MINUTES OF THE
PEDIATRIC ETHICS SUBCOMMITTEE of the
PEDIATRIC ADVISORY COMMITTE

The Legacy Hotel, 1775 Rockville Pike, Rockville, Maryland

December 9th, 2008

On December 9th, 2008 the meeting was convened at approximately 9:00 a.m.

Subcommittee Members and Consultants
Jeffrey R. Botkin, M.D., M.P.H. *(Subcommittee Chair)*
Amy Celento (Subcommittee Member)
Douglas Diekema, M.D. (Consultant)
Leonard Glantz, J.D. (Consultant)
Melissa Hudson, M.D. (Subcommittee Member)
Harvey Klein, M.D. (Consultant)
Alexander Kon, M.D. (Consultant)
Michael Link, M.D. (Consultant)
Theresa O'Lonergan, M.A. (Consultant)
Geoffrey Rosenthal, M.D. (Subcommittee Member)
Victor Santana, M.D. (Consultant)
Elaine Vining (Subcommittee Member)

Executive Secretary
Carlos Peña, PhD, MS

FDA Participants
Robert M. Nelson, MD, PhD

Office for Human Research Protections (OHRP) Participants
Jerry Menikoff, M.D., J.D.

Guest Speakers
Stephan A. Grupp, M.D., Ph.D.
Tim Wysocki, Ph.D., ABPP, CIP

Open Public Hearing Speakers
A public letter to FDA from Dennis L. Confer, MD, Chief Medical Officer, National Marrow Donor Program, was read into the meeting transcript.

A public letter to FDA from American Mothers Organization, was read into the meeting transcript.

FDA and OHRP Presentations:

Overview of Expert Panel Process, Subpart D, and Questions for Panel	Jerry Menikoff, MD, JD Director, Office for Human Research Protections, HHS Robert M. Nelson, MD, PhD Pediatric Ethicist, Office of Pediatric Therapeutics, FDA

Subcommittee Presentations:

Background and Overview on the Use of G-CSF in Stem Cell Transplantation	Victor Santana, MD Consultant, Pediatric Ethics Subcommittee

Guest Presentations:

Background and Overview on Protocol ASCT0631	Stephan A. Grupp, MD, PhD ASCT0631 Study Chair
Referring IRB Presentation	Tim Wysocki, PhD, ABPP, CIP Chair, Nemours Oncology IRB

Questions to the Committee:

(1) What are the risks of G-CSF administration?
   (a) If these risks are appropriately considered to be minimal risk, have the general criteria for IRB approval been met?
   (b) If not, are there additional stipulations that the panel would recommend?

(2) If the risks of G-CSF administration to the sibling donors are more than minimal risk, does the intervention offer the prospect of direct benefit to the sibling donors?
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.

(3) If the G-CSF administration does not hold out a prospect of direct benefit to the sibling donors…
   (a) Are the risks of G-CSF administration appropriately considered to be no more than a minor increase over minimal risk?
   (b) Is the intervention likely to yield generalizable knowledge about the sibling donors' disorder or condition that is of vital importance for the understanding or amelioration of [that] disorder or condition?
   (c) Does the intervention present experiences to the sibling donors that are reasonably commensurate with those inherent in their actual or expected medical,… psychological, [or] social… situations?

(4) If the G-CSF administration does hold out a prospect of direct benefit to the sibling donors, are
   (a) The risks of G-CSF administration justified by this anticipated direct benefit?
   (b) Is the relation of the anticipated benefit to the risk is at least as favorable to the sibling donors as that presented by available alternative approaches?

(5) If the research does not satisfy the conditions of either §46.404 [50.51], §46.405 [50.52], or §46.406 [50.53]…

(a) Does the research present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children?
(b) Will the research be conducted in accordance with sound ethical principles?
(c) Are adequate provisions made for soliciting the assent of children and the permission of their parents or guardians?

The Subcommittee had a number of recommendations, which are included in the Chair's summary of the meeting. This meeting summary was also presented to the Pediatric Advisory Committee on December 9th, 2008 and can be found at the dockets website for that meeting. It is also included below.

Meeting Summary
Prepared by Jeffrey Botkin, MD, MPH
Chair, Pediatric Ethics Subcommittee

Introduction

The Pediatric Ethics Subcommittee (PES) of the Pediatric Advisory Committee (PAC) met on December 9, 2008, to review a clinical investigation entitled "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." (ClinicalTrials.gov Identifier: NCT00450450) The review was requested by the Nemours Oncology Institutional Review Board (IRB) under 21 CFR 50.54 / 45 CFR 46.407.

