports of individuals receiving G-CSF that have developed adult

respiratory type of syndrome which is really a very complex, physiologic process that occurs when there is a lung injury which is primarily mediated. I think, I'm not a pulmonologist, maybe you should chip in too, which is primarily mediated by cytokine effects on the lung tissue. And it usually occurs in the setting of some sort of lung injury, pneumonia, you know, radiation in terms of the cancer irradiation or chemotherapy and so on.

And so that's kind of the background of that. Those are -- it's there in the medical field that this does occur. But it usually occurs in the setting where there's been an insult or an injury.

And then patients are getting G-CSF to, you know, deal with their sepsis or their pneumonia. And then when this inflammatory response gets augmented then this lung injury occurs. And these individuals are very ill and on respirators and, you know, have a lung injury that's very severe.

The third comment I was making is my recollection of the case reports is that it hasn't been seen in the setting of normal individuals.

It's usually seen in the setting of a background where's there's been another incident or damage to the lung for whatever reason. But you may want to elaborate on that based on your experience. So I didn't list it in terms of the common side effects because it's not something that -- it's very rare. And it usually occurs in a background where's there's been additional injury to the lung.

Mr. Glantz: You mentioned the possible sibling effect. I have sort of a related question. If there is an issue of leukomogenesis, would it more or less likely be of concern in younger children, older children or adults. Is there a developmental, sort of a biological, developmental aspect of it?

Dr. Santana: Well you know the current theory of leukomogenesis in terms of ALL. Dr. Bennett and others who've done this basic research really indicate that there may be a period of vulnerability in terms of for example, lymphoid development, which really puts children at risk in terms of developing, for example, ALL. So it's not a continuum in terms of risk.

But there's something developmentally that occurs in a time period in terms of the development of lymphoid system that predisposes. Not predisposes, but has the setting in order for leukomogenesis to occur in the setting of ALL I'm specifically talking about. So, yes you are correct that when it comes to ALL, you know the age group under eight or nine years is really the risk age group that we're most concerned about. If there should be a second event that induces the development of ALL in those children.

AML is very different. AML is really a continuum. And those events are not as clearly, in terms of the pathogenesis, delineated as it is in terms of understanding the developmental biology of ALL.

Mr. Glantz: I'm not a physician so I just need a little more clarification. So the question that I'm actually asking is would you expect to be more risk, less risk or the same risk if you give the drug to one year olds, two year olds, three year olds or ten year olds?

Dr. Santana: We don't know. That's the honest answer.

Mr. Glantz: Would you have a guess, an educated guess of course.

Dr. Santana: Very low.

Mr. Glantz: Ok.

Dr. Rosenthal: Just a quick question to help me understand the kinds of risk we're talking about in general. Can you help me quantify the risk of developing a hematologic malignancy in an otherwise healthy appearing sibling of a child who has such a malignancy?

Dr. Santana: So I think the data suggests that if you have a sibling, for example hematologic malignancy, there's a two to four fold increase in the probability of developing a malignancy in your lifetime.

Dr. Botkin: Dr. Link?

Dr. Link: I just wanted to follow up. Some of the theories of leukomogenesis is that initiating leukomogenic event occurs in utero.

Dr. Santana: Right.

Dr. Link: But there's a lot of people who have, it's documented now, who have the initiating event but never develop leukemia. So this is sort of one of those arguments that can go on forever. Many people are walking around who are predisposed to leukemia, but never get leukemia. It's not clear that G-CSF has any effect on potentiating that risk.

Mr. Glantz: It is not clear either way.

Dr. Link: It is not clear any way. Right.

Dr. Santana: You know there have been studies looking with all these very sophisticated, you know, techniques at cells of normal people. And you know, there's a background rate of people that have these abnormalities. And many of these individuals never develop hemonologic malignancies.

So I think it's inherent in the biologic process that these things occur in a developmentally in a tissue that's rapidly dividing, differentiating. It's growing. It's under the influence of various environmental factors.

But many individuals have these prints in some of these cells. But they never develop frank

hemonologic malignancies. And I think we've learned that.

Dr. Link: Thank you.

Dr. Botkin: We're taking a little bit of leverage with our schedule here given the importance of this discussion.

I had one question that I didn't see discussed in any great length in our background materials. Do we have data on the psychosocial impacts of the donation process in this context? This would be sort of irrelevant to the G-CSF administration or not presumably. But is there literature out there that documents the benefits and risks of being a donor in this context?

Dr. Santana: I see your colleague to your left shaking his head. And he probably would be a better expert in that area than I would. So maybe he wants to comment.

Dr. Diekema: Well there is data as a matter of fact. My understanding of the data is that most donors will actually cite the psychosocial risk as higher than the physical ones. And these studies

that have been done are not great. There needs to be better work.

I think the National Marrow Donor Program is probably trying to do some of that. But it's clear that some donors do experience some guilt if the outcome is not good on the recipient. There's often a feeling -- and some of these are difficult to sort out between whether it's related to be a donor or just the sibling of a child with cancer.

But there is at least some evidence that there are some psychosocial risks. But there can also be psychosocial benefits.

Dr. Klein: If I may. At the National Marrow Donor Program those were unrelated donors. And they are donors who are very carefully selected because they have really volunteered to donate. So in many ways they're really not similar at all to siblings.

Dr. Diekema: The ones in the marrow program. There have been other studies though that have looked at siblings. And those are the ones that actually suggest a higher risk.

Dr. Botkin: Thank you very much. Our next

presentation is by Dr. Grupp, who will be talking to us about the background and overview of this particular protocol. And Dr. Grupp hasn't had the opportunity to introduce himself.

So if you would take 30 seconds to provide us with some personal background.

Dr. Grupp: Sure, I'd be more than happy to. I really appreciate the opportunity to come and discuss this study and some of the background material with the panel. My name is Steve Grupp. I'm a Pediatric Bone Marrow Transplanter at the Children's Hospital of Philadelphia and the University of Pennsylvania.

I'm also the Study Chair of the study that's being discussed by the panel today. And I am the Chair of the Stem Cell Scientific Committee of the Children's Oncology Group. So I sort of come to you wearing all three hats, my clinical hat, my regulatory hat and my responsibility as the Study Chair for the conduct of this trial.

So I think that for folks who don't do what I do for a living I just want to spend two minutes

clarifying some of the language that we're using. And what I really want to do is discuss two of the sources that we use in pediatric transplantation for hematopoietic stem cells. And this is a key thing to understand in terms of understanding how you pick cell sources for your patients. And very briefly, we can get cells from two different places, actually three if you include umbilical cord blood, but that's not relevant to our discussion today.

And the first place is from the bone marrow. And bone marrow harvest is sort of the long time, standard way of collecting hematopoietic stem cells. It's collected by needle aspiration from the hip. It's performed generally, especially in pediatrics under general anesthesia.

The characteristics of the cells that you get under those circumstances is that there isn't a lot of T cells. And that's important to one of the major risks of stem cell transplantation which is the risk of a phenomenon called graft verses host disease. And graft verses host disease is one of the things that complicates our use of stem cell

transplant.

The other characteristic of bone marrow is that compared to the next thing I'll talk about which is peripheral blood stem cells, it has a lower stem cell and progenitor cell content. Now you can trace that to a newer form of stem cell collection. And that is peripheral blood stem cells.

And peripheral blood stem cells are actually collected after treatment with this drug which we've been discussing which is G-CSF. And it's typically given for four to five days in a broad range of doses. But typically 10 micrograms per kilogram is the median dose.

These cells are collected from the peripheral venous system by aphaeresis, so by basically hooking the patient or the donor up to a machine, processing the blood through the machine for a period of four to five hours. The patient or donor is awake during this process. There's generally no discomfort associated with the actual collection process.

And you do this on anywhere from one to three days of collection. So the time commitment is much

higher. But there's not a trip to the operating room.

The characteristics of these cells is that there's a much higher content of T cells. And with that goes a higher risk of graft verses host disease. And one of the principle benefits of this cell type is that it has a much higher stem cell, to a certain extent, and certainly progenitor cell content. And this really goes directly to the issue of how quickly you recover from a stem cell transplant. So these are the kind of the background cell types that we use in these situations.

Now I'd like to spend just a couple minutes talking about the study design here. So what we're attempting to do in this study is to improve the standard of care of patients, pediatric patients, undergoing stem cell transplantation. And so what we do is for patients who have a diagnosis of acute leukemia for whom a bone marrow transplant would be appropriate as a standard of care, and in whom a matched sibling donor is available, both the donor and the recipient enroll on this trial.

And if the fact that the donor enrolls on the trial is of course an important characteristic of this trial. And the one that really necessitated a lot of discussion as I'll go through in term of trial development and understanding how the donors participate in the research. The donor is actually the person who undergoes the randomization.

So the donor will either undergo a conventional bone marrow harvest or the donor will undergo an exactly similar bone marrow harvest. But it will be preceded by five shots of G-CSF at a dose of five micrograms per kilo which is half the usual dose that's used for peripheral blood stem cell mobilization. The primary end point of the trial is leukemia free survival in the recipient at two years after transplant.

So I think that the ethical considerations here are extraordinarily important because of the issue that this research involves minor sibling donors. So I'd like to comment on this really from the perspective of a bone marrow and stem cell transplanter. And the first comment I'd make is

that bone marrow donation, by minor sibling donors, is standard of care for pediatric transplantation in the United States.

And I would actually go further than that. And say that in the situation where we have a choice between a matched sibling donor where the degree of matching for the patient is much greater and an unrelated donor from the National Marrow Donor Program who will be an adult, we will, every single time, choose the related donor over the unrelated donor. So that, I think, demonstrates the fact that we feel that this is indeed a standard of care for the vast majority of patients who have a matched sibling donor available as long as the donor is, of course, medically suitable for a bone marrow donation.

So I think the question then comes is/are the sibling donors in the study under consideration research subjects? And you know, there's no question in my mind that they are. They undergo the randomization. And they receive the G-CSF.

And so the issues that we have to address for

our study development and for the discussion today is, is there a potential for direct benefit? And what are the risks of the experimental intervention? Which is administering G-CSF or not.

The background is that all of the patients whether they were on this -- I'm sorry. All of the donors whether they were enrolled in the study or not would undergo the process of bone marrow donation in the operating room. That is a constant. So the issue, the experimental intervention, is actually administration of G-CSF or not.

So I want to address the issue that was briefly discussed just a moment ago. And make my comment that among pediatric oncologist and especially among pediatric bone marrow transplanters, our position and our consensus is that the bone marrow donation provides a direct benefit to the sibling. And I'd like to go through the reasoning for that very briefly.

You know bone marrow transplant is used to provide a curative option to patients with cancer and some non-cancer conditions. A large number of

patients who undergo bone marrow transplant do not have another curative option. And in other cases bone marrow transplant is chosen because it provides a greater likelihood of cure than any other treatment, for instance than chemotherapy or than supportive care.

So in both cases we're in a situation where the likelihood of the recipient of the product of either the bone marrow or the stem cell product is going to have a greater likelihood of survival if they undergo the procedure. In addition I've already made the case that it is preferable for the recipients' safety, outcome and long term survival to use cells from matched sibling donor when such cells are available over an unrelated donor. So I think that our argument under these circumstances to the impact of the death of a sibling in the family context is devastating.

I think there's direct impact on the non-affected sibling and indirect impact because of the very significant impacts of the death of the sibling on parents or others in the family. So under these

circumstances we feel that there is a very significant impact in the possibility of the death of a sibling. And because the bone marrow transplant procedure substantially reduces the likelihood of that event, that is a potential, direct benefit to the donor. And that consensus is what allows us to collect bone marrow from minor sibling donors, many of whom, well most of whom are not able to fully consent.

So can I extend that argument to the study under consideration, ASCT0631? So I think I've made the case that the survival of the affected sibling is of direct benefit to the healthy sibling donor. And the study design is looking for an improvement of leukemia free survival or event free survival in the patient that's undergoing the bone marrow transplant.

Therefore it's a position of the Pediatric Bone Marrow Transplant Community that was developed in a consensus paper that was published as part of the process of the ethical review of this study and in all of the discussions about this study, that this

trial meets the 405 standard for both recipients. That's very clear, and for donors enrolled on the study.

So then the issue of risk comes up. And I think the fundamental question here is are five shots of S-CSF risky for normal marrow donors? So the first comment I would make is that the vast majority of adult transplanters, whether they're using unrelated cells or related cells, use G-CSF in the donor as a standard of care. So that is nearly universally used in the setting of adult transplant. So clearly the use of G-CSF under those circumstances is acceptable for the treatment of these patients and for the collection of cells from the donor.

Twenty percent of pediatric transplants in a recent report used G-CSF in the donors in a 2004 report. And almost all of those were children who were given peripheral blood stem cells and not bone marrow for their matched siblings who were undergoing transplant. So clearly within the pediatric transplant community there's a willingness

to use this agent in the setting of stem cell collection in pediatric donors.

The most common short term toxicity has already been discussed. And that's bone pain. And that's absolutely seen in adults who receive G-CSF. And it's absolutely seen in some children who receive G-CSF.

This complication has not been reported in children. But Dr. Santana did discuss that there were at least five cases of rupture of the spleen which had been reported in adults who have gotten G-CSF for some indication. And generally these are adults, I mean it's a small number of patients, but adults who were undergoing peripheral blood stem cell collection for another donor whether related or unrelated. The estimate of the likelihood of this significant event which is serious, but was not life threatening in those five cases, is somewhere between one in ten thousand, but that is just an estimate.

So then the issue comes forward since G-CSF is a drug that stimulates white cells, does it increase

the risk of leukemia? And so for this we have retrospective data. And I think Dr. Santana really emphasized this. And I think it's extraordinarily important. But there's a substantial amount of retrospective data.

So the National Marrow Donor Program has followed almost 2,500 unrelated donors since their donation for a total of about 10,000 patient years of follow-up. No AML or MDS was reported in this cohort. And this is a paper that's in press and blood.

Now in a retrospective analysis performed by the EBMT they looked at a large number of donors that did receive G-CSF and a large number of donors that did not. And you can see that the incidence of hemonologic malignancy in the non G-CSF group and the C-CSF group is exactly the same. And again, this is subject to the limitations of a retrospective study.

There's no question about this. But it's the best data that we have. And it does include the experience of a very, very large number of patients.

So these two bits of information don't give us any indication that there is indeed an increased risk. Although proving the negative, of course, is very challenging from a statistical standpoint. And the NMDP has estimated that it would require between 10 and 20 years of follow-up, of between two and 5,000 donors to conclude more conclusively than the data that we have to date that's there is no risk of hemonologic malignancy in patients who are exposed to short course G-CSF.

And just as a reminder, of course, G-CSF is a chemical or a protein that exists in the body normally that is responsible for the regulation of your white blood cell count. It goes up naturally when your white blood cell count goes down and responds to issues such as an infection. So clearly each of us experiences increases and decreases in G-CSF concentration in our blood in response to just the normal regulatory process of the body all of the time. So what we're really talking about is a different in dose. When you give this stuff pharmacology, you get more of it.

The other comments I would make as regards to issues that came up in Dr. Santana's presentation. The first I think is the extreme importance of the experience with G-CSF in severe, congenital neutropenia. Now as you'll recall from that slide, there is an increased risk of AML and MDS in those patients. That increased risk is due to their underlying condition. In the past when G-CSF did not exist as a treatment modality for these patients, they all died. They died of infection because you can't go through life without normal white cells to protect you from infection.

G-CSF was a major breakthrough for this group of patients. The survival in this group of patients has been very significantly extended. And it is the opinion of the investigators in this severe, congenital neutropenia registry that we see these AML and MDS cases in these patients because they are surviving long enough for the disease to manifest itself.

So I think that there is considerable argument in that group whether there is any degree of cause

and effect between treatment with G-CSF and actually getting leukemia. As opposed to the issue of as these patients survive longer. We're seeing the fact that they do get leukemia as part of the natural history of their disease.

So when we submitted this protocol to the Pediatric Central IRB, their review which was included in your packet. And I thought was extremely thoughtful. Their review felt that the study met the standard of a minor increase over minimal risk for the donors.

And this was taking all of these issues into account, both the theoretical risks and the actual experience with G-CSF treatment in a large variety of normal donors. This study was approved at over 30 IRBs at the time of referral to the 407 panel. And as you know, is now currently suspended.

So I want to spend two seconds reading along a bit of information because I think this really represents what the pediatric -- no, I'm sorry, what the transplant community, not the pediatric community, but the transplant community, feels about

the risk. So this is standard consent form language as written by the NMDP. And we utilized a form of this language within our protocol.

But I really wanted to use their language because this is really their consensus view on this. And that is normal individuals are at risk for developing cancer including leukemia, lymphoma or other blood diseases throughout their lifetime. It is unknown whether filgrastim or G-CSF increases or decreases an individual risk of developing cancer.

The data being collected during follow-up will help establish if there are any positive or negative, long term affects from receiving this drug, filgrastim. Based on limited long term data from healthy people who have received G-CSF or filgrastim, no long term risks have been found so far. So that is the -- I'm sorry, that's the language in the consent form for patients undergoing short course, G-CSF for collection of peripheral blood stem cells.

The other issue that I wanted to sort of emphasize is that there was an exchange between the

panel and Dr. Santana. And the question was asked what is the increase of risk for hematologic malignancy? A two to four fold excess risk was cited.

And I just wanted to check with Dr. Santana. My understanding is that that is the risk of a sibling contracting cancer if they have a sibling who already has a hematologic malignancy and not an increase in risk though to actually be caused by the G-CSF. Is that correct?

Dr. Santana: Correct.

Dr. Grupp: Ok. So I'm not misrepresenting your? Ok. I just wanted to make sure that that potential area of confusion was clarified for the panel.

So we take the issue of using pediatric stem cell donors in a study extraordinarily seriously. And so this protocol went through an 18 month long, multi-layered and interdisciplinary review in order to hash these issues out to everyone's satisfaction. And then I think the packet that was sent out gives you a sense for what that process what like.

And there were a lot of peoples' opinions weighed in. There was certainly a spectrum of points of view. This was integrated at multiple levels. And I think the final arbiter of all of this information was the Pediatric Central IRB.

So the Children's Oncology Group Stem Cell Discipline initiated the study. There was involvement with the Pediatric Blood and Marrow Transplant Consortium. And they actually came together with the Children's Oncology Stem Cell Transplant Group to do the consensus paper on the risks and benefits of G-CSF in children.

There was direct input from disease committees relevant to the development of this trial, especially AML and ALL. There was strong involvement with both NIH and Children's Oncology Group Bioethics and review of this protocol at those levels. Those reviews were, especially the bioethics review from the Children's Oncology Group were an important part of the review of the Children's Oncology Group Scientific Council.

The protocol was reviewed at the Cancer Therapy

Evaluation Program of the NCI and then of course, finally reviewed by the Pediatric Central IRB. So that's multiple layers, multiple regulatory bodies, multiple, multiple individuals. The vast majority of which were not directly involved in the development of the trial.

There was also a pilot trial that we did to establish the feasibility of this approach in Pediatrics. This was performed by Dr. Frangoul and was recently published in blood. 42 matched sibling donors were enrolled on this trial along with their sibling recipients. It was approved at nine IRBs. The median age was nine.

And basically there is nothing to report from the trial in terms of toxicities. And just like Dr. Santana indicated, there's not long term follow-up. Because this is a study completed within the last few years, but there are no reported donor complications or SAEs, severe adverse events, either at the time of collection or afterwards.

Now this is a lot of transplant speak. And I'm not going to go through it. What I would say is

that we were very excited about the results of this pilot trial because we had the characteristics within the collections of these patients who underwent marrow harvest after G-CSF that we were looking for for the national trial which is an extremely high stem cell and progenitor cell dose, which implies more rapid recovery from transplant and the potential for better survival after transplant. And no impact in terms of extra T cells collected which would have increased the risk of graft verses host disease which is that negative consequence of transplant. So these numbers all indicate extraordinarily rich, high cell content grafts that might have the potential to provide benefit for the recipient.

This is just the event free survival on the trial. And I only present this to say, to remind myself that the patients on this trial did well within the context of the range of diseases of patients who were enrolled in the trial with an overall event free survival of two years of 69 percent. Which, in the context of bone marrow

transplant for leukemic conditions, the vast majority of these patients were patients with leukemia, is certainly a good event free survival.

In a Phase II setting you don't prove anything under these circumstances. But certainly this is the sort of data with the cell recovery data and the engraftment data which suggests that the approach might be promising for testing in a Phase III trial.

So I think I've made our case that this protocol could have been and was approved under 406 and our opinion about potential approvability under 405. But I think it's extraordinarily important for this panel to address a really fundamental question which is why is this good science? And how will we help the kids if we have a successful trial?

And so fundamentally, I've said to you that peripheral blood stem cells collected after G-CSF mobilization is standard of care in adults. And I said it's not standard of care, although it's used in a minority of children, about 20 percent. It's not standard of care in children.

Why is that? And really that's especially

puzzling because there have been good randomized trials that show that stem cells are better than bone marrow in the adult population. But it is the consensus about -- among pediatric transplanters that this data, which is clearly there in adults may not apply as clearly to children. And the main concern is this risk of the post transplant complication chronic graft verses host disease.

There is, without getting into the details. There is reason to believe that some degree of graft verses host disease might actually provide some benefit to patients. But the very significant degree of graft verses host disease that's seen with stem cells seems to not provide benefit.

At least in retrospective analyses which are, of course, always challenging in pediatrics. And so really we have not as a pediatric transplant community been willing to go to peripheral blood stem cells. Everybody is voting with feet in that regard. And we haven't seen the adaptation of peripheral blood stem cells as the cell product of choice in pediatric transplantation.

So what we'd really like to do in this study is to provide the same benefit of higher cell dose to pediatric transplant recipients without taking any of the excess risk of chronic graft verses host disease. And so we feel that the way to approach that is to do G-CSF stimulated bone marrow collection where you don't increase the T cell dose. You don't increase the graft verses host disease risk. But you do get all the other benefits that have been shown in both randomized and retrospective studies for having a high cell dose product.

So what are we looking for in this trial? Well, what our fundamental hypothesis is, is that the larger cell doses in our G bone marrow collections will improve leukemia free survival in the recipients of these stem cells. We expect the G bone marrow will speed the engraftment which is to say the recovery of white cells, red blood cells and platelets after transplant.

There's really near certainty because this has been studied over and over again. That there will be lower rates of chronic graft verses host disease

as compared to peripheral blood stem cells. So both the pilot trial data and a great deal of other comparative data between bone marrow and peripheral blood stem cells shows us that there's no reason -- that we have a reasonable likelihood, a very high likelihood of showing lower graft verses host disease in either of the marrow collections compared to the baseline rate of graft verses host disease in patients who get peripheral blood stem cells which will not be included on this trial.

We're looking for the possibility that there may be an impact on chronic GVHD compared to conventional bone marrow. But that is entirely speculative. And is not something that we're -- that is one of the major endpoints of the trial. But we are -- we do have an analysis intended to look for that possibility.

Secondary objectives are typical for a transplant trial. And we want to look how long the kids stay in the hospital. We want to look at an impact on treatment related mortality. We want to look for a possible impact on immune reconstitution

which again relates to cell dose.

And then I think extraordinarily importantly, we want to look at long term and short term toxicities of G bone marrow verses standard bone marrow. And the way we're accomplishing this is through the related donor safety study which was just funded by the National Institutes of Health through the NMDP. So the comment was made NMDP doesn't study related donors.

And so, that's true. The main purpose of the NMDP, the National Marrow Donor Program, is to provide unrelated donor stem cells and bone marrow cells to patients who require them for their transplantation. But they are very, very cognizant of the issue of any of the risks associated with donation.

And they would like to expand their analysis to patients who are undergoing donation for their sibling or a family member. And the existence of this trial and the ability to co-enroll these patients on the related donor safety trial will really give us the prospective, long term analysis

of risks and potential benefits for patients who are undergoing their -- I'm sorry, for donors who are undergoing stem cell, bone marrow or G bone marrow collection for family members. Most of whom are going to be siblings.

So it's absolutely the intent of the NMDP to include pediatric patients. And one of the major sources of pediatric patients on this study is intended to be patients who undergo their treatment and donors. Sorry, who undergo their collections on the ASCT0631 trial.

Eligibility. The recipients who get the cells have to be less than 22. The donors who give the cells have to be greater than six. And then the other eligibility issues are related to the recipient which I don't need to get into here. Again, it's all leukemias of all sorts which are appropriate for transplantation. And this is a list we don't need to review because it's really about the recipient.

Eligibility of the donor is very tightly controlled. The issue of size is on your handout.

I don't want to read this to you. But basically we need to make sure that a small donor to a larger recipient is still safe for the small donor. So the emphasis is on safety for the donor in terms of donor size and in terms of the other potential exclusion criteria.

The exclusion criteria are entirely consistent with the National Marrow Donor Programs. Exclusion criteria HIV positive, sickle cell trait because G-CSF can be harmful to patients with sickle cell trait, at high risk for donation for any medical reason, pregnant or lactating, uncontrolled infection. And because of this issue that the adults, some of the adult retrospective analyses have seen worsening autoimmune phenomena in adults who have gotten G-CSF. The patients with autoimmune disease are excluded from this trial. Although in all honesty the likelihood that we'll have normal sibling donors with a significant rate of this particular problem is very low.

This is a 425 patient study. And it has an 80 percent power to detect a hazard ratio of .67. What

does that mean? We're looking for a one-third decrease in events, the vast majority of which are going to be relapses of leukemia in the recipients undergoing treatment on the study compared to the standard. And this is estimated to be about a four year study.

So bottom line. And I'm almost done. I think that our argument is that a successful study would improve the practice of pediatric bone marrow transplantation.

The higher cell doses in addition could translate to less volume collected from the pediatric donors. Now this is a future benefit. It is not a benefit that would accrue to the donors on this trial because on this trial we're defining volume and not cell dose.

However it's very clear to see a path forward to reducing the volume taken from these patients. And potentially their time in the OR in the future if the study is successful. And our bottom line is that if we have a successful study we feel that we will define a new standard of care in pediatric bone

marrow transplantation.

And with that I just want to acknowledge without reading the names of all of the folks actually on the study committee who helped to do all of this work. And I would be more than happy to take any questions.

Dr. Botkin: Excellent. Thank you. We're a bit over time here. But again, given the importance of this information we want to take a few minutes for questions.

Dr. Diekema?

Dr. Diekema: I have two questions. The first is you mentioned that there's a strong preference for siblings in terms of donation, but didn't provide any data to support that. I'm just wondering what the incremental value is in having siblings act as marrow donors. So that's my first question. Yeah.

Dr. Grupp: Ok, so the first question is that the use of a matched sibling donor verses the range of unrelated donors available to us approximately cuts in half the risk of treatment related

mortality, so dying during the transplant from the effects of the transplant. And in addition, and this factors into the treatment related mortality number it substantially decreases by half to two-thirds, the risk for severe graft verses host disease. So two of the major complications of transplant are decreased if you use a matched sibling donor than the range of unrelated donors.

And to sort of you know narrow in on this and look at each kind of unrelated donor gets a little bit more complicated. But generally speaking that's why, I think, nearly every. I mean, you never want to say every, but nearly every pediatric transplanter, given the choice between a matched sibling donor without a medical condition and an unrelated donor would go for the matched sibling donor.

Dr. Diekema: Thanks. That's helpful. My other question concerns donor eligibility of the criterion you just showed us.

One of those criterions is a high risk for donation due to pre-existing condition. I'm just

wondering why not any increased risk would be an exclusion criterion? I mean any pre-existing condition that posed any increase in risk as opposed to a high risk.

Dr. Grupp: That's a reasonable question. It's not something that came up in the review. I would say that we should take that back to both the study committee and to the Children's Oncology Group Stem Cell Discipline and maybe try to nail that down a little harder. I think you've made a very good point.

Dr. Botkin: Dr. Menikoff?

Dr. Menikoff: Two questions. On peripheral blood stem cell collection you noted it's not standard of care, but a fairly substantial percentage of the donations have, for at least a few years, been done that way, about 20 percent. Assuming that was done as clinical care, I haven't heard anything about this being done as part of research studies.

Dr. Grupp: Yeah. The vast majority of the 20 percent of patients who were identified as having

received peripheral blood stem cells from their minor sibling donor were just done as --

Dr. Menikoff: Ok.

Dr. Grupp: I mean, it's the standard of clinical care at that institution.

Dr. Menikoff: So in effect in terms of how that was legitimated in our society, presumably that would be under some ethical understanding as you mentioned that there was a significant benefit to those donors.

Dr. Grupp: Right.

Dr. Menikoff: Ok.

Dr. Grupp: Yeah.

Dr. Menikoff: So it would be then an issue if on this side a determination was made that there's, for example, no benefit or virtually no benefit because it's so speculative, some issue of inconsistency between the current clinical practice and what we might then be using in terms of research ethic standards.

Dr. Grupp: Right. I think it's fair to say that there's a substantial percentage of pediatric

bone marrow transplanters who would be willing to use peripheral blood stem cells after G-CSF stimulation without the context of any clinical trial.

Dr. Menikoff: Ok.

Dr. Grupp: I think I was trying to say that.

Dr. Menikoff: And just on your pilot study you said there were nine IRBs involved in approving the pilot study and then there were 30 on the current study. I assume of the 30 some of them did not just opt in to accept the NCI central IRB approval. I'm just trying to get at do you know anything about the rationale of any of those IRBs in terms of -- they had to approve it under some thing, so presumably 404, 405 or 406.

Dr. Grupp: I think that's a great question. And I don't know the answer. The only IRB deliberation to which I have access is the one --

Dr. Menikoff: Is the one --

Dr. Grupp: -- That resulted in the referral for the study to this panel.

Dr. Menikoff: 407. Ok. Thank you.

Dr. Botkin: Dr. Link?

Dr. Link: Just a question about, two questions really related to the use of G-CSF. So when you said 20 percent, does that include auto BMTs or these are 20 percent of sibling donors?

Dr. Grupp: Sibling donors for allogeneic bone marrow transplant. Essentially every patient who undergoes autologous transplantation --

Dr. Link: Yeah, right.

Dr. Grupp: -- which is to save stem cells from themselves --

Dr. Link: The 20 percent doesn't include those.

Dr. Grupp: Does not include, correct.

Dr. Link: And then the second question sort of, you included in there, not in your slides here, but in one of the papers it sort of said that people use C-CSF stimulated bone marrow harvest as well. And so what would be the rationale outside the context of this trial just because people already kind of believe it or?

Dr. Grupp: Right. So there's adult data that

show two things. There's adult data that shows that there is a very significant impact on cell dose.

And then there is adult data that shows that if you, in the context of a clinical trial, if you stratify patients by high cell dose and low cell dose, the patients who get a higher cell dose do better. So if you put those two things together and there is a willingness among some doctors to use G stimulated bone marrow as a stem cell product.

Dr. Link: Yes, I'm trying to help you here. So people are already adopting this based on the adult data which is often done because it kind of works. So, you know, we don't need a weather man to know which way the wind blows sort of thing, ok.

[Laughter.]

Mr. Glantz: I wonder if we can talk about the benefits. We've been talking about the risk pretty much up to this point and one of the pieces that I've read, and I've been searching through it. I have all this paper here. It said that the aspect of that right now without the G-CSF stimulation is about a 49 percent survival rate and that it had

gone to 61 percent or something like that. You used a 69 percent number.

So what is, in your opinion, in general, what is the survival rate for the recipients with and without this?

Dr. Grupp: Well I'll answer that in two different ways. Clearly the study is looking for a decrease in one-third in events, most of which are going to be relapses. So that's what we're looking for.

The actual percentage survival, unfortunately, is going to be dependent, very much, on the characteristics of the patients who come in. And there are patients who undergo transplantation for leukemia that have a 70 or 75 percent survival. And there are patients who undergo transplant for leukemia who have a 25 percent survival.

So the actual numbers involved are going to depend on the kind of patients who actually enroll in the trial. And that slide I showed you with all the different kinds of leukemias. Those leukemias have, unfortunately, a very wide variation in

outcome which is why we actually did the analysis based on a reduction of events.

Mr. Glantz: Well I understand, sort of, the complexity, based on that. But it's hard to make a determination without having some sense of what the benefits might be. For some of the literature, for example, looks like if you use this stuff than everybody lives and so the families will be happy and you know, all of that sort of thing. But that's not the case, right. There's still a substantial number of these kids will unfortunately die.

Dr. Grupp: Yeah, there's not a 100 percent survival with anything I've used.

Mr. Glantz: And so the question is what is it we're getting? Does it look like a ten percent increase? Your statistics will look for a one-third increase. It doesn't mean you'll find it, of course.

I'm just wondering that in the use of this in other populations, how much of a benefit has there actually been?

Dr. Grupp: So that 30 percent decrease, you

know that one-third drop in event rate is based on the large retrospective analysis of stem cell dose, not stem cell dose, bone marrow dose in adult patients undergoing bone marrow transplantation. So that is the difference that we're looking for.

Mr. Glantz: So in adults it goes from what to what in terms of survival?

Dr. Grupp: I don't know the answer to that question.

Mr. Glantz: So in children if there were a 25 percent where you're dealing with a kind of disease where there's a 25 percent survival, you would expect, you would hope to find a 33 percent survival, or something like that, 34 percent?

Dr. Grupp: That's correct.

Mr. Glantz: Is that right?

Dr. Grupp: Yeah. And I think in general in terms of study design it's easier to see an impact in a group of patients that have lower event free survival than it see to see an impact on patients of higher event free survival. And so one of the things we did in the protocol was really try to make

our best guess based on the kinds of patients who were undergoing transplantation of what the mix of that might be. But that, in all fairness, is very much dependent on who actually enrolls in the trial.

Dr. Botkin: I too wanted to pick up on this question of benefit. It sounds like the study team was looking at a 405 justification with direct benefits to all the participants. And you note on several occasions here direct benefit to the donors.

As I understand the protocol though, the purpose is to give the G-CSF to the donors to enhance the quality of the bone marrow that's acquired from those kids. That enhanced quality will mean reduced morbidity and mortality for the recipient and the improved outcome of the recipient is then what benefits the donor.

Dr. Grupp: Exactly correct.

Dr. Botkin: Isn't that a classic description of an indirect benefit? I mean it may be substantial. But it requires that chain of events in order for the intervention to lead to the benefit of the donor.

Dr. Grupp: Yes. That is correct. So that is precisely the same indirect benefit to the donor that justifies our ability to collect peripheral, I'm sorry, to collect bone marrow from minor siblings who are either unable to consent or not fully able to consent. That's exactly the reasoning that we use.

Dr. Klein: Thank you. That was a very clear presentation. But I would like to ask you a question about an issue I didn't see addressed that at least in a small study in adults.

This was John Barrett's study in 1998. There was delayed loss of graft in bone marrow that was stimulated with G, so much so that they stopped stimulating bone marrow with G. I didn't see that as a possibility in here. And maybe you don't believe that that could exist.

But my real question is what happens if that does occur? Is there a second collection from the donor? And if so, is that a G stimulated collection or how are you going to address that?

Dr. Grupp: So, the protocol has stopping rules

in terms of graft failure. So that's something that's being monitored for is the first question. In studies that use the stimulation strategy that we proposed here, there has not been evidence for an increased levels in graft failure.

So we feel that although we're looking for that possibility and would find that to not be acceptable. We're not expecting that to happen. I will say that we do not mandate the approach for the Center in terms of how they deal with a graft failure because there are multiple causes of graft failure and the reasons can be highly individualized.

There can be immunologic basis for graft failure. There can inadequate cell doses. There can be a number of other circumstances.

So we don't, in the protocol, tell the collecting institution what to do. Typically in a matched sibling donor situation you would go back to the donor. And to be honest with you, typically, now I'm speaking from a clinician's point of view and not from a study chair point of view.

What I would do in that situation is I would get peripheral blood stem cells, stimulated by G-CSF from that donor because I know that that is going to provide me the most, the quickest road to recovery.

Dr. Klein: I guess if I could follow up on that. The reason I ask is in the pilot study there was one delayed graft failure. Although that was an aplastic anemia patient, that may not be relevant, but it may be relevant.

So I guess the answer is that's it's each center determines whether or not they go back for a second procedure on the donor. Is that correct?