Protocol Abstract (adapted from ASCT0631 Protocol, Version Date: 10/29/07; posted at http://internet-dev.fda.gov/ohrms/dockets/ac/08/briefing/2008-4406b1-00-Index.html)

ASCT0631 is a Phase III trial comparing two graft sources for allogeneic transplantation using HLA-identical siblings as donors: non-stimulated bone marrow and filgrastim (G-CSF) stimulated bone marrow (G-BM) in children undergoing allogeneic transplantation for leukemias in which matched sibling donor transplantation is appropriate. The protocol implements a novel strategy to integrate transplant questions concerning the donor source of bone marrow into treatment studies, allowing patients on disease-specific treatment protocols co-enrollment on a study designed to investigate a transplant-specific question in a manner which does not adversely impact the primary, disease specific, treatment question. Thus, there will be two categories of leukemia patients enrolled on ASCT0631 – those for whom ASCT0631 is the only study enrollment, and those who are also enrolled on ASCT0431, AAML0532, or other leukemia treatment studies.

The major hypothesis of this protocol is that the increased bone marrow cell dose provided by the graft collected on the stimulated G-BM arm of this study will improve the event-free survival of these patients with leukemia. A further hypothesis is that patients on the stimulated G-BM arm will show more rapid engraftment kinetics with equivalent rates of acute and lower rates of chronic graft vs. host disease.

Any patient with acute or chronic leukemia or myelodysplasia needing bone marrow transplantation with a matched sibling donor available is eligible for this study. Eligible diseases include AML in CR1 or CR2; myelodysplastic syndrome; ALL in CR2 or high-risk CR1; CML in first or second chronic phase and JMML.

G-BM will be collected from donors on the experimental arm after five days of G-CSF treatment of the donor. Target volume for both BM and G-BM collections is 15 cc/kg of recipient weight, with a maximum of 20 cc/kg donor weight.

Biological studies will correlate graft characteristics with the incidence of GVHD and measure the rate of immunologic recovery of the patients. The experience of the donor and family during participation on this protocol will also be assessed. There will be collection of acute adverse donor events and long-term donor experience using the national standard RDSafe approach pioneered by the NMDP and CIBMTR/NMDP.

Explanation of the Need for Review under 21 CFR 50.54/45 CFR 46.407

As documented in the materials submitted for review by the PES, the ASCT0631 clinical trial was developed by the Children's Oncology Group (COG), and it was reviewed by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) and by the NCI Pediatric Central IRB. The NCI Pediatric Central IRB reviewed the ASCT0631 clinical trial and determined that the inclusion of normal child donors satisfied the requirements of 45 CFR 46.406 and 2 1 CFR 50.53. The ASCT0631 protocol was activated by COG in December 2007. At the time of the hold pending the outcome of the PES/PAC review process, the protocol had been approved by IRBs of 31 COG member institutions. A total of 14 subjects at 11 different sites had been enrolled.

The referring IRB (Nemours Oncology IRB) determined that the protocol offers no direct benefit to the sibling donors (and thus could not be considered under 21 CFR 50.52/45 CFR 46.405). In addition, siblings of children with leukemia have an elevated risk of developing leukemia themselves. G-CSF carries a theoretical risk of initiating the onset of leukemia (leukemogenesis) in these healthy siblings, a risk that is difficult to confirm or disprove because of the required sample size and follow-up duration. G-CSF also carries other risks, e.g. enlargement of the spleen (rarely rupture), bone pain, fever and others. These rare but serious risks of G-CSF have not been seen in pediatric donors, but sample sizes have been small. As the Nemours Oncology IRB found that the risks of G-CSF administration exceeded a minor increase over minimal risk, the additional determination under 21 CFR 50.53/45 CFR 46.406 that sibling donors have a "condition" was left undecided.

Based on these findings, the Nemours Oncology IRB concluded that G-CSF administration to the healthy siblings of pediatric cancer patients constitutes more than a minor increase over minimal risk (and thus could not be approved under either 21 CFR 50.51/45 CFR 46.404 or 21 CFR 50.53/45 CFR 46./406). Absent a prospect of direct benefit for the healthy sibling donors, the G-CSF administration could not be approved under 21 CFR 50.52/45 CFR 46.405. The research offers the potential for improved outcomes of bone marrow transplantation which could benefit

pediatric leukemia patients. Thus, the protocol ASCT0631 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" (45 CFR 46.407 and 21 CFR 50.54). The Nemours Oncology IRB thus decided by unanimous vote to refer the protocol to OHRP and FDA for review under 45 CFR 46.407 and 21 CFR 50.54.

Issues Discussed

The PES discussed the general question of the ethics of sibling BM donation in a clinical setting. Among the issues considered was (1) whether or not a third party should be involved as an advocate for the potential donor; and (2) whether the justification for parental discretion in the decision to permit BM donation from one sibling to another sibling is based on any purported benefit (whether considered direct or indirect) to the donor or on the absence of significant risk of serious harm. There was general consensus by the PES that the use of siblings for BM donation in clinical care was ethical as long as the risks to the donor were not significant. That is, the ethical use of sibling donors in clinical medicine is not contingent on a benefit to the donor. The PES also touched on the question of precedent, and the relationship of recommendations made during the course of deliberations today and future protocols involving healthy siblings as BM donors.