Dr. Grupp: They would either go back to a second procedure on the donor or they would choose another donor. That's what we would. But that's a clinical question, not a study question.

From a study standpoint we're monitoring for the possibility of increased graft failure.

Dr. Botkin: Dr. Santana?

Dr. Santana: Can you comment on -- I thought I had read it and obviously I just looked at it again. I couldn't put my finger on it. Maybe you could

help me about what is going to happen with the follow up or the donors and how that information may or may not be helpful given the limited sample size in terms of the number of donors which would be roughly equivalent to the number of recipients.

So I hope --

Dr. Grupp: I hope it's exactly --

Dr. Santana: Is it going to be follow -- I know, that's the problem. Is there going to be follow up with the donors? And if so, how is that going to be accomplished? What are you going to be looking? What's the end points? And how are you going to use that information?

Dr. Grupp: So I think that we've already clearly stated that. Because of the extraordinary rarity of the potential serious events which is really the spleen issue. And then the theoretical issue, hemonologic malignancy, 425 patients is not going to, even if we follow them for 50 years, is not going to statistically be able to allow us to prove a negative.

However, I think that we are still committed to

the issue of follow up in these patients, so there will be two ways that that will happen. The first is that the patients will be offered -- I'm sorry, the donors, the families, will be offered the ability to enroll on this NMDP RD Safe study which will follow patients out to five to ten years and look for any events associated with the collection. They also will do a questionnaire, a psychologic questionnaire, the content of which I would refer you to Dr. Pulsipher who is the PI of that study, intended really to get to the issue of what is the impact on families, on caregiver burden and on the donor of the cells down the line in terms of really looking at this.

And there a 425 patient study or even a small fraction of that would provide much better data than actually currently exists. For patients treated -- or donors treated as centers that do not have access to the RD Safe study, they can opt in to the same long term follow up using the same questionnaires. And the NMDP has committed to performing that long term follow up under the auspices of our study.

And there, there's no question that the main intent is not data collection, but just making sure that we do adequate donor safety monitoring for the donors on our study. We won't be able to use that data to say anything meaningful about the long term risks. But we're still doing long term follow up.

However, if a family says either at the time of their collection that they opt out or later on if they withdraw their consent, then we will not have an option for long term follow up.

Dr. Botkin: Dr. Link? And I think this should be our last question for this session.

Dr. Link: So just a quick question about your hypothesis. Why this should improve leukemia free survival or reduce or less. I understand why using stimulated bone marrow might decrease the risk of graft failure because you have a higher cell dose.

Although it's, you know, graft failure in leukemia patients, especially with this regiment is not going to be very common.

Dr. Grupp: Right.

Dr. Link: And I could understand how, you

know, increase recovery rates so that you would have a decrease in transplant related mortality. So I can get that. But how is it going -- what's the hypothesis for why this should prevent relapse?

Dr. Grupp: Well, you see, if you look at the retrospective analyses of cell dose given to patients undergoing transplants for leukemia in the bone marrow setting, almost all of the benefit that's seen in terms of event free survival is in terms of decreasing a relapse. So first off it's consistent with the retrospective analyses that we would see a decreased relapse. The mechanisms by which a decrease in relapse might be achieved are clearly speculative.

There's a lot of data recently that the absolute lymphocyte count which is an indirect measure of immune recovery after transplant correlates with the recovery and the likelihood of recurrence in the patients. And there is no question that higher cell doses result in higher absolute lymphocyte count. So you could argue there's going to be a small impact on treatment

related mortality, but I agree with you, that's not where the meat is.

We do -- are really are looking for a decrease in recurrence. And we think that that -- it may be related to the immunologic effects of the graft and especially more rapid recovery in that critical time period where immune recovery may actually impact on the likelihood of the few leukemia cells that are still around, being eliminated or not being eliminated.

Dr. Botkin: Thank you very much. Excellent presentation and discussion. We're going to alter our schedule a little bit here and jump to our open public hearing at this point. And after comments if any exist, go to break.

So are there members of the audience who wish to speak to this issue before the committee?

We have two letters that have been submitted via the website that we will touch on after the break.

So at this point we're going to take a 15 minute break until a little after 15 after, about 17

after. There's food across the hall and rest rooms are down the hall this way. Thanks very much.

[RECESS]

Dr. Botkin: I wanted to open the opportunity first for again any members of the public who may wish to speak to the Advisory Committee, the Ethics Subcommittee that would be.

We have two letters that have been submitted. And I want to touch on one relatively briefly and one in a little bit more detail. The first letter -- and these are posted for you in their entirety on the website.

The first is from Dennis L. Confer, Chief Medical Officer for the National Marrow Donor Program. Dr. Confer is providing some information about some data relevant to this protocol. I will not read the entire letter, but I will read fairly substantial portions of it.

"National Marrow Donor Program is a non-profit organization entrusted to run the C.W. Bill Young Cell Transplantation Program and is dedicated to the mission of facilitating allogeneic hematopoetic cell

transplantation from unrelated adult donors and from umbilical cord blood. As such the NMDP (that is the National Marrow Donor Program) has a large experience relevant to the discussions regarding this protocol. Dr. Confer and Miller recently published a letter in the British Journal of Hematology that provides valuable information about G-CSF for peripheral blood mobilization from unrelated healthy adult donors.

PBSC (that's peripheral blood donors) facilitated by the NMDP received a total dose of 10 micrograms for five days followed in perpetuity at the time of the BJH letter a total of 4,015 peripheral blood donors and 9,785 person years of observation, including 897 donors followed for more than four years. There were no reported cases of leukemia or lymphoma in that cohort. Of note, 20 cases of various solid organ malignancies were reported consistent with the age adjusted U.S. incidence of cancer in the adult population.

These cases confirm the applicability of the data obtained from the NMDP follow up system and

suggests that the adverse event reporting system is functioning appropriately. Currently the NMDP experience now includes over 7,000 adult peripheral blood stem cell donors. The NMDP experience with adult marrow donation is shown as 0.7. The incidence of long term serious complications mostly related to the collection procedure.

And NMDP data further show that the shorter collection time in the operating room in younger donors are correlated with decreased incidence of complications. G-CSF stimulation for bone marrow collection is not currently performed for NMDP facilitated donations. But anecdotal observations with G-CSF stimulated bone marrow collection suggest that collections are far easier and therefore result in shorter collection times. The implication of shorter collection times is that G-CSF stimulated bone marrow donations may result in fewer marrow collection associated complications."

So that's obviously directly relevant to the donor population here. And they go on to note that this is the data they are quoting are from adult

participants. They say it is not clear how these differences will translate to differences in adverse events in the pediatric population. Further efforts to acquire long term safety data are underway at the NMDP.

The second letter does not speak specifically to this protocol, but expresses a general concern that committees of this sort are "in the pocket of big Pharma and not properly protecting the interests of the people of the United States." Concerned about the self interest of those who may serve on these panels and revolving doors that are alleged by the writer to exist between committees like ours and big Pharma with salaries, potentially biasing the process that we are undertaking here. So there is encouragement for change in the system broadly such that financial conflicts of interest do not corrupt or bias the process that we are undertaking.

Does that sound like a fair summary?

Dr. Pena: It would also be helpful to note the letter focuses on vaccine therapy.

Dr. Botkin: Alright. Now we have the

opportunity to hear Dr. Wysocki from the Nemours Oncology IRB which is the IRB that submitted this protocol for 407 consideration.

Dr. Wysocki: I am now. Well thank you for organizing this discussion, for letting me play a small part in it and thank all of the previous speakers for putting this all in context and providing a good, clear frame of reference for these deliberations.

I'll try to take you through as clearly as I can our IRB's decision making process in referring this study for these deliberations. I would also direct you to the cover letter that was written under far less duress than I'm feeling at the moment.

[Laughter.]

Dr. Wysocki: And probably will be much clearer and succinct in the points made.

First, a little bit about the structure of Nemours Human Subjects Protection Program. The foundation operates pediatric medical centers in Florida and the Delaware Valley with support from

the Alfred I. Dupont testamentary trust. Nemours Office of Human Subjects Protection directed by Paul Garkinkle manages three IRBs under our single FWA.

The Nemours Oncology IRB reviews and oversees all hematology, oncology protocols at all of the Nemours sites. The members included at the time of this review, three physicians, one of whom was a pediatric hematologist oncologist, and representatives of nursing, epidemiology, psychology, social work and physical therapy as well as a parent of a child with cancer. I should note that our agendas are probably 98 percent pediatric research and rarely, if at all, do we concern ourselves with adult research, only in the areas of epidemiology. Our meetings are conducted monthly by video conference.

The IRB initially considered this protocol at its July 7th meeting. The review and discussion of the protocol led to several crucial questions from the primary reviewer as well as other IRB members. The IRB questioned both the risks and potential direct benefit to healthy donors of receiving G-CSF.

The IRB voted to defer approval of the protocol pending further information.

We asked Dr. Eric Sandler, the local PI, to clarify the possible risks and direct benefits to healthy donors and to forward the pediatric CIRB rationale for approval of the protocol if it could be obtained. And note that the protocol we were provided put forth the opinion of the study steering committee that, not explicitly, but implicitly, that the study was approvable under 405 and 52. That it provided, although it included more than minimal risk, it provided the prospect of direct benefit to the donors.

And early on we began to question the merits of that perspective of the study. So we asked for this additional information and Dr. Sandler provided it to us. We reconsidered the protocol at the September 3rd meeting. And that included a review of various documents that were supplied to us. These included the NCI Pediatric CIRB document detailing its basis for approval and as has been noted it was approved by them under 46.406 and

50.53.

We also reviewed a variety of pertinent journal articles which were review articles of the pertinent issues regarding the risks and benefits of G-CSF that were submitted at that time by Dr. Sandler. And we considered very heavily the opinions of one of our members, a pediatric hematologist oncologist, about the risks associated with G-CSF in siblings of children with cancer. And in particular she was concerned about the possibility that siblings of children with leukemia are a vulnerable population that faces special risks of developing leukemia themselves. She cited two to five fold increase. We've heard two to four fold increase.

And in particular she was concerned that G-CSF administration had the potential to initiate or hasten the process of leukemogenesis. And we've heard much about this. Clearly it's a theoretical risk. But this physician's perspective of the issue was that there were several laboratory studies showing evidence of genetic insults, consequence of G-CSF administration.

And she expressed concerns that G-CSF administration could represent either the first genetic hit or the second genetic hit thus accelerating the onset of leukemia. There was also concern that although there are studies out there, the NMDP studies and so on that speak to this issue. Many of those studies are based on adult, unrelated donors rather than siblings of children with cancer.

And a related concern which has also been already expressed is the possibility of under reporting in terms of the follow up of the donor outcomes. We further evaluated other risks mentioned in the COG protocol and the Pediatric CIRB summary, all of which, I believe have been mentioned earlier today.

Our deliberations revealed many issues along which we agreed with the Pediatric CIRB conclusions.

We agreed that transplant recipients involvement is approvable under Section 405 and 52.

We agreed that sibling donors are indeed research subjects.

We concurred that G-CSF administration could

not be viewed as a minimal risk procedure.

And we also concluded that G-CSF cannot be construed as offering the prospect of direct benefit to donors.

The journal articles we reviewed as well as the study protocol appealed to several possible sources of direct benefit. Those being the enjoyment of sibling surviving pediatric cancer and the possibility of requirement of a smaller dose of bone marrow aspirate required for transplants. And I'd like to comment a little bit on our view of those two possibilities.

Enjoying the survival of a sibling and requiring a smaller -- I'm sorry, enjoying the survival of a sibling is, in our view, at best, an indirect benefit of being a bone marrow donor. And I think others today have noted that it is certainly not a guaranteed benefit. That the process of donating is immensely complicated from a psychological standpoint and the outcomes of the recipients' transplantation can hardly be guaranteed at this stage.

Whether bone marrow donation accrues these psychological benefits to donors is certainly something we can discuss. But appealing to that as a benefit of G-CSF administration appears to us to take the indirect nature of the benefit to another order of magnitude of indirectness. And so that left a number of the members uneasy with that kind of interpretation.

Requiring a smaller sample of bone marrow to achieve equivalent stem cell dose may benefit future donors, but not those in this study. So it really can't be appealed to as a direct benefit of participation.

But most importantly we agree that the study has the potential to yield information of substantial benefit to children with leukemia who receive bone marrow transplants via sibling donors.

Our ultimate conclusion about this study was that we were very uneasy about calling this only a minor increase over minimal risk. And we felt that there was some likelihood that this should be at least reviewed as a 407.54 determination. And so we

made the referral in the spirit of an inquiry. Do you agree with us that this is indeed the case? And so here we are today.

Now a couple points about our take on some of the journal articles we were provided. We also devoted considerable discussion of these primarily in terms of what they could offer regarding whether G-CSF administration in healthy donors does or does not constitute more than a minor increase over minimal risk. And this of course is a big determination central to the approvability of the study under 406 or 53 of the DHHS and FDA regulations.

We noted that few studies of G-CSF risks have been done in healthy children or in siblings of leukemia patients. Some additional data has been provided today. But again, one would have to argue that the shear amount of data that's available in assessing the magnitude and likelihood of these risks, in our view, still caused us considerable consternation.

The risks of leukemia, leukemogenesis, in

donors after G-CSF administration which has been implicated in some laboratory studies is unknown and difficult to disprove because of the large samples and duration of follow up that's required. There are other rare but serious risks associated with G-CSF that have been shown in studies with adults. And on the one hand we're hearing that we should appeal to the low risk of leukemogenesis in the adult studies that are out there. But we should ignore the risk of ruptured spleens and other kinds of risks that are also out there in the adult population.

Now I grew up in a pediatric health care environment. And the one sentence I believe I've heard more often than any other is children are not little adults. And I believe that our IRB is very much convinced of the truth of that statement.

So the relevance of all of these findings is unclear due the need for lengthy follow up of very large samples. And it's noted that those studies will probably never be done.

So the key points of our discussion at the

September meeting were that the protocol offers no direct benefit to donors.

That siblings of children with leukemia have an elevated risk of developing leukemia themselves.

That G-CSF carries a theoretical risk of initiating onset of leukemia.

And that in the healthy siblings and this is a risk that is difficult to confirm or disprove because of the required sample size and follow up.

And that G-CSF carries other risks such as enlargement of the spleen which is rarely progressed to rupture, bone pain, fever and others.

And that the rare but serious risks have not been seen in pediatric donors in studies to date.

Now while we carefully considered the argument that sibling donors have a condition as required for approval under 406 or 53, this remained a point of contention among our members. Since we eventually concluded that the study posed more than a minor increase over minimal risk, this issue became irrelevant. But several IRB members expressed concern that this might be an overly inclusive

interpretation of this term and that it may contradict the spirit of the special protections afforded by these regulations.

So the Pediatric CIRB had asserted that sibling donors have a condition. We had much contentious discussion about this with the notion that this determination might be too broad. Parenthetically I would remark that if these siblings have a condition, we should also consider part of that condition to be some elevated genetic propensity to develop leukemia. That might in fact be a defining characteristic of their condition. So that question eventually became irrelevant and we left it for you.

Ok. Our conclusions -- let me get on my right page. In the end we concluded that G-CSF administration to healthy donors constitutes more than a minor increase over minimal risk. And that this aspect of the study is therefore not approvable under 406 and 53.

The essential difference between our opinion and that of the Pediatric CIRB lies in our IRB applying a somewhat more conservative perspective of

the adjective minor. This fine distinction between our positions illustrates the difficulties that IRBs face in applying this aspect of the regulations. A topic that Dr. Nelson has written and spoken about extensively.

We agreed with the CIRB however that the study carries a definite potential prospect for direct benefit to stem cell transplant recipients both in this study and in the future. We therefore concluded that this protocol appears to be research not otherwise approvable that offers an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children. And in the spirit of wanting to move this study forward, we decided to seek FDA and OHRP opinion regarding whether the study was eligible for this 407.54 review. And their concurrence with that inquiry brings us to today's proceedings.

So thank you all very much.

Dr. Botkin: Dr. Wysocki, thank you very much for your thoughtful presentation. And thank you for the quality of your work with the IRB. We have some

time for questions.

Dr. Wysocki: I didn't know it would be so easy to convince you all.

[Laughter.]

Dr. Botkin: Thank you again. Thank you.

Alright we're still on track, I think, for lunch at noon. So we've got about 15 minutes or so to begin our discussion process about the protocol. And I would just remind our group of a couple of things.

I think everybody is interested in having a 407 process that's efficient and functional. So I think this is a relatively uncommon opportunity to engage in this process. And so again thanks to everybody for doing that.

And in that process I think we have the opportunity to walk through a variety of considerations that have been part of the prior considerations relevant to this protocol by other IRBs and ethics committees. And ultimately make a recommendation about whether this is a study that should be approved or not. Again we're not making

that decision, but providing a recommendation with that in that regard.

Obviously that's the overarching question. Should this research go forward? A closely related set of questions is well if it should, what should be the justification for moving forward? And if it shouldn't, what should be the justification for not moving forward?

I think that as everyone knows there's a wide variety of literature out there on many of the questions that we'll be addressing here shortly and this afternoon about the specific criteria. But as we know many of these determinations are subjective. How we make these decisions will have some degree of precedential affect on other considerations. So I want us to be cognizant of the precedential affect of our discussion and our determinations in that regard.

So in that vein, we may pick up some parts of the discussion that may ultimately not be critical or directly relevant to our final determination. What I mean by that is to say that we might find

that this is a more than a minor increase over minimal risk, for example, but still want to engage the question about whether this is a condition or not. As Dr. Wysocki indicated they ultimately didn't make a determination on that because it became a mute point.

It may indeed become a mute point for us. We may want to forego that same kind of conversation. But I will encourage us, assuming we have time, to pick up on at least some of that conversation if we have the opportunity to do so.

In our process I think I'm going to raise a series of questions as Skip had prompted us to do that we'll be walking through the regulation to a certain extent. If there seems to be wide consensus on certain issues then we'll note that and move on. If there is active debate over questions than we may come to a vote and my understanding is I don't vote unless it's a tie, right? I'm kind of the tiebreaker should that situation arise.

Any questions about that process in general?

Mr. Glantz: Who does vote?

Dr. Pena: All of the consultants and members of the subcommittee will be voting.

Dr. Kon: I was just wondering if at some point there will be an opportunity to also comment on if we have concerns about the informed consent document. If there is consensus about moving forward, will there be an opportunity to talk about some specifics?

Dr. Botkin: I think we will have the opportunity to make comments about those types of issues as well. As Skip had said, we are not an IRB to go into great depth with, you know, wordsmithing, etcetera. But I think if there's a basic concepts about the consent process than that is part of our -- yes, please.

Dr. Wysocki: The consent documents that were submitted are purely that they were never reviewed by our IRB.

Dr. Botkin: I believe if we have consent in assent documents that were approved by COG IRB. We'll confirm that. But I believe that's the case. So we don't have their initial drafts. We have ones

that have been approved for enrollment of a small number of participants actually in this study prior to the time it was suspended.

I believe Dr. Wysocki and Dr. Grupp also have -- are going to be able to join us for this discussion. And so the opportunity may arise to go back to them for questions should that be appropriate.

Alright. Since this is an ethics group I wanted to raise one set of questions first for any level of discussion that we might be interested in entertaining. And that has to do less with the specific regulations that we'll be diving into in great depth here shortly, but about the background ethics of the use of siblings as donors for transplant purposes.

Some of the background literature here addresses specifically that question which seems to justify this is a practice. As we've learned in that literature and from these presentations that it's now common practice. But given the fact that that's a background circumstance for the conduct of

this research I wanted to entertain any discussion about that practice whether folks have questions or ethical concerns about that as a clinical enterprise, not in this context as a research enterprise.

Mr. Glantz: I think there are concerns. I don't know whether the concerns are such that people shouldn't do it. But there is the concern that it's very similar to the initial kidney transplant cases which were not done in the context of IRBs.

They were done in the context of treatment in which the question was raised whether or not parents have the authority to have an operation conducted on one child for the purpose of benefiting another child. And you know, what Massachusetts's courts sort of invented the benefit theory that we're hearing here because the argument was made that children do get benefits. The donors do get benefits.

But that was never actually litigated because the donors never had a lawyer. So everybody sort of agreed that they got benefit. In the one case where

the lawyer, Gary Cole, he said to the psychiatrist who was brought in to testify that there was a benefit. He said, are you sure? And she said, no.

You know, and then the court said, we shouldn't be thinking about benefits.

[Laughter.]

Mr. Glantz: You know because it's just made up. You know. And so the question for the court was, you know, how do you justify this sort of thing, if you can. And what it said essentially was that this is the kind of risk that parents can take. That oftentimes parents trade off needs of one child for another child. You know kid may go to college and the other kid may not. And that unless there's reason to sort of interfere from a legal perspective it wasn't the kind of risk that was so grave that it should matter.

The court wasn't referring to, you know, the ethical consideration. It was referring to legal consideration which has overlaps here. And one of the ethical considerations, I think the important one, has to do with the parent's own conflict of

interest and the parents sort of being trapped in this very, very difficult situation and who is actually able to make the decision for really both of those kids since their interests may be conflicting. And the parent's interests are so conflicted.

Dr. Link: Well I think the courts did deal with that. In fact in the early transplant days, at least in California, one child, the donor was usually made a ward of the court where the court would be the decider for the donor as to whether it was ethical. And so we went through a lot of shenanigans about every time we did an allegeneic sibling transplant that the parents could consent for the recipient, but the court would be the advocate, if you will, for the -- so I don't know if they consider the ethical issues. But certainly they considered the conflict of interest.

We don't do it anymore because it became sort of, you know, so routine and so accepted that, you know, it was sort of dropped. I'm not sure whether they actually, sort of put out a directive that says

please don't plug us anymore. But we certainly do it as a routine now without involving a third party.

Mr. Glantz: Well again, some of the courts have sort of split on it, just that you need to involve a third party of some sort. And one of the questions that could be raised here is should there be some third party involved that wouldn't necessarily have to be a court, but somebody who does it. So the idea was for it to be public.

One of the big issues, the initial issues, was the kids who, for example, who were mentally retarded, were being used as donors for kids who weren't. And there was never a transplant in the other direction from a normal kid, if you can use that word to a mentally retarded kid. And so there were those concerns.

I've never seen any reported --

Dr. Botkin: Is the ethics of this clinical enterprise contingent on there being a benefit to the donor or would we say -- would we be comfortable in saying this is an ethical enterprise as long as the burdens or risk to the donor are not excessive,

however we might define that?

Dr. Hudson: I would say I would agree. It's the later. It's not going to be excessive risk to the donor because there's really not a benefit otherwise in my opinion.

Dr. Botkin: A defined benefit.

Dr. Hudson: Right.

Dr. Diekema: I think I would agree with that for two reasons. One is I think we generally allow parents that discretion. And the second is part of the reason we do that is that as a general rule when families benefit so do the children within that family. And it's part of the reason I think we allow these sorts of decisions that don't put one child at significant risk of serious harm to be made by parents because they're largely about the family as much as they are about individual children.

Dr. Santana: So I want to follow up on that. I would also agree with the comment in the context that we ascribe to parents always to make decisions that are in their best interest of the value of that family. And as long as we recognize that it's

within their own value system that they define the benefits unless it's clearly abusive or one of those scenarios, that we wouldn't really question that that we would think that parents in a general sense would advocate for their children in any given circumstance with few exceptions obviously as defined by law.

Dr. Link: So I wonder if we can frame the question just a little bit differently because I think we're going to -- you're going to have this convening of this committee every time that a transplant question comes up. And I think that it was very well framed in one of the articles that if you have a new indication for bone marrow transplant it becomes an experiment. The donor becomes an experimental subject.

So in other words if you decide you're going to transplant baldness let's say. Take a personal. And you want to use minor siblings or minor donors, that would become then since the transplant wouldn't be done unless it was indicated that doing anything to the donor at this point, even the harvest, which

we consider that sort of standard, that then becomes an experiment because you wouldn't do the transplant, you know, unless you proved that it had efficacy.

Mr. Glantz: I just want to say I don't think that point is given, that the fact that something occurs in the context of research doesn't mean that every part of it is research. And so taking blood from a kid that might be used in research doesn't mean that the blood draw is research. So there is a distinction between donors and research subjects.

And the distinction that's been drawn here is that the donors are getting a drug. Unlike the other circumstances in which that if the drug was not being used in this circumstance that we wouldn't be here.

Dr. Link: But this donation wouldn't be considered because the experiment, even to the recipient there's no indication to do this for baldness or for whatever new disease we have. So the reason I'm trying to -- I would like to sort of -- we have to think of a transplant as by definition

it's a package deal. You can't have a transplant without a donor.

You know, you can talk about it all you want who's benefiting. And who's not benefiting. But the whole idea of doing a transplant is that you have to have somebody donating blood.

Now if you're an adult you can consent to doing it. It's -- you have you know, the idea that you're altruistic. But in a child and especially since we all know that a sibling or a family donor is much better than an unrelated donor. So this is always going to come up.

So if the transplanters come back here and say we're going to do a transplant for a new genetic disease where we have some indication in that, you know that, using, you know, hematopoietic stem cells have the possibility of ameliorating the disease. But it's not an indication which has been proven. It's not leukemia. It's something that's a new thing.

Every one of those donors is an experimental subject because they wouldn't be subjected -- this

is different than a blood draw. You wouldn't put a kid under general anesthesia and subject him to 200 bone marrows and drawing blood and potentially transfusing them unless it was an indicated procedure. It becomes an experiment.

And this was spelled out in one of the papers very nicely that, you know, that once the procedure itself is experimental, than the donor is an experiment. Whereas if it's an indication like leukemia where we know it works in certain circumstances, than the standard donation procedure, meaning putting them under general anesthesia, forgetting the G-CSF for the moment. That becomes standard. That's not part of the experiment. That's part of clinical care and accepted.

Mr. Glantz: I think that is not correct.

Dr. Link: I didn't say it. One of the papers said it.

Mr. Glantz: Ok, than one of the papers is not correct. Well that's something we can discuss that in the kidney transplant circumstance no one ever thought that the donor was a research project. That

was never an argument that was made because taking kidneys out is just done. People know how to take kidneys out in all sorts of ways. There's nothing experimental about that that the recipient was the experimental subject, not the donor.

So that if you just wanted to take kidneys out to save them or take bone marrow to store, something like that. It doesn't make those people research subjects. It makes them donors. And there's a distinction between being a donor and a research subject.

I'm saying that this is good news for you in terms of your concern. It's not bad news for you. That I think the one has to define very carefully what the research question is and what makes a procedure you know research.

So again taking out a kidney is not research.

Dr. Link: But it might be.

Mr. Glantz: But taking the kidney out is not an experiment.

Dr. Botkin: Well, the individual still might be experimental for research subjects if you were

following them longitudinally and collecting verifiable data on them. The research intervention wouldn't be the harvesting of the kidney.

Mr. Glantz: Yes.

Dr. Botkin: So, right.

Mr. Glantz: I'm not disagreeing with you. I'm saying you can do all kinds of research around donors in which case the donors would become research subjects. I think here they're research subjects.

It's like not an issue. But it's because of the following of the administration of a drug that they wouldn't otherwise get.

Dr. Botkin: So you were still proceeding to make a point about I think, the implications of our determinations here for other kinds of research in this domain?

Dr. Link: I'm talking about the precedence. So we have to understand that, you know, this is going to continue to come up because the donor, whatever you do, you know -- let's make it simple. There's going to be further manipulations of a graft

from the donor and perhaps manipulations of the donor that would be considered, you know, not wild and wooly kinds of things. But things that actually are what you consider possibly more than minimal risk.

And yet it is in the interest of doing the transplant and making the transplant work. And so I think part of the precedence setting thing is we have to think in terms of you don't want to convene this committee every time the bone marrow transplanters come up with a new indication. Because I think it will be an issue.

Dr. Botkin: Alright. Valuable point. And I think that the transplant enterprise given the relationship between donors and recipients, particularly in this context, does raise issues that I think as we've seen, weren't adequately anticipated by the current regulatory scheme.

And maybe that's of course why it's landed here under 407 consideration. But part of the question will be are there close enough analogies to what we're more familiar with to make that process easier

for future transplant or is this a domain in which new considerations have to be added to the regulations or guidance that govern this particular area.

Other comments or questions? Again we're thinking about the clinical enterprise here and whether we have thoughts about the propriety of the background circumstances here.

Dr. Diekema: Yeah. I just wanted to add on to my comment before because I also don't disagree necessarily with some consideration for an advocate of some kind for donors who are minors. When I make the argument that I think as a general rule these decisions fall into the realm of parental discretion, it assumes an intact family. It assumes non-neglectful or abusive parents. It assumes a situation where, for example, the siblings have a reasonably close relationship.

So it may be, even in that context that some advocacy role is appropriate, if only to sort of monitor that this is not one of those situations where the parent really, truly can't or isn't taking

into consideration the interest of both siblings.

Mr. Glantz: A point that I would make is that I think if we're going to discuss the ethics of it we can't defer the ethics of it to the parents. That it seems to me that what we do is decide whether or not it's an ethical undertaking for the parents to be approached. But that the consent itself doesn't turn something which isn't ethical into something which is ethical. But that consent is a condition of an ethical undertaking but not the only condition.

I'm just saying I don't think we can turn it over to somebody else and say, oh, they'll decide if it's ethical. It's our job is to make a determination of that sort. Than we need to do it.

Dr. Botkin: Alright. Thank you. Let me see if I can just in a few sentences summarize where we are with that discussion.

I didn't hear any overarching, ethical concerns about the current conduct of this sort of transplant enterprise in the clinical realm. Meaning I didn't hear anybody say that they didn't think we should be

doing this. But there are legitimate concerns about the process that the nature of the benefits that have been proposed for the donors remain to be carefully evaluated, that there may be harms in addition to benefits depending on individual circumstances that the enterprise may not be consistently ethical simply because parents might choose this, that they have to have independent decision making.

And in some circumstances when we were talking about a higher risk donation process, a lung, a lobe of a liver, something like that that would raise serious ethical concerns and would not necessarily be something that would be acceptable. I don't know what actually clinical practice is currently in that type of regard. Does that sound like a fair summary of where we are?

Alright. Let's have some lunch. What's our lunch protocol?

[LUNCH RECESS.]

Dr. Botkin: We have until three o'clock. This is going to be a rich discussion. I encourage you

folks to raise any comments, questions along the way as you can in as concise a fashion as possible.

I will try not to cut short any discussion. But it may be essential. Now what I've done with my own notes here is sort of outline what I think is a progression of important issues for us to touch on.

Some of the first ones that I will raise for our discussion may not need any discussion. They may be relatively straight forward. But I think for the purposes of completeness with our full discussion of the protocol I've got them listed here for us to address. If there are other issues that I failed to list here that folks think need to be discussed than of course, folks should be -- I'm encouraging folks to raise those.

One of the background questions I had then that we dealt a lot of the morning with was the issue of the scientific merit of the project. And I had a specific question in that regard. And I would want to raise for anybody else's consideration whether they have any additional questions about the scientific merit issue.

Are there any alternatives to this protocol design in order to answer the question at hand? Now I couldn't, personally identify any. But others have much more expertise in this domain than I do.

Is this the sole best way to answer the scientific questions at hand?

Dr. Link: I just want to make one comment and that is that in one of the reviews they suggest that an ideal protocol would have a three arm trial using G-CSF stimulated peripheral blood stem cells. I just think it's not feasible, it's an infeasible study. But it's, you know, in terms of the patient numbers and the time it would take to accrue those patients. But you know, that would be a better study. It just can't be done.

Dr. Botkin: That might be better from a scientific perspective, but not necessarily resolve any of the human subject issues.

Dr. Link: Oh, no.

Dr. Botkin: But, right. No, but that's a good answer to the question. Other thoughts on alternatives that would be feasible?

Ok. I think my question that I had as I read the materials has been answered. The age restriction on the donors is six months of age, is that correct?

Ok. Any other questions than about scientific merit issues?

Alright, next question then. This was addressed I believe by the COG IRB. Any question that the donors are themselves human subjects in the conduct of this research?

It seems to be straight forward.

Alright now I see four groups in this protocol. Two recipient groups. Two donor groups. So I want to talk about the less controversial groups first and just get those off our table. And then invite any questions or concerns about those groups.

Any concerns about the protocol with respect to the recipient groups themselves? And recipient groups are of course those who will receive bone marrow that had been stimulated in a donor with G-CSF and those that have not. I believe prior IRBs have looked at this group as approvable under 405

given the prospect of direct benefit for those individuals through their participation in the research.

Dr. Diekema: That's certainly true. It seems for the group that is getting G-CSF. The other group, it's not clear. They're participating in the research actually offers them the prospect of direct benefit that they wouldn't get otherwise from standard care.

So that group may be minimal risk. It may be a minor increase over minimal risk. But it's probably not direct benefit.

Dr. Klein: I'm sorry, what is the increased risk to that group?

Dr. Diekema: Well research -- any research related procedures which are probably minor or minimal risk or a minor increase over minimal risk. But my point is that they're probably not 405. Because that group doesn't get anything of benefit that they wouldn't get from standard care.

Mr. Glantz: The one group would be 405 and one group would be 406, the recipients.

Dr. Botkin: Or 404 potentially since they're getting standard clinical intervention.

Any additional thoughts about that?

Now a different way to look at that is to say are those children who are the recipients of un-stimulated bone marrow being denied the benefits of what might otherwise be a clinically -- in other words are they analogous to a placebo control or non-intervention control given the fact that we know a substantial number of children are already receiving this intervention on a clinical basis.

Any concerns about that issue?

Dr. Klein: I'd say just the opposite. I don't think that we have any good data to suggest that this is better, that stimulated is better. It could potentially be worse.

Dr. Botkin: Right.

Dr. Klein: Absolutely.

Dr. Botkin: No sense that they're being denied any standard of care at this point given the current use of G-CSF? Ok.

Alright. Let's move on then to the donor

groups. The donor group that's not randomized to receive G-CSF, and is there consensus that this group can be approved under 404, minimal risk category? Or perhaps I shouldn't bias the debate in that respect. Under what category would this group be approved?

Mr. Glantz: I'm not sure how to think about this because what we're approving is a randomization into the arm, right? We're not approving them being in that particular arm. Is this making any sense?

It seems to me that everyone who's in it will either be in one of those two groups. We don't know. So you can't have research in which one of them is in the non-intervention group, I guess.

Dr. Botkin: Well, I guess --

Mr. Glantz: Maybe I'm not making any sense.

Dr. Botkin: Perhaps the question is whether we consider their -- the category of approval prior to the randomization process or after. And I think my sense of the emerging consensus on this issue is to look at the groups after randomization rather than before. Because there's been some tendency in the

past to say, there's a prospect of benefit because you might be randomized to the intervention group as opposed to the placebo group.

Right. I'm talking about the donors. So we would look at the groups post randomized to the no intervention group, presumably are still research participants by virtue of having information about their course of their medical care and outcome collected.

So the question would then be what category of research would they be approvable under?

Dr. Santana: Just for semantics sake, I hope we get away from using the word placebo in this scenario because those are really active controls. Those groups are really getting an intervention which is the standard of care. So they're serving in a randomized trial as the active control arm.

And you could argue, you know where placebos are active controls too. But I, for the purpose, since this is a public meeting and the perception of the public of placebos raises all sorts of additional discussion. I hope we can refer to these

groups as the active control group rather than the placebo.

Dr. Botkin: Thank you. I agree entirely. That was a misstatement on my part.

Any additional discussion on this point? We're comfortable now with the approval of that group presumably under 404? Alright.

Alright, let's then dive into the donor group that will be randomized to receiving the G-CSF which I think is of course, the focal point of the discussion around this protocol in general. The research intervention itself, I think, we're understanding to be the G-CSF per say and the follow up evaluations that will evaluate the children for the impact of that agent. The intervention is not bone marrow harvesting itself or the other associated interventions in that regard. Although they're all of course wetted together.

So, yes?

Dr. Klein: Can I go back for a just a minute because I'm not always as friendly with 404 and 405s as maybe some of you all. But it seems to me the

bone marrow harvest isn't minimal risk. Are we saying that is minimal risk, like blood drawing?

Dr. Botkin: I think what we're saying is these are kids who are getting a bone marrow transplant or donating as part of clinical enterprise. And that therefore the clinical procedures that are being conducted are not part of the research intervention. And the research intervention is the G-CSF administration.

Dr. Klein: Yeah, I would certainly agree with that. But it's certainly not minimal risk such as blood drawing.

Dr. Botkin: Good. And I think we should be in agreement if the bone marrow transplant itself was the research intervention that would not be approvable under minimal risk enterprise. Alright.

So the first question I think this again was part of the COG's analysis. And I wanted to raise it for our discussion here. Does this intervention mean the G-CSF administration to the donors present no greater than minimal risk?

Mr. Glantz: Yeah, I think it is greater than

minimal risk. I think that just from the point of view, I mean, even if we didn't talk about the issue of leukemia, that nausea, vomiting, bone pain and the other sorts of issues. And the chance of bad things happening makes this far from a minimal risk.

So it isn't a question of it has to happen. The question is the risks. And the risks are such that it seems to me that this is far from minimal risk.

Dr. Botkin: Is there general consensus than on that point?

Alright then the next question would be moving on to our considerations under 405. Several considerations in this for that regard and we'll need to spend, I think, some time addressing these issues. So I'll go ahead and read the regulatory language.

Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research. To approve research in this category IRB must make the following determinations.

The risk is justified by the anticipated benefits.

Relation of the anticipated benefits to the risks presented by the study at least is favorable to the subject as that provided by available alternative approaches and adequate provision is made for soliciting assent and the permission of their parents or guardians as set forth in the 45 CFR 46.408

So the question then I think or a central question is does the intervention present the prospect of direct benefit to the donor children by virtue of their involvement in this research?

Dr. Diekema: I think that hinges on what we consider to be a direct benefit. I think the benefit that I see is related to the potential for a greater likelihood of survival of the sibling or potentially fewer side effects for that sibling. And by my way of thinking those are, although they're important benefits, they're indirect benefits.

But that does hinge on one's definition of

direct.

Mr. Glantz: Yeah, I think those would be benefits if you struck out the work direct. That there's a reason why the term direct is in there. And that to find this to be a direct benefit would mean that there are no indirect benefits.

So the fact that the ones talking about a direct benefit means something which accrues from the intervention to the child, him or herself, I would think and not this sort of indirect type of benefit which is really, very speculative at best anyway.

Dr. Klein: We're thinking about a study in which by G-CSF there's going to be a different kind of graft. And the proposal is or at least theory is that that's going to be better. It could be no better.

It could be worse. So I'm struggling to see how the donor in this study is going to have a benefit. Suppose it's worse?

Dr. Botkin: Well, and I would say at least one caveat is it's always prospect of benefit and in any

trial in which new agents are used it may turn out to be worse. But at least you're testing it because there's the prospect of benefit.

Dr. Klein: I'm thinking now the prospect of benefit to the donor or the prospect of it not being benefit. I don't see how the donor benefits by getting G-CSF because we don't know what the outcome will be.

Dr. Botkin: Now so one hypothesized route in terms of the direct benefit. And at least personally I'm convinced that this is an indirect benefit that may be substantial, but indirect. Or of course, it could be some orderly prospects of psychological harm by virtue of this protocol as well.

But the other angle that was presented and Dr. Wysocki addressed is a little bit with the Nemours IRB review is the question of whether the decrease in bone marrow volume that might be taken from the donor by virtue of prior stimulation might shorten the procedure, shorten anesthesia, improve recovery, whether that would be -- may benefit would accrue to

the participants themselves or whether is that a benefit to the potential future donors?

Dr. Link: That's future. They're targeting now fixed volume. So in the future when you target the number of stem cells and we'll know the answer from the study. So it's future.

But these people are going to get the same volume harvested whether or not they get G-CSF based on the recipient weight, actually. So I don't think there's any. We shouldn't construe that to be even a potential benefit for these patients.

Dr. Santana: As a follow up to that. There's no research question protocol question addressing that. So the donors are not being presented with a research issue that this study will answer in the context of whether reduced collection reduces similar results. And so it's for the future individuals that this would be important.

The proposed currently donating now. There's no question being asked related to that.

Dr. Botkin: Other comments about the prospect of direct benefit? I'm hearing consensus that

again, the benefits may be significant and real, but they do not accrue directly to the donors by virtue of the G-CSF. That they may accrue through indirect benefits through the recipient who may have improved clinical outcome by virtue of the G-CSF stimulation. And we're classifying that as indirect, but not direct.

Skip?

Dr. Nelson: Just a question to hear people's thoughts. Is it the number of steps or is it the fact that there's a person in between those steps. In other words, I mean, there could be a causal mechanisms that we could postulate for other interventions where there could be multiple steps along the way to that potential benefit.

So I guess the question is, is what undermines people's confidence that you could call this direct. The fact that there's another individual in that causal mechanism or is the fact that there's a sort of -- you could count four or five steps that need to take along the way for that to happen.

Mr. Glantz: Both. In this case it is both

that the benefit is not proximate.

Dr. Botkin: So I'm going to speculate. I mean part of what seems attractive, and I would say Dr. Grupp in his presentation talked in several points about direct benefit. And I think the anticipated route of approval for that group was through a 405 mechanism.

And I guess I'm in full agreement that this is not a direct benefit situation. But I think it's somewhat different than what we often times think of in these circumstances. Where in a normal research circumstance today you would enroll a child with cystic fibrosis, you're looking for general understanding of the disease with possible benefits to other kids who have the disease down the road.

If you learn something, we would all say that's indirect benefit and not approvable. It seems to me it's the closer relationship here between the recipient and the donor and how closely those are wetted in the context of this research that might tempt us to say it's more of a direct benefit because of the magnitude and the family

relationships, etcetera. And that's sort of speculation about how people might be thinking about this.

But it sounds like we are of a mind that this is not approvable under 405 by virtue of a lack of direct benefit to the donor children.

Dr. Link: Well I just have one -- I mean I have to agree with you. But I have one question. This is sort of underpinned the ethical justification for doing bone marrow transplantation in general. So in other words this is sort of a, you know, a minor intervention compared to what we do to the donors, off study, not a research thing.

What we're doing now is we're putting them under general anesthesia doing 200 bone marrows etcetera. The justification for doing that has been legal courts that sort of opted out. And ethically it's because of exactly what you just said.

So I'm a little nervous about sort of trashing what has been the underpinning of this for a long time. Forgetting this study, just, you know, we say here that we don't believe being a bone marrow donor

gives any direct benefit to the donor. So we're sort of undoing a lot other people's precedent.

Dr. Diekema: I don't think we need to do that though. I don't think we're trashing the possibility of benefit. I think what we're saying though is that under the regulatory language that the benefit must be a direct benefit.

This doesn't work, but that's different than saying at a clinical level you could argue there is sufficient benefit even if it is indirect to justify the practice. So I don't think a decision here to say this isn't a direct benefit doesn't have to undermine the clinical decision too.

Dr. Link: Ok, well I worry about the fact that the intervention we're proposing is the risk benefit. So the risk is the risks of G-CSF. The benefit is, you know, whatever you call that whether it's direct or indirect. We're sort of worried about that balance.

And yet when we take the other balance which is here's the risk of anesthesia which is finite, measurable and a lot more probably than the risk of

G-CSF. Plus the risk that many kids get transfused. So you pile that on verses, you know, the same benefit basically.

Whether you say we're undoing it or not, however you're going to couch that, it's going to sound like we're just undermined the entire concept of allogeneic sibling donation. I'm not an ethicist. I'm just telling you how it sounds to me. I'm just a, you know --

Mr. Glantz: Yeah.

Dr. Diekema: Two comments there. There are two things. You have to do both as an IRB.

One is you have to determine whether there's direct benefit, but even having established that you still have to determine that that direct benefit justifies the risks involved. So it's a two step process. But again, the difference between the research context and the clinical context is we can only look at direct benefit. We can't look at indirect benefits.

Dr. Link: But you can in the clinical context.

Dr. Diekema: Yes, you can in the clinical

context. This is really regulatory language. It's not necessarily an overarching ethical analysis.

Dr. Link: That explains why I don't understand it.

[Laughter.]

Dr. Botkin: Skip?

Dr. Nelson: Well, Doug, actually that might be helpful than for briefly just to hear just some reflections on that balancing, independent of the direct and indirect component. Looking at the other criteria, if you will, under 50.52, to ask about that risk benefit balancing, just to sort of flesh out people's thinking independent of the indirect/direct nature of that benefit since you're sort of on that category at the moment.

Dr. Botkin: Jerry?

Dr. Menikoff: If I could just clarify. And certainly from the point of the view of the agencies involved here, assuming we'll -- it's clearly true there is an interpretive issue of what direct means assuming there might ultimately be a decision that direct means something different than what is being

discussed here. It would be very helpful to get your evaluation assuming, kind of, all the benefits were deemed to be direct.

How do you come out on the other provisions? Which is exactly, you know, what Skip is asking you to do.

Dr. Santana: But isn't in part this transition from indirect to direct kind of a consensus that evolves over time based on, for example, clinical experience. So it's not that, you know, it's not that boxed in. But what I may consider an indirect benefit ten years ago of an intervention, now through experience, outside of the research setting, I've learned that it provides a direct benefit, in global terms.

I'm not talking specifically about this example and the context of, you know the donation or not. Because if not, all donors would be exposed to the same principle, forget about bone marrow donation. It would apply to all donors whether it's kidney, heart or whatever, you know.

Do you see what I'm getting at? That I think

if there's -- You know what I'm saying. So I think there's an evolution in terms of when something indirect becomes direct. In part that's predicated by the experience.

Dr. Botkin: Well, I want to keep our focus though on the research intervention in this context because it's the G-CSF that's the intervention. And is that intended to benefit the donor? And I think if the answer is no, it doesn't say that donation per say doesn't benefit children or that there might not be direct benefits from the donation process.

But I think we're focused on the research intervention more particularly in this context. And I'd be hard pressed to see how that would ever turn into a direct benefit as long as it has to function through the impact of the intervention on the recipient. But I think the other criteria are going to be -- that we should discuss here are important in helping us decide perhaps whether the protocol is approvable. If we get to a 407, if it's approvable at all, is this ethical to do even if it doesn't fit the criteria we're talking about.

And I think this other discussion of those may help us with that determination. So let's look at those issues.

Dr. Menikoff: Well I think it would be useful again purely from a 405 point of view. Again assuming all of these benefits, however you rate them meet the standard of being direct almost as if assume that the word direct wasn't in there how would you ultimately make an evaluation under 405? Would you say this is or is not approvable under 405?

It would be helpful from the OHRP viewpoint. And I assume the FDA viewpoint just to have the answer to that question on the record. Even though, granted, you've already said you don't think any of this is a direct benefit.

Dr. Botkin: Ok. So this is an opportunity to comment on these issues that may in a strict content be mute, but still important to think about for the purposes of precedence of the second criteria. That is, is the risk justified by the anticipated benefits?

Yes, Leonard?

Mr. Glantz: I was just wondering if I could make a suggestion that as important that might be that we finish the task we're assigned by three o'clock. And then we can come back to that because we don't have to do that in order to finish our task.

Dr. Menikoff: From our viewpoint this is part of your task. It's an interpretive question of what does it mean to be a direct benefit as you've been knowledged. And we don't what ultimately the decision is going to be on how in fact, as a question of interpreting regulation direct would be interpreted.

So the easiest way to give guidance on that is let's be generous in assuming any of the benefits you're talking about here might, under some viewpoint, be considered direct. How would you then come out on this? You may conclude 405 is not met in any event even if you look at all the benefits.

Some of you have indicated these benefits are pretty hypothetical. And that would be another

piece of information that is very useful.

Dr. Diekema: I'm willing to take a stab at that. I think a reasonable person could conclude that the benefits, whether they're direct or indirect, justify the risks in this case. I think one way to think about that that might be would a reasonable adult consent to this?

Not out of a sense of duty, but because they really thought there were realistic benefits? And that justified the risk to themselves? I can certainly see myself in that position.

Again, sort of removing any sense of duty I might have to a relative but just in the terms of I'm offering the potential for someone I have, at least, a somewhat close connection to, the potential for a better outcome I think would justify this level of risk in my mind. So my answer to that would be I think a reasonable person could conclude that.

Dr. Link: I was going to say people obviously have concurred. That is the whole underpinning of the unrelated marrow transplant donation program.

Mr. Glantz: Yeah. I can't see how the risk can be justified by the benefit to the subjects. There is a benefit to the subjects.

I mean it just seems to me, so obvious to me. We've decided there's no direct benefit, but that's what benefit means. I'm not convinced by the way, and I don't know if there's literature on this in your profession that the thing that justifies the bone marrow transplants in a clinical setting is the benefit to the donor.

I would have guessed it would have been lack of risk to the donor and the benefit to the recipients and the parents making that decision. But is that why it's ok? It's because some group made a finding that donors benefit from this? Is that like written down somewhere?

Dr. Botkin: No. I think that was the point of our earlier conversation about this. I thought the consensus that went around the table was the benefit to the donor was not necessary in order to justify from an ethical perspective. But the lack of significant risk --

Mr. Glantz: No. But what I'm saying if we go back and look at it. What has been argued is there's a consensus there's a benefit to the donor. Outside of this I'm saying that I don't that there is a consensus on that.

I'd be interested in seeing if there is no benefit to the donor, again there may be benefit to the research. But it is hard to see how's there's any benefit to the donor that comes out of this.

Dr. Diekema: Do you not even see indirect benefit, Leonard?

Mr. Glantz: No.

Dr. Diekema: It seems to me that if a family member benefits from this that there is some at least indirect benefit. I mean I would agree I don't see that as a direct benefit.

Mr. Glantz: It just strikes me as so speculative. I mean with respect to as whether it will happen or not, but as, you know, whether or not the kids liked each other or didn't like each other. I don't know if you want to do like a family analysis of whether or not there would be benefit.

Dr. Diekema: And I agree you do have to make a certain set of assumptions about the family relationships that exist in that particular group of people.

Dr. Grupp: Can I address the consensus question?

Dr. Botkin: Let me pick up on Alex's comment. And then we will invite your input. Thank you.

Dr. Kon: So I would certainly agree that I don't see any direct benefit. But I personally believe that there is an indirect benefit. But I don't think there's good evidence of that. And I think that here in lies some of the issues is that there's very little evidence for a great deal of what we have here.

I think a lot of us believe that having a sibling not die from cancer is beneficial. But we don't have a lot of good data to prove that. There's certainly a number of case reports that I found in my prep work for this meeting taking normal, healthy adults who were given G-CSF to prime them as a donor who ended up with an ARDS.

One of those people died which isn't surprising given the mortality rate for ARDS is about 40 to 50 percent. So while we haven't done it in a whole lot of kids there's certainly a risk that this could lead to ARDS which has a real risk of death. There is this theoretical risk of hematological malignancies which again we haven't seen and there's some question about.

But I think what it comes down to is there's a lot of sense that, at least in my mind, that's there some very real risk to the child. Although it maybe very low and that there's some very real benefit to the child to which may be much more tangible. But there's no good evidence.

So I am left in a position where I'm faced with this question of is the relationship of the anticipated benefit to risk at least as favorable as alternative approaches. And is the risk justified by the anticipated benefit. And I don't know what to do with that because I have a gestalt that this kid, that there's a real chance that this child would benefit by having a sibling survive.

And I think that there's a real risk that this child could develop ARDS and die in the ICU. But I have no numbers. So I don't know how to compare them.

And so I am worried that making a decision, making a statement saying well, yes, we believe that the anticipated benefit out weighs the anticipated risks. I don't think you can say that. I think you may be able to say, well we don't have any evidence that the anticipated risks outweigh the anticipated benefits. But I think the best we can say is we don't know.

And then the question becomes when you're in a situation where there is a potential for risk and there's a potential for benefit, but you really have no idea the magnitude or chance of those. How do you make a rational weighing?

Dr. Diekema: Is that any different, Alex, than any of the other oncology trials we approve as IRBs? We always struggle with sort of what -- because you're dealing with a research context you don't know what ultimately this research is going to show.

So when you subject somebody, for instance, to a Phase I trial and you approve that under the prospect of drug benefit that you do that fully realizing that 95 percent of those trials, and we could quibble on the numbers here. But 95 percent of those trials will not really make any difference to those kids.

So I'm not sure that's radically different from what we do every day in the IRB world. And again that is where I sort of fall back on this. Could a reasonable person come to the conclusion that yes, these risks and benefits line up at least in a way that we're not seeing any evidence that somebody will be clearly harmed without. Also a corresponding prospect for benefit that at least justifies that.

Mr. Glantz: You know I think that the realistic -- I mean I think what you have when we have to get real about this protocol which is not being done to benefit the donor. The reason why we're having this conversation is to see whether or not we can approve it under the standard. But no

one would actually say, oh, this is wonderful for the donor. Aren't they lucky to be able to have this done to them because they can get such a benefit?

Or if a parent said, I'm not interested in doing this. People would say, well you know what you've done to the donor? It's a terrible thing that you've done to the donor to deprive them of this benefit.

I'm saying that we are really working on stretching this term benefit to try to put it into a more acceptable category than I think is real here. And again, I just want to say the purpose of this, the secondary part of it and the primary part of it, is not to see if this benefits the donors.

Dr. Klein: Well I agree with that. I have to tell you that the experience in the unrelated donor is that many people, not only volunteer, but are quite disappointed if they're not called to donate. And sometimes after they've donated and there's graft failure, want to donate a second or even a third time. Now is that benefit to them to have

done that? I don't know.

But it's more than just duty. It's some feeling of satisfaction or something more than that. And maybe that wouldn't apply to a child. I don't know that there are any data.

Dr. Botkin: Yes.

Dr. Hudson: So I don't feel there's a direct benefit. But can the ethicists make a comment about other areas of pediatric care research in which altruism on the part of the individual has been indicated as this is a benefit because of that. I mean, it's kind of like the indirect benefit to the family.

But certainly that's why adults do this. You know, they have altruistic motives. Do we have anything in research that indicates that there's a positive effect of this altruism if you do it as a child, if you are a minor when you do it?

Mr. Glantz: Well I think you can say convincingly a six month old, a two year old, a three year old, a four year old and probably the five and six year olds, don't have a sense of

altruism. I'm saying so once you go to like the six month old one particularly and the question is how does one think about altruism in that context? When you're talking about 15 and 16 year olds, you know it may be another thing. So there's some developmental issue.

One of the differences between the children though and the volunteers is that you have a very self selected group of people who are lining up to have needles put into their bones that, you know, they obviously think a lot about this. As opposed to kids who are being more or less drafted into it because of their circumstances. But again, I don't think you can make altruistic assumptions about little kids.

So even if wanted to --

Dr. Hudson: I didn't say little kids. I said once they reach an age where they can give assent or even if they're older kids. I was just curious.

Mr. Glantz: Maybe 14.

Dr. Kon: So I think that perhaps you could make the argument that in older kids there is

benefit to being altruistic because it makes them feel good or what have you. But I think if we get back to this question of weighing the risks and benefits, I think with case of reports of people dying from this therapy which there are, from this intervention. I think you'd be very hard pressed to say that the benefit of feeling good by being altruistic is somehow justifies the risk of possible death.

I think if you were an adult and you understand that look, people have died from doing this. But it's a very tiny chance. And it almost certainly won't happen to you. But it is possible. And you still feel like you really want to do it, I think that is reasonable as an adult.

But to say that in a child, who's a special population that requires certain protections, that the benefits outweigh the risk. I just don't think you can.

Dr. Link: I want to raise a point that parents do this all the time. And who would advocate more for both children than a parent. I mean we're in

this situation. Hopefully, not this exact situation, but you do have to balance risk and benefits all the time.

And if a parent is willing to sign a child up knowing there's a risk, this finite risk, and admittedly they're conflicted. But they obviously weigh this very heavily, even more than the altruistic donor who can always opt out. So I would say that you have -- there is sort of -- it's not like it's data free.

There is data. There are data on this. That parents volunteer. That normal people who have no business in this at all other than that they donated some blood are willing to donate. That there obviously is some people think that there's benefit for the party.

This is why I mentioned before that we should consider the whole thing as a package deal because the people that are actually signing both consents is actually the parents. And they obviously have to weigh the whole package, the risks and benefits for the recipient and the risks and benefits for the

donors. And that's the way I would try to think about this.

Dr. Botkin: I think we will get to that point without question.

Ms. Celento: I could hold my comment then. But I do want to say I disagree that parents look at it as a package deal. I think some parents, their first born child has this -- they're determined that their child will not die regardless of the impact on their younger child.

So I really want to disagree with that. I just don't feel that that's valid here to make that assumption.

Dr. Diekema: So could I ask, because I'm hearing different answers to this question that is currently in my head. Is there not a difference between the family context and the non-familial context? In other words there's no question in my mind that this study is not justified if you're talking about using children as donors for anonymous recipients.

Mr. Glantz: Can you say why that is?

Dr. Diekema: Well I think it gets back to this notion of benefit. I think a six year old doesn't benefit from donating the way an adult would to an anonymous recipient. But within the family context, assuming there are ties that are different within most families, than there are between a donor and an anonymous recipient.

It seems to me you can make an argument there is an indirect benefit there that exists between most family members. And again, that we're making some assumptions. But I think they're assumptions that apply to most families that don't exist between donors and anonymous recipients.

In other words I think there is a difference in the family context than there would be outside of the family context.

Dr. Botkin: Dr. Grupp, did you want to make a comment and at the microphone, please?

Dr. Grupp: So the discussion has evolved a little bit but the issue that I wanted to address is something that I can address directly which is, is there a consensus among the people who do this for a

clinical living about whether or not there's benefit to the donor? And so I can address that question. And the answer to that question is yes.

And the basis of my answering the question in that fashion is that during the process of reviewing this protocol through the Children's Oncology Group. We've had these discussions within the Stem Cell Committee. And this includes the large Children's Oncology Group meetings where a large number of more than a couple of hundred people involved in bone marrow transplantation at all levels have been present in the room.

And so then there's been an explicit discussion about whether what I internalize as my own reason for doing these collections in children actually was reflective of the point of view of the people who do pediatric transplantation across the country. And I think that to answer that specific question, the answer is yes.

And fundamentally, you know, I think that no one is making the altruism argument. If you are an unrelated donor undergoing a procedure for a

complete stranger I think that's extraordinary. I think that is only altruism. It's amazing anyone is willing to do it. Not to mention the fact that 80 percent of the people who are asked to do it are willing to do it.

And so that is amazing to me. But in the family context we're really talking in a clinical intervention which can, in a number of patients, not just the occasional patient, a number of patients, offer the difference between life and death. We are absolutely looking at a circumstance where there is one family where the child has passed away and the parents are dealing with the sequellae of that and the sibling is dealing with the sequellae of what's happening with the parents.

And there is another family where that child is alive. And those events have not occurred. So you just, from the clinical standpoint, and reflecting the consensus of pediatric transplanters across the United States, I can offer that as our sense for direct benefit.

Dr. Botkin: Thank you.

Dr. Rosenthal: So actually, I have a question for you Dr. Grupp regarding this consensus opinion of the Children's Oncology Group and the other organizations that you alluded to. Has there been a great deal of input from Parent Advisory Groups regarding this? I mean, do you have consensus from parents or do you just have consensus from clinicians?

Dr. Grupp: Consensus from clinicians. I mean we have parent advocates at COG. But I would not say that we've been in a situation where a parent advocate has stood up and made a strong statement in either direction. So I can say they were in the room but I can't say that there were enough folks there to really represent parent opinion. And so the answer is I'm only representing the consensus of the clinicians.

Mr. Glantz: I just want to ask you one thing. I assume also that everyone in the family is happier. The other kids who weren't the donors are happier in the family and the grandparents and the aunts and uncles. And they're all happier.

The fact that one of them had -- was actually the donor is not what the benefit is. Right? It's just that the family, I'm saying.

And by the way I'm not going to disparaging that. That's a good thing. I'm just saying that the research subject, himself or herself, is not receiving a benefit different from that entire population. And that is because it is such an indirect benefit. So it's a good benefit.

Dr. Grupp: So the answer to the question is that the child who undergoes the bone marrow donation accrues no greater benefit except by argument by altruism which we're not arguing, than anyone else in the family. I think that's accurate.

Dr. Nelson: I was just going to say, Jeff, is what I've certainly heard is the discussion around the issue of benefit with some difference of opinion, but not much of a difference of opinion around the direct/indirect. I'm not sure. I'm just watching the time. And knowing there's other issues that need to be addressed to whether you think it's appropriate to try and formulate what you've heard

and move on.

Dr. Botkin: Good timing. So let me see if I can do that. Again, I think there is consensus that the benefits that may flow to donor children who are recipients of G-CSF may be significant and real although we don't know that based on the absence of good, quality research to address that issue at this point as indirect or not direct.

The second question is, is the risk justified by the anticipated benefits? And I construe our conversation to be focused on in this context, is the risk of G-CSF justified by the anticipated benefits that may occur to those children whether we categorize them as direct or indirect? Is it relevant to that question?

But what I'm hearing is differences of opinion. No consensus elements or comments of uncertainty about whether the risks associated with that intervention would be justified by the anticipated benefits.

Mr. Glantz: Can I ask why you add indirect since the requirement is to be direct?

Dr. Botkin: I think we're trying to think hypothetically here and to play out the discussion for the purposes of trying to establish some precedent about thinking about these kinds of issues. So if we were to assume as Dr. Menikoff asked us to do, that these were direct benefits whether we didn't care whether they were direct or indirect, what would we want to say about the risk/benefit ratio in this context? Would we want to say that those benefits, however characterized justify the risk?

And I think that I'm seeing just uncertainty on that. That we need more discussion and thought about that issue.

Dr. Menikoff: And it is helpful. And thank you for answering that question.

Dr. Botkin: Let's move on then to the next category. And this is 406 or 50.53. And there are a variety of questions as everyone knows that are underneath this category.

The one I would focus on first is do the subjects have a condition? And as we know that the

regulations require that the children have what is construed as a condition in order to be approvable under this category.

Would it help at all for me to read the regs at all or does everybody have them enough control there? Ok, thanks, Skip?

Leonard?

Mr. Glantz: Yeah. I don't think they have a condition at all. They're in a situation, a difficult situation. But I don't see them as having a condition because somebody else has a condition.

That the regs talk about condition as something the person has. It's a possessive. Just to put this subject's condition. And it seemed that one had to draw a distinction between someone having a condition and simply meeting the inclusion criteria for study, which is what the argument is. That is anyone meets the inclusion criteria for the study, for any study, that then they have that condition.

And the condition can be that they go to school or the condition can be all sorts of things outside of the realm of themselves. And that that's a

humungous expansion of what the term condition was supposed to be, especially in the context of this which is talking about research which otherwise is pretty unethical. You know, that it puts kids at risk without benefit. And it has to be justified by their condition, not the condition of the kids.

Dr. Diekema: I more or less agree with that. It looks like the Central IRB came to the conclusion that these kids did have a condition by virtue of being already selected donors. What I would add I think is that this is only one criterion.

And I know you want to work through them sequentially. But once you've established that a group has a condition and if we're to give the Central IRB the benefit of the doubt. And say, ok, being a pre-selected donor gives you a condition.

It still has to be the case that the research has to be of vital importance for the understanding or amelioration of the subjects' disorder or condition, which I would argue this has nothing to do with. So in my mind the two combined in particular, just don't work here. I just can't see

the relationship that you can make it happen under 406.

Dr. Botkin: And I would say that the latter criterion we will talk about does help, me at least, better understand how the regulations were written to describe what a condition is. As a condition requiring amelioration because it has negative connotations to have this condition whether it's a disease or a risk of disease etcetera.

Dr. Kon: So, you know, I tend to agree with what's been said already. And just to put my thoughts into it just a little bit. And I apologize if I'm repeating what others have said.

But I would agree that it becomes difficult to separate them. And I think that there's a great deal of discussion about what one can mean by disorder or condition. And in some respects I think it is ok for that to float a little bit.

But if one can look at well, what's being studied and how this truly ameliorates people with this disorder or condition that that can, in and of itself, help to define whether what we're talking

about is a disorder or a condition that could be construed under this regulation. And so it's a slightly different take on it. Because I, in some respects, feel that I would not off hand label these people as having a disorder or condition.

But if there was a study looking at, you know, kids who are donating for their sibling have a great deal of psychological angst about something. That's a word designing a study that's going to somehow really help them deal with that angst. But there's something about this study that makes it slightly more than minimal risk.

I might be willing to say that for the sake of that study, I would construe that these children as having a disorder or condition. Because we've defined something that we're going to really try and ameliorate through this study. And I'm not sure that's necessarily a bad way to look at it.

But again coming back to Doug's point which is clearly that's not what's being proposed here.

Dr. Klein: So following that line of discussion. So I think the Central IRB, as Doug

alluded to, you know, in the context of a condition probably defined that these were not just general donors. These were donors who were HLA selected. And so, by definition, they were a group of people that otherwise would not be donors.

And then my next step would be that is a research question in the context of those individuals. That would then answer the question of ameliorating the condition or addressing the condition. And that was what I was alluding to earlier.

There is no research question in this study that addresses the donors directly. So if they were asking whether less volume or less cells under the influence of G-CSF with the donors than I could construe that these individuals did have a condition. And that there was a specific question in the context of the study that was going to answer a research question to ameliorate their suffering or condition or whatever. And I think that is what is lacking there.

Dr. Link: I'm not sure I agree with that. If

you define condition as if the protocol is addressing a scientific thing which will ultimately ameliorate the condition for similar people or people in a similar condition, that's in fact one of the endpoints of this study is to see if you can get a higher stem cell yield so you would then have less, you know, you'd need to collect less stuff from the recipient -- from the donor. And how is this beneficial?

Well there's certain kids that need to get transfused in order to give sufficient amount of blood, a sufficient amount of stem cells or bone marrow. And so you could actually say that if we only have to take half the amount of volume because we get the same number of stem cells with G-CSF stimulation, which is in the protocol. That we then subsequent donors will not have to undergo as much volume and therefore they won't, maybe not need a transfusion.

So I don't happen to agree with you that that defines them as having a condition. And I don't think that having a particular HLA type should

define you as having a condition either. But if you accept that this -- this protocol clearly addresses a potential benefit for future donors. And therefore would be scientifically, you know, would therefore really is addressing a donor issue, not only a recipient issue.

Dr. Santana: I would agree with you Mike, but there is no objective in the study.

Dr. Link: Not for these donors, but for subsequent.

Dr. Santana: For future I would agree with you. For the individuals that are currently participating, I just briefly read the objectives and secondary objectives again. There is no question for the donors.

Dr. Nelson: So I guess I'd be interested in asking a specific question, if there was such a question. I mean I've heard general consensus and everybody has spoken about not having a condition within this protocol, but if you added a research question, without changing the design really, would that begin to address that issue or not?

Dr. Santana: Well I think as a secondary, you know, objective of this study if you define that you really are interested in learning that information, I think that alleviates some of my concerns. It doesn't necessarily have to be the primary objective of the study. But I think if you intently, within the context of the study, had a research objective that tried to help us understand better how this information could be used in the future. I would buy it. I would go for it.

Dr. Nelson: I guess I'm trying to be concrete. If you or if other people want to go that way, then you should propose that. If it has an impact on what category you think, as a panel, you would allow this to go forward.

Dr. Santana: But we're here today to potentially depending upon how the discussion goes and the final conclusion to eventually consider alternatives that could enhance this research and balance the risks and benefits for all the groups that are participating. I'm not saying we should do it. I'm just putting that I would be more favorable

of accepting that the donors do have a condition by the nature that they have been pre-selected because of their HLA typing.

And there's some intent in the protocol design as a secondary objective to try to gather more information of those donors in the context of how that could potentially impact donors in the future. To me that would be a great benefit.

Dr. Botkin: With that intervention would you have to change the intervention in a way in which there would be direct benefit to that participant group? In other words vary the volume of aspirate you were taking or something of that sort in order to, you know, if there's a prospect of direct benefit than of course the question of a condition disappears, at least under the regs. Or could there be a research objective you're thinking about that would be observational in the context of this study that didn't confer a direct benefit to the kids.

Dr. Santana: I was referring to the latter because I think it's going to be very difficult in the context of this study to have a wide range of

donor volumes and things. You're designing a completely different study. And I don't think we want to do that.

But I think if you did it in the observational category, I think that would help me justify what we're discussing today in a different way.

Dr. Botkin: Let me go with Geoff here.

Dr. Rosenthal: I guess I need someone who would say that the donor has a condition to help me understand what you mean by that because I'm really having a hard time just with that first step. You know, as I think about it, it may be that the only condition that the donor has is that someone can hold them down.

Dr. Rosenthal: And you know, those are the people that we need, you know, to protect. And so what is the condition? You know they're HLA type is not a condition per say as far as a cardiologist is concerned.

Can someone help me understand this?

Dr. Hudson: Well initially with the beginnings of the discussion on condition I agreed it's sort of

black and white. Now they don't have the condition because I was thinking medically. I can broaden that if we get a little vague.

They have a condition that they're the sibling of a patient with cancer, you know. And cancer does have impact among the whole family. So if you take it within that context and the protocol does address, even in an exploratory fashion in a secondary aim, the impact of the experience on that individual. Could that not suffice?

Dr. Rosenthal: So that that would be an indirect condition, right? If the child was adopted --

Mr. Glantz: It's not a mission. It's a situation.

[Laughter.]

Dr. Botkin: Alex?

Dr. Kon: So I would like to take a stab if I may. So I think I would agree that merely being the sibling of someone with cancer is not a disorder/condition. If this were a study looking at, for example, bone marrow donors who have

psychological angst, that I could conceive of as a group that has a disorder/condition.

If we're talking about, for example, decreased need for transfusion. If this were a study looking at very young donors using G-CSF as a potential way to ameliorate the need for transfusion, that I could then accept that these people have a disorder/condition because then you're not talking about well, just anybody. You're talking about children who something is happening to them that there is something that we can say, this is hard for that child, like psychological angst or like getting a blood transfusion.

And then if we have a study that specifically looked, that's of vital importance to that condition. Than I think that it would be fair. I think that throwing on another condition of this, like looking at whether or not kids actually need more transfusions isn't necessarily a bad idea.

But I don't think that that somehow means that now this study has a vital importance to ameliorate that disorder/condition because we haven't really

defined the disorder as a disorder of requiring transfusions. If we do that then we're talking about only a subset of this group. And so I think that that's how I would look at it personally.

Mr. Glantz: In having discussions like this it's always hard to know what we're discussing because we're not discussing ethics at the moment. It is not how people feel about it. It is not how people are thinking about it.

This is a regulatory term. And the question is what is this regulatory term mean. And so it's weird to think -- so if we took a donor, let's assume that this kid, Joey, and we did a full examination of him. And we looked at their HLA and we did all that. And we were done and we say so does this kid have a condition?

And the answer would be, no. It looks like a perfectly, healthy, normal kid to us. And then his brother gets, you know, leukemia and now Joey has a condition. It's like -- it's just too odd to think that those things outside and what happens to Joey gives Joey a condition that is something inherent to

him.

When you look at for the regulations themselves if we want to talk about how, you know, regulatory interpretation. If you look at Section B of 406, they talk about the medical, dental, psychological, social, educational situations as opposing to use the word condition. So this child is now in a psychological or social situation which is tough, but it doesn't mean that they have a condition and that there's a difference between having a condition and being in a circumstance which is tough.

And then, but so if these children went like psychotic as a result of doing this, then they would be in a condition. They would have a condition. But the thought that two kids who are exactly the same in every possible way, one has a condition and one doesn't because of a condition, a problem with their brother, it's just an odd way to think of the word condition to me.

Dr. Botkin: Let me add a couple of comments. I would say that obviously the term is pretty fluid and probably context specific. And it seems to me

that in some circumstances, if I were an investigator and I wanted to go and get the database of kids who've been donors and study those kids to find out what their psychological health is. Now that's unlikely to be a 406 kind of thing. But let's hypothesize that maybe it is.

Would we say that by virtue of having been a donor in the past and there's let's assume some health risk associated with that, might that be a condition in that context? And I would say, that's probably a reasonable way to think of it in that context in part because, I as an investigator have found kids who, as a group, we would say, hypothetically have some negative outcome that I want to try to address. Now there aren't any negative outcomes and there's no issue there. But I think what is problematic in this particular context is that the circumstances of the child donor are being assigned within the context of the study itself.

So if they have a condition it's being assigned by the investigators. You're having a -- because

we're making you a donor, we're now going to justify applying a higher level of risk standard to you by virtue of the decisions that we've made in our assignment. So I think it's the internal structure of this study where it's a double jeopardy for those kids if they have a -- you know it's in the interest of the investigators who assign them a condition as a donor that then in turn justifies a higher level of risk than they might otherwise be subjected to if they didn't have a condition.

So I'm of the opinion here that the condition term doesn't work for these kids.

Dr. Klein: I agree with that. But again I don't want to reduce this to the absurd. But it seems to me if you said being the sibling of someone with leukemia gave you a condition and you were going to study that.

Then you would really have to have a non-related child. You would have to have the sibling who is getting the harvest. And you would have to also compare that with a sibling who is getting the harvest with G-CSF and demonstrate that in fact the

G-CSF made a difference in the condition in terms of benefit.

And if you didn't I guess it would be poor science. And we're clearly not doing that here. So I don't think it is the condition. And I certainly can't see the benefit of G-CSF in this circumstance.

Dr. Botkin: Yes, and I think we're talking about a couple of the criteria under 406 which I think is ok because I do think they're inter related. And whether we're ameliorating something or not is relevant to whether we're thinking about this as a condition.

Dr. Diekema: I just want to add that when I think about this category, you know one of the ways to do that is to sort of think about what they probably had in mind when they wrote this category which my guess is this was really intended to apply to populations of kids that have awful diseases, JRA, cystic fibrosis --

Mr. Glantz: What conditions, like blindness?

Dr. Diekema: Cancer, blindness, conditions like that. Not the sorts of things that we -- it

could be argued we inflict on a child by virtue of the fact that they have a sibling with leukemia. I mean in this case the only "condition" this child has is something that we've actually created socially.

In other words we've said you will be a marrow donor because you are this child's sibling and the closest match. And it just seems like a very different thing that what this category was probably intended to address.

Mr. Glantz: I wouldn't bother saying this if it wasn't being recorded. But I just wanted to say that I -- if this whole thing wasn't being recorded, I don't believe that the kids who you describe you're looking at their records, have a condition at all. And I think it's important to draw a distinction between meeting an inclusion criteria and having a condition that kids could have.

You could have inclusion criterias in which kids don't have conditions at all. Some of those kids may have conditions by the way. But what you're doing is you're creating an inclusion

criteria for all kids who did it. And you're not at all saying they all have conditions or even that they'll benefit from it.

And that's actually the basic error that SACARP made is that it confused inclusion criteria with conditions. And that those are really very separate categories. So to say that we want to have black kids doesn't mean that the black kids have a condition. That being black is not a condition.

It seems to me. It might be a status, you know. It's a racial category, but not a condition as one uses the word.

And SACARP, I think, you could fairly read that to say that, you know, race is a condition. It's an inclusion criteria, but not a condition. And it's very dangerous, I think to expand it out.

And one of the things we want to do is try to help these kids. But we shouldn't do it by, again, just torturing the words to mean something that they didn't mean.

Dr. Botkin: I would say part of that emphasis was, I think in understanding that, it was a

condition only in the context of the discussion around that research protocol. And I think it very quickly bleeds into a larger context to say, well, what are saying black kids have a condition. Nobody wants to say that might they have a condition under the regs in the context of a particular protocol if by virtue of that trait there are negative, social, biomedical outcomes that are the subject of the study that it would seems to me be a different question. But --

Mr. Glantz: It's still not a condition. It's an inclusion criterion. It's a characteristic.

And the word condition has been used for just this purpose when we talk about amelioration. And in the context of this is for research which is sort of prima fascia unethical. When you look at the beginning of it, it's for kids doing research on kids who will not benefit where there's more than minimal risk.

That's the, you know, this is the criteria that the National Commission argued about in which the Commission said you can't do it at all. And the

question is so if it's not ethical, it seems on its face not to be ethical. What is the counterbalancing importance issues?

And that's where you get, you have to have kids who will benefit. They have a serious condition. They can be ameliorated and all of, you know, that sort of very positive kind of things for kids who have the conditions. And the information has to be of vital importance, not just importance. And the word vital is there for a reason too.

Dr. Botkin: Skip?

Dr. Nelson: Jeff, again I've heard no disagreement on the absence of a condition in this protocol. So I might suggest given that there's only 45 minutes left it would still be useful to hear an opinion about the risk categorization relative to is it a minor increase or not before moving out of this category even if condition gets you out of this category in the first place.

Dr. Botkin: Thank you. So do we have any further discussion about the issue of condition? I guess I am sensing a fairly broad consensus that

these kids do not have a condition. Is that the consensus of the group here? Does anybody wish to take a counter argument to that determination?

[No response.]

Dr. Botkin: Alright. So let's look at the other criteria. And again I think what we're deciding here is that this isn't going to fly under 406. But again it would be helpful for us to have some discussion and helpful for OHRP to hear our discussion and others about these other issues. They are interlinked to a certain extent.

But let's talk about the risk issue. Do the risks represent a minor increase over minimal risk? And again we want to focus specifically on the G-CSF administration to the donors, not the bone marrow, not the balance of risks and benefits here. We're just looking at the risk side here.

Do the risks of G-CSF represent a minor increase over minimal risk or greater than a minor increase over minimal risk?

Mr. Glantz: I have a question. Could someone tell me what bone pain is? I mean I know it's pain

in the bones. I got that part. But like what, I mean, can you describe it?

Dr. Hudson: As the neuro elements are increasing they expand in the cavity and you just have this aching, aching bone pain.

Dr. Santana: It could be specific to ribs or the femur. It could be generalized too.

Mr. Glantz: How uncomfortable is it? Is it like bad pain?

Dr. Hudson: It varies.

Dr. Santana: I mean in the context of this it usually goes -- it is transient in the setting that once you stopped it. Because it's really related like Melissa and I expressed earlier to the expansion of the marrow cavity. So once you shut off the G-CSF there's a period where you go back into some normal hematopoiesis. So the effect of is -- kind of goes away.

So if you give G-CSF for four or five days and you get pain on day three or four, usually when you stop the G-CSF within one or two days the pain is gone.

Unknown speaker: And it is usually manageable with analgesics like Tylenol.

Dr. Santana: Right.

Dr. Kon: So I hate to keep harping on the ARDS issue. But I'm looking right now at a publication in chest from 2001 that reports two cases of ARDS in previously healthy individuals. One of those individuals died. And they were given the G-CSF in preparation for being a donor for transplantation for another individual.

And I guess I personally have a hard time labeling something as only a minor increase over minimal risk where there has already been a report in the literature of someone dying from this exact thing. Now, granted, it's a very small risk, it would seem. But it hasn't really been studied so it's very difficult to know.

But I would have a hard time classifying it that way.

Ms. O'Lonergan: I think when we talk about risk we have to talk about the probability, which may be low. But also the magnitude so that the fact

that ARDS is the magnitude of that risk is very large, I agree with you even though the probability is low.

Dr. Link: In the interest of time does anybody think this is less than minimal? Does anybody even argue the point that this is more than minimal risk? I mean I appreciate what you said. I don't think anybody thinks this is minor.

You're getting an injection every day. It's more than minimal risk on its face. I don't think we have to discuss it.

Dr. Botkin: Is it more than a minor increase?

Dr. Link: It's more than a minor increase to get a shot everyday and then to have all of these risks, not necessarily of ARDS, but of all the other things. I mean is anybody trying to fight this?

Dr. Botkin: We only have a modest amount of information obviously in which to make this sort of decision. So does the relatively high level of uncertainty about the risks associated with this agent in and of itself mean that we ought to be reluctant to categorize it as a minor increase over

minimal risk?

Do we have consensus on that issue? Any comments from the audience on that point?

Alright. Let's pick up on the commensurate experience. And I think we want to have probably at least a half an hour for our discussion of the 407 approval or disapproval which is where we're headed with this. But let's pick up on these final criteria under 406 and get some feedback about those.

Are the interventions or experiences reasonably commiserate with those inherent in the actual or expected medical, etcetera situations for the donor children. And again, the Children's Oncology Group IRB felt that these experiences were reasonably commiserate with those that the children would experience. Meaning the injections, the blood draws, the other interventions that were associated with well, being a bone marrow donor.

I actually don't know if there's injections otherwise, other than the G-CSF. So let me just open that for comment.

Mr. Glantz: Again I have a question that there was a list and I forget who was presenting. It was one of the early presenters who described diarrhea, nausea, a whole series of sort of unpleasant things that were 20 percent, five to 20 percent. Somewhere between five -- and again there seem to be --

Dr. Santana: So that's a slide that is a pool of many different datas. And actually I was trying to get a copy of the protocol consent. That should have a table in there that should have the standardized language we use in all of the oncology groups when G-CSF is administered.`

That slide was more of a global overview of the side effects of -- focusing more on ones that are very common, like the myalgias and the bone pain. The other ones are invariable, you know, infrequent. I can't use those two words in the same sentence. But, you know, very infrequent depending on the population you're looking at.

Mr. Glantz: Well again I'm not sure about infrequent. I know that it's characterized here as common, less common and rare. But those are just

value judgments.

Dr. Santana: Yeah, those are --

Mr. Glantz: As opposed to data where I see five to 20 percent rate. This is again what was on the slide. I have no idea why I'm asking about it.

Dr. Santana: Yeah, that was --

Mr. Glantz: That was nausea, vomiting, diarrhea.

Dr. Santana: Right.

Mr. Glantz: That nausea, vomiting and diarrhea are like, unpleasant. And I don't know if those are part of the how long it lasts. How serious it is? And whether and how that compares to other bone marrow --

Dr. Santana: You have to understand the context of that slide is for side effects for all populations of patients.

Mr. Glantz: Ok.

Dr. Santana: So some of that is bias because nausea, vomiting, diarrhea may be associated with the condition that the patient who has cancer and is getting the G-CSF for fibril neutropenia. So this

slide was not meant to reflect side effects in healthy children. It was reflective of all the side effects that have been reported in general on all individuals that have gotten G-CSF which may not be attributable to G-CSF.

Mr. Glantz: So what are the side effects?

Dr. Santana: So once again, bone pain and myalgia are really the side effects that one can ascribe directly to the G-CSF.

Mr. Glantz: But not nausea, vomiting, diarrhea?

Dr. Botkin: I guess, Leonard, this raised an interesting question in my mind as to whether we think about what interventions are we thinking about or experiences? I hadn't usually thought of those in the context of the side effects of the interventions rather than the intervention per say. That being hospitalization, shots, IVs, you know what you're sort of physically doing to the child as an experience as opposed to the side effects of the intervention per say.

I don't know whether others have thoughts on

that subtlety.

Dr. Diekema: The regulations specifically say experiences I think, don't they? Which would include side effects, it seems to me. So I think it is broader.

Ms. Vining: On page 14 it does say the side effects associated with G-CSF administration to normal individuals are similar to those seen in cancer patients. And they include bone pain, headache, fatigue and nausea. More rarely reported side effects include anxiety, non-cardiac chest pain, myalgia, insomnia, night sweats, skin rashes and other local reactions and vomiting.

So it seems to indicate here that it is a little bit beyond bone pain.

Dr. Botkin: Ok. So, let's get back then to the central question here. Kind of categorized, I think what experiences might be on the table for consideration when we consider these reasonably commensurate with those inherent in the child's actual lower expected, medical situation.

Mr. Glantz: One more thing. Is the length of

hospitalization the same?

Dr. Santana: This is all done outpatient.

Mr. Glantz: I'm sorry. It says that the kids will be in the hospital a day or two.

Dr. Santana: Right. So Steve can talk about --

Mr. Glantz: He's had no impact on time in the hospital.

Dr. Diekema: It's dealing with these criteria separately is always difficult because whether it's commensurate or not depends on whether you consider this to be a healthy child or in which case it obviously is not or whether you consider this to be a bone marrow donor where it becomes at least a little closer to being commensurate with the sorts of experiences they're having as a donor. So again, in many ways it comes back to that first question which is do you consider these kids to have a condition or not?

Dr. Botkin: Let's take the hypothetical that if we were to consider it as a condition, for the purposes of this discussion would the G-CSF

administration be commensurate with their experiences as a donor? I think that is how the COG IRB interpreted the question.

Dr. Santana: Certainly when they go the actual bone marrow procedure there's pain associated with that from the 100 plus needle, bone marrow aspirations that you do. There are side effects of the anesthesia. There are side effects of other things that may be happening to the patients.

So I think in terms of the side effect profile, the nausea, the vomiting, the bone pain, those are also exist in the realm of experiences that they would have under the circumstance of having the bone marrow aspiration and collection.

Dr. Grupp: So that question is actually answerable by data. And the answer to the question is the bone pain associated with the harvest is considerably greater than the bone pain on the average experienced by the patient receiving G-CSF, the incidence of narcotic use is extremely low after G-CSF administration and in the most patients get it at least several doses of narcotic pain medication

after their bone marrow harvest. So from the pain standpoint, from a nausea standpoint, the experience of the actual bone marrow donation is not commensurate it is significantly more painful to undergo the bone marrow donation.

And this is reflected by the fact that we do not hospitalize the children for the G-CSF, but we do hospitalize the children for the bone marrow harvest.

Dr. Botkin: Thank you. Further comments about this whether we have much in the way of a clear consensus about this issue? And again, a hypothetical, so it's not critical we come to any consensus, but any further comments about the commensuratabilty criterion?

[No response.]

Dr. Botkin: Alright. And finally then likely to yield -- is the research likely to yield generalizable knowledge about the subject's disorder/condition which is of vital importance to the understanding or amelioration of the disorder/condition? I have a fairly strong sense

that we've answered that question essentially by the virtue of our comments and thoughts about the condition label itself.

Other comments about the -- and I guess from my personal -- it's hard to describe it as vital importance to the donor because that's not the purpose of the research.

Alright, very good. Ok. I don't think we have a break scheduled so hopefully everybody's ok with -- Elaine, did you have something you want to say?

Ms. Vining: I just wanted to, a point of clarification. In this minor increase over minimal risk, if any one of these questions is not seen as addressing -- the risk represents a minor increase over minimal risk, if any of those four bullets is seen as the answer is no. Then it doesn't meet the criteria for 406. Is that right?

Dr. Botkin: That's correct. That is important. Thank you.

Let's then launch into our discussion of 407. I think we made a determination so far that the protocol is not approvable under 404, 405, 406 or

51, 52, 53. But now we're entertaining discussion under 407.

The criteria here are not explicit. The research needs to be conducted in accordance with sound ethical principles without telling us what those principles are. And the research has to represent a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the welfare of children.

So let's take that question first. Does this research represent a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the welfare of children? And now I think we're looking at the research project globally as opposed to simply the donors per say who have been the focus of our prior conversation.

Dr. Kon: Yes.

Dr. Diekema: Are we done?

Dr. Botkin: Alright. So I want some -- what I've heard around the table here is a number of comments in favor of saying this, that it does

represent a reasonable opportunity. I would like to hear a little bit more discussion about how people are thinking about that criterion and say more about, for those who think this is.

And of course, anybody who doesn't think it is needs to speak up as well.

Dr. Klein: We know that the hypothesis that it's going to significantly reduce the mortality. May reduce chronic graft verses host disease, may end up benefiting in terms of knowing what the graft consists of in terms of immune cells and stem like cells and may end up benefiting the donor as well, in the future, if you have to use less volume or fewer cells. So I think there are a lot of potential benefits for the children who have severe disease.

Dr. Botkin: So literally life saving proportion of the kids potentially with leukemia and potentially preventive of serious morbidities in the form of either acute or chronic graft verses host disease. Enough said on that.

Well let's speak to the donor population. And

again we've decided there's no direct benefit here. Will this research provide information that will help clinicians better deal with the donor population over time?

Dr. Diekema: Well I think there's some possibility of that, but to sort of expand on this question. If assuming this question is actually the place where we should be talking about additional protections that I think would be necessary. I have some suggestions.

In other words I think this can be done in a way that makes it safer for donors.

Dr. Botkin: We definitely want to have that conversation. Let me make sure there isn't anybody else that's dying to make a comment before we move into that part of the conversation.

Dr. Link: I just want to make the comment that we have a program that we think is going to be very important to do and a potential benefit to a lot of kids. And it can't be done without donors. You can't do a bone marrow transplant without a donor. I guess that would be the next technology. I mean

for right now.

So I can't understand how you can unwind the two. And I think that perhaps, not for this meeting, but I think that it would be worthwhile getting a panel together of trying to preempt further discussions or further convenings of this panel to discuss the same which is basically going to come to the same thing. It's all going to fall under the -- going through the why it is not 405. Why it's not 406? And then getting to this.

I think you're going to end up with the same question each time with every new indication that applies to children.

Mr. Glantz: In terms of the donor I would say it just seems much more speculative. And it's not clear to me if that were the only thing we were looking at that it would be justified to do it. But add that as an additional benefit in the whole process that it adds an additional element of benefits.

Dr. Botkin: So that the study is designed in such a way that depending upon what the results are

they could confer some benefit on kids who are donors in the future by virtue of smaller donor volume, shorter anesthesia. Those types of things could be fostered by this research even if it is not a direct outcome. Is that fair to say?

Dr. Diekema: In sort of keeping with sound ethical principles I think there are just a couple of issues I would raise. The first, and I alluded to it earlier when I talked about exclusion criterion. And there are two of them I would modify.

The one, as I mentioned earlier, is I don't think -- I think all donors with any increased risk for bone marrow donation ought to be excluded, not just those with a high risk. And one of the other exclusion criterion is donors with uncontrolled infection. And I guess what I'm wondering is if, I mean, we've talked a little bit about this risk of ARDS.

There was some discussion of whether that has been associated with patients who are already diseased in some way. I'm just wondering if maybe

that exclusion criterion ought to include any child with an active infection, excluding those who have influenza. I mean any potential for a disease that might cause lung disease and predispose their lungs to whatever risk it is that G-CSF might present.

And then finally it seems to me that there ought to be some criterion here that says if there is a medically equivalent, histocompatible adult relative that they ought to be prioritized. In other words that the -- but there could be an adult sibling. So my point is if there's an 18 or 19 year old sibling and a six year old sibling, the preference ought to go to the older of the siblings.

Dr. Link: Just be careful about there's other considerations besides that the CVM status of the donor, the AVO compatibility between the donor and recipient. So we have to trust our transplanters are going to pick the best donor. And obviously if the two are equivalent, they're gong to go for an older donor just because it's easier to transplant a big donor into a little person than the reverse.

So I think you're starting to meddle now, micro

manage how transplanters choose donors. And I think that, you know, if you're going to start to write criteria, you've got to be very careful.

Dr. Diekema: Well, I think that --

Dr. Link: That is not necessarily to the benefit you may be choosing, actually a worse donor.

Dr. Diekema: You can write it any way you want. But I think the point is I'd like to see that explicitly made. I mean it, yeah.

And then the final one I'll just raise as a question. And that is whether this is the sort of situation where a donor advocate ought to be required.

Dr. Kon: So are we on to number two then?

Dr. Botkin: Well conducted in accordance with sound ethical principles, I think that this, Doug's comments, pertain in that particular area. So obviously we're entertaining comments on Doug's comments in potential revisions as well as any other issues that relate to our ethical assessment of this protocol.

Dr. Kon: So I guess we were talking over here.

How do you -- what does that mean, sound, ethical principles? I don't know. But I guess what I would think about is would a reasonable parent agree to this for their child say outside of the research setting? And I think everybody would say, well, yeah. I think that would be a reasonable.

It sounds like there are some risks that may be real, but the potential for benefit is very great. And so I think that it would be reasonable to say that this could move forward under sound, ethical principles. Again, I don't mean this to be nit picky, but in looking at the permission document on page six of 16, where we list the rare but serious.

I think part of being consistent with sound, ethical principles is making sure that we have truly informed permission. And I'm struck that under severe damage to the spleen at the end it says and may be life threatening which I think could be strengthened a little bit. But then under the ARDS and the possibility for hematologic disorders there's no mention that that could actually lead to death, which I think is unfortunate.

And so I think if we're going to be consistent with sound, ethical principles that that requires fully informed permission. And I would say that that would include on that list that the last three bullet points each state at the end, which can cause death. Because I think parents need to understand that if they're going to agree to let their child be in it.

Dr. Botkin: Other comments related to the ethical principles we need to be guided by or the investigators should be guided by here as well as specific comments on Doug's thoughts?

Dr. Klein: I would like to hear a little bit more discussion about the patient advocate issue. Again some of my best friends are transplanters. So you'll forgive me for saying this, but the transplanter is the advocate for the patient with leukemia.

And there clearly is a conflict of interest here. And whether it's for the first harvest or the potential for subsequent harvests I would like to hear what people think about patient advocate for

the donor.

Ms. O'Lonergan: As a patient advocate I think this is perfectly in keeping with the research subject advocates that are at all the CTSAs or if you're still funded by GCRC and it's something that I do at my center, not particularly with BMT, but with oncology trials. And it's a fairly simple thing to set up. And our IRB will specify when they would like me involved in the consent process or other things.

So I think it's a viable requirement depending on the site. If they have a GCRC or a CTSA they can usually lay their hands on a research subject advocate. And it's within their purview to do that.

Dr. Botkin: Is there data on the efficacy on research participant advocates in this context? And do we know is this the right context to try to get specific about how such individuals should be engaged in research? Understanding that many of the research locations may not have those sorts of people on staff, the budget may not have anticipated paying these sorts of folks.

So I have a variety of questions about that recommendation even though I think, theoretically, it sounds attractive.

Ms. O'Lonergan: Well it is theoretical. And I think it is one of those absent data. We assume they're working kinds of things in PI's report that they like having an advocate there because they're worried about being objective. And so it's anecdotally seems to be a good idea. But I don't think we have solid data.

I also think that the way we operate is varied across sites. There are some, the ABO Med that did the heart transplants did a very specific criteria for their research subject advocates. Harvey Morheim has written on that extensively. And I think those might be a starting place as to what -- it's not a directive function. It's a supporting function.

So I think if we were asked as a body, the RSAs could come up with, sort of a working set of criteria. It wouldn't be here tomorrow, but.

Dr. Botkin: I want to go back to Doug quickly.

And I don't think we've heard enough about this proposal to understand what the job of this person is. Is it to figure out when kids don't actually want to be donors and make sure that they tell folks about that? Or is it to help smooth their course through the research protocol?

What would you see as the job of the person?

Dr. Diekema: I think it's most of those things. At my institution we've created something called a research family liaison that plays some of that role. And in the context of this study I think we would see that person -- first of all as somebody who could try to control for the fact that PI does see the patient with cancer as the patient. And there's good evidence that the donors often do sort of get left behind.

It's a very difficult situation to put a family in. And ask them to be objective and protect both children when protecting one may mean compromising a little bit on the welfare of the other. So the advocate is not there to be necessarily, you know, certainly in the legal sense somebody who's opposing

what the team is recommending.

But rather they're making sure that the family understands the issues here. That they understand there are implications for the donor. And making sure those do get discussed thoroughly in the consent process. Making sure the donor child's well being is not being forgotten and left behind, those sorts of things.

Mr. Glantz: I think the theory is to find someone who doesn't have a stake in someone saying yes or no. That it doesn't have any impact on their job or their success. They're hard to find by the way if they're inside the institution.

And I think that that's the goal because we actually want the oncologist being the advocates for the children with cancer. We expect them to do that. So it is not a bad thing. It is just is there a way to attenuate that bias, if that is the right word.

But you raised an important point, Jeff. And that had to do with what about the 16 year old who doesn't want to do it. And somebody's saying, again

going back to the early kidney cases. I know that.

Physicians who are -- who I knew who did this stuff, who take the older donors aside and say do you really want to do this? Do you really want to have your kidney taken out? And sometimes they would say no. And then the solution would be for the doctors to lie.

So it's sort of an interesting ethical thing to say, you know your child, we did one final test. And it's not compatible and that that, they were sort of protecting those kids. And so the question and maybe this is what the research advocate question is particularly for the older donors.

Where can they go to express what their real sense is? What they want to do without their mothers and fathers being there? And that goes to the assent question I think.

Dr. Botkin: Alright on this point then. And I want to pick up on the other comments. And clarify the other ones that Doug had made here.

So it sounds like there's a general feeling this would be a good thing to have a participant

advocate engaged in the research to make sure that the significant focus of that participation is with the donor as opposed to the recipient here. And that's justified by virtue of the fact that we're looking at a protocol that doesn't meet the traditional criteria. And in order for us to feel comfortable about this we want to try to maximize whatever protective measures that are reasonably available for the donors in this context.

So do we want to make this a stipulation? Or is this a strong recommendation? In other words are we going to say this research should not go forward without a participant advocate engaged in the project or do we want to make this a recommendation that says when such people are involved in your institution you should involve them in this research?

Dr. Santana: I would suggest from a practical sense that it would be a very strong recommendation. But not a stipulation just because there are a 100 plus institutions that may ultimately participate in this trial with varying degrees of resources and

individuals that clearly are trained to do this the way we want it. And so I think we should strongly recommend that when there is such a person in the institution that it be done.

And when there isn't, that there should be other options to consider. But I don't think we should make it a stipulation because it may be impractical.

Dr. Link: I agree. I have to look at the numbers. There's going to be about 20 or more institutions for 44 patients. So that means you need -- you got to be careful. You'd have to hire a person to do this for maybe putting one patient on the trial.

So I think we can recommend -- I think there should be some stipulation, not stipulation, but a recommendation about the scope of what this person is to do. Because it can get taken out of hand that, we're going, you know take the patient to court, get a judge order. I mean you've got to be very careful to what level it's going to be taken.

Dr. Diekema: I just think we need to be fully

aware of the fact that if we make it a strong recommendation it almost certainly won't happen. So we have to be comfortable with that. In other words, I guess the question I would ask is if we think it's important than we either have to decide that it's important enough to require or we have to decide that although it's important, it's ok that it doesn't happen.

Dr. Botkin: Let me double check with Skip here about the ultimate process. If this is approved under a 407 and the Secretary approves it, what happens at those institutions where the IRB has already approved this? Do they need to revisit it? Or is it simply restarted at those institutions?

In other words if we provide some additional either stipulations or recommendations can those get seriously considered at the institutional level again through an IRB process or how does that work?

Dr. Nelson: Well all three prior protocols have been single institutional protocols. So the answer is there is no procedural precedent as yet for how to deal with that. There's no reason why

these can't be dealt with.

I might also add you're making a recommendation. So whether or not -- I mean I think if you say something is a stipulation, what you're saying is that this as a stipulation that this shouldn't go forward unless there is that change at all institutions. Whether that recommendation would be carried forward ultimately to then have OHRP work with the institutions to put it in place is a separate question.

Dr. Grupp: Just a very brief practical answer to that question is this protocol, as a result of this discussion, will undoubedly undergo changes in the consent form which will require resubmission at all of the IRBs. So that you can take as a given. It will happen.

Dr. Botkin: Thank you.

Ms. O'Lonergan: So again as a practical matter there are 82 sites in the United States. And we cover all the pediatric sites that have research subject advocates in the institution. And so it is conceivable, even if that they didn't go through

CTRC funding, that they could access someone like this and on a regional basis. So I don't think it would prevent it from being done.

Dr. Link: I just have a question on the other things you suggested, the eligibility requirements would change. So they would have to get IRB approval anyway. So that sort of makes it mute.

Dr. Botkin: Well, let's finish up on this one. Touch on the other ones. We've only got about five minutes here.

Dr. Wysocki: Just to introduce one intricacy to the consent process. If we offer parental permission to the parent regarding the recipient how is that same parent not then going to provide parental permission for the donor? And once the parent has provided parental permission for the recipient do we not have essentially a coercive situation which would make it exceptionally difficult for the child donor to dissent. So I'll just throw that wrench in the works for you to contemplate.

Dr. Botkin: I would think that would always, I

mean, the parents won't be coercing themselves into signing the second consent form because they would obviously be decision makers for both. Would each child then be pressured? Coercion I think is too strong a word.

But might there be undue influence on their decision making by virtue of their sibling's decision around this. I think that's an important point. Although I'm not sure that it's avoidable in this context.

Dr. Link: Now we're getting the patient -- the parent has already agreed to getting the transplant which implies the donor will get harvested. So that's already a done deal. The issue here is that we're trying to protect the donor.

So it's only a matter of whether they will enter this randomized trial. In other words the kid is going to get, one way or another, he'll either get G-CSF in peripheral stem cell, G-CSF in bone marrow or just the bone marrow for harvest depending on what the institution would do normally. Or he will enter this trial.

So that's the only thing that's under discussion here. Not whether we have to worry about the parent's consenting for their recipient. They wouldn't even get into this process.

They would even get HLA typed if they weren't interested in getting a bone marrow transplant. So I think that that's sort of a mute point.

Dr. Botkin: Alright. Let me see if I can summarize then where we are. And I actually want to finish off first with the patient advocate recommendation and then touch on these others.

And I think our consensus is all of these are good thoughts. Would be improvements is what I want to say. But perhaps the question remaining is whether we want these as stipulations or as recommendations as this goes forward.

So the patient advocate recommendation. Doug, would you want to express that exactly how you'd like us to think about that? In other words we may end up with a vote on this.

Dr. Nelson: Would you like me to read what I wrote down?

Dr. Botkin: Ok.

Dr. Nelson: Each research site should appoint an independent person to function as an advocate for the potential sibling donor. So the question is where do you want to put that?

Dr. Botkin: And what is your proposal?

Dr. Diekema: Do you mean as to whether that's a stipulation or a recommendation?

Dr. Botkin: That's right. It came from you. I want your initial thought on that.

Dr. Diekema: So I recognize that there are practical issues here, but I think from the standpoint of sound, ethical principles, this is if there's any situation where such an individual is justified, it's this one. So I would make it a stipulation.

Dr. Botkin: To include institutions that don't have such individuals now, meaning the research would not be conducted at those institutions?

Dr. Diekema: My preference would be that that would not be the route. I mean I think there may need to be some effort made to allow those

institutions to create a structure. I mean this should not be a difficult thing to achieve. Every institution has, certainly the kinds of institutions where COG studies are occurring, have individuals within them who could play this role.

It shouldn't be somebody associated with the HEMARC team, but their social work department, there are pastoral care departments, there are patient advocacy departments, patient navigators. I mean they call them different things all over the place. But I can't imagine a children's hospital, they wouldn't have somebody who could do this.

Dr. Botkin: Alright. So stipulation. Geoff?

Dr. Rosenthal: You know, I just want to make the comment that I'm not sure. I'm sitting over here thinking about where we are in the discussion and where we've been for the last six hours. I'm not sure that, in my mind, that the appointment of a patient advocate raises this potential research project to one that adheres to sound ethical principles for all of the reasons that we've discussed all day.

So yeah, I think it's a necessary concept to include in the mix. But I still have a question about whether we meet the other ethical principles that need to be met in order to consider this at all.

Dr. Botkin: Ok.

Dr. Nelson: Jeff, can I make a suggestion?

Dr. Rosenthal: Yeah.

Dr. Nelson: You have very little time, alright. You've worked your way up to this category. I think if there are people who think it fits/it doesn't fits. And there's a point at which you just have to take a vote and find out where people put it.

If there's changes that would put it into sound ethical principles, like the advocate. That's fine. But if there's people think there are none, then I assume they would vote against that category.

I mean, ultimately, you know, because we have the Advisory Committee meeting starting at 3:30. Now can we go longer? Yes. But we're going to need to stop this meeting and start the next one.

Dr. Botkin: Agreed. I think we do need to hear from Geoff. I mean my sense of the group's attitude here was that this was approvable under 407. But that we were looking at details of the study that would reassure us that it was the most protective design that could be conceptualized here.

So let me get back to Geoff and see whether that was a false assumption on my part. Are you thinking that this might not be an approvable study?

Dr. Rosenthal: Well, I don't know all of the nuances of the rules to the extent you guys do. But just in my crude understanding. Yeah, I do have a question about whether it adheres to sound ethical principles, even if you can identify a completely objective advocate for the patient in this setting.

Dr. Botkin: I think we're going to have to come to a vote here in just a second. Go ahead.

Dr. Klein: I would like to follow up. Is your concern the entire harvest and transplant? Because I think we're just talking about the G-CSF at this point. Or is it the G-CSF that concerns you?

Dr. Rosenthal: My concern lies in what I

perceive to be a complete disconnect between the person who assumes the risk and the person who is going to gain from the participation basically. The risks and benefits are being experienced by two different parties. So for me that's the central theme.

Dr. Klein: I just wanted to point out there's going to be a transplant in any case with the harvesting part whether it's a regional anesthetic or a general. That's all going to happen.

Dr. Rosenthal: Right. You're talking about clinical medicine. I'm talking about this is the research context.

Dr. Diekema: As the Chair of the IRB again, this is what we struggle with every week. I think it is also important to recognize that G-CSF can be used in children. It is being used 20 percent of the time in children.

And so to a certain extent one of the questions here, sort of the big question, is do you do this research or do you just let people use it clinically. In which case we don't learn anything

and we don't know anything about it. And so although I would completely agree that's there's certainly are concerns.

And Geoff has sort of, very nicely, articulated those concerns. The alternative here is that this will still be done. Only now we won't have the opportunity to sort of learn anything from it. And that also concerns me from an ethical perspective.

Dr. Botkin: Alright. We need to finish up. So let me touch on the issues that have been raised, that others have recommended or potentially stipulated as improvements to enhance the protocol.

Alex had mentioned including death as a potential outcome in the consent form obviously for the donors. Is that something that is in your mind, a recommendation or stipulation?

Dr. Kon: I think it's a stipulation.

Dr. Botkin: Stipulation. Good. We talked about the patient advocate position. We're making that in this initial proposal. And we're going to vote on this here in a minute.

Older age for the donor, all other things being

equal, preference for older age donor, all other things being equal, a stipulation?

And then the last I heard was that any risk to -- that would increase the risk of the donor to the G-CSF administration should be an exclusion criteria and not just a risk that's categorized as a high risk. And that would be a stipulation as well.

So I think our proposal on the table then for a vote is approval under category 407 with the four stipulations articulated.

All in favor?

Dr. Link: Patient advocate was not a stipulation.

Dr. Botkin: It was a stipulation. They're all stipulations.

Dr. Pena: So why don't we go down the line. People just raise their hands simultaneously and just read for the record their vote. Yes or no?

Dr. Klein: Yes.

Dr. Santana: Yes.

Ms. O'Lonergan: Yes.

Dr. Link: No.

Dr. Kon: Yes.
Mr. Glantz: Yes.
Dr. Diekema: Yes.
Ms. Vining: Yes.
Dr. Rosenthal: No.
Dr. Hudson: Yes.
Ms. Celento: Yes.
Dr. Nelson: It would be helpful, Jeff, for the two people who voted no, since you linked the approval with the stipulations whether if you remove certain stipulations if they would then consider approval under that category. It would just be helpful for the two no votes to say what was that motivated their no vote.
Dr. Botkin: That's good.
Dr. Link: I would definitely vote in favor of running the trial, but the stipulation that I objected to was the stipulation for an advocate that was put in there.
Dr. Rosenthal: And for me the presence of the stipulations didn't sufficiently impact my perception of the adherence of the protocol to sound

ethical principles.

Dr. Botkin: Very good. Thank you. Alright.

My thanks to everybody. Excellent discussion. The Advisory Committee is going to be here in about half an hour. And we will present our findings to them. Will there be -- or what sort of follow up might happen with the Ethics Advisory Committee in terms of the overall outcome? How can folks here track what is the response to the --

Dr. Nelson: Well, you and I will put together the minutes from this meeting which is why I've been over here scribbling and the like. Some of that you will present to the Advisory Committee. And then basically those flash minutes become part of this public docket. And so all this will end up posted on the website as well.

Ultimately the communication around the final Secretarial determination would ultimately be part of, I think the OHRP website because that's gone up in the past. But, you know, so ultimately people will find out. I can't give you a date on that. But you'll find out.

Dr. Pena: So we'd be happy to circulate the minutes also to all the Committee members here at the table today.

Dr. Botkin: Alright. Thanks again everybody. Terrific discussion.

[Whereupon, at 3:05 p.m., the meeting was adjourned.]