The PES discussed the scientific merit of the referred protocol. Although a three arm trial (i.e., including the use of peripheral blood stem cell procurement or PBCS) may have provided useful information, such a trial would not be feasible. Thus, the scientific merit of this protocol, as designed, was considered acceptable. No alternative study designs were identified that would answer the scientific questions at hand.

The PES then briefly discussed whether the sibling BM donors are research subjects, and thus whether the inclusion of the pediatric BM donors in this protocol needs to be evaluated using Subpart D (2 CFR 50 and 45 CFR 46). As the sibling BM donors are being randomized to either receive or not receive G-CSF, and data is being collected concerning the BM donors, the PES determined that they are appropriately considered research subjects under both FDA and HHS regulations.

The PES focused the discussion on the research intervention, noting that the sibling BM donors who are included in this protocol would already have been selected (and parental permission obtained) as an appropriate matched BM donor. Thus, the analysis of the risks and potential benefits of being in the research protocol (for the sibling BM donors) should focus on the administration of G-CSF. Prior to discussing the sibling BM donors, the PES considered the Subpart D approval categories for the BM recipients (i.e., children with leukemia). The consensus opinion was that the inclusion of the BM recipients could be approved under either 21 CFR 50.52 / 45 CFR 46.405 for those who received the G-CSF stimulated BM, and either 21 CFR 50.51 or 53 / 45 CFR 46.404 or 406 for those BM recipients who would not receive the G-CSF stimulated BM (as the BM donation and other aspects of the protocol could be considered "standard of care" and thus not involve any increased research risk).

The PES then turned to the analysis of the sibling BM donors. The PES noted the emerging consensus that the two different groups (i.e., those randomized to receive G-CSF prior to BM donation and those randomized to standard BM donation) should be assessed post-randomization. Thus, the incremental research risk of inclusion in the protocol (when compared to standard of care) for those who do not receive G-CSF would be considered minimal (i.e., data collection). The group that is randomized to not receive G-CSF can be approved under 21 CFR 50.51 / 45 CFR 46.404, as the research presents no more than minimal risk. The PES, having made these consensus determinations, then turned its attention to the analysis of the inclusion of healthy sibling BM donors who would receive G-CSF prior to BM donation. The below question were answered by the PES with respect to this group – the healthy sibling BM donors who would receive G-CSF.

Questions to the Pediatric Ethics Subcommittee:

(1) What are the risks of G-CSF administration?
(a) If these risks are appropriately considered to be minimal risk, have the general criteria for IRB approval been met?
(b) If not, are there additional stipulations that the panel would recommend?

The PES determined that the risks are not appropriately considered minimal risk, even setting aside the question of whether G-CSF increases the risk of leukemia in siblings of children affected with leukemia. The PES then reviewed the documented and theoretical risks of G-CSF administration, and concluded that the severity of some of the documented (e.g., bone pain) and theoretical risks (e.g., leukemia, ARDS, splenic rupture) and the lack of significant data on the risks in children meant that the risks are not a slight increase over minimal risk. Thus, the PES concluded by consensus that the risks of G-CSF administration are more than a minor increase over minimal risk.

(2) If the risks of G-CSF administration to the sibling donors are more than minimal risk, does the intervention offer the prospect of direct benefit to the sibling donors? 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.

The PES identified the potential benefits to the BM recipient as increased survival and/or fewer side effects (such as acute or chronic GVHD). Although these are direct benefits to the BM recipient, the PES came to the consensus opinion that these potential benefits are indirect (i.e., not direct) for the BM donor. That is, G-CSF administration to the donor does not provide a direct benefit to that child, but does provide a potential indirect benefit if the intervention leads to reduced morbidity or mortality in the donor's sibling.

The discussion included the following points made by individual members, often with general assent from the other members of the PES: (1) The direct benefit should accrue to the research subject from the intervention itself; (2) Due to the lack of research on the psychological impacts of sibling BM donation, it is unclear whether and how much the BM donor benefits from the G-CSF administration; (3) Although there is the future potential for using a reduced BM volume

depending on the results of this study, there is no research question in the protocol that addresses this issue; (4) The benefit to the sibling BM donor of the increase chance for survival of the recipient sibling may be real and significant, but the number of necessary steps and the presence of the recipient response in the causal chain argue against this being considered a direct effect of the G-CSF; (5) The benefit of increased survival of the BM recipient accrues to the entire family, and not simply the BM donor, arguing against this benefit properly being considered a direct effect of enrollment in the protocol and/or the administration of G-CSF; (6) The assessment of the possibility of benefit to the BM donor requires a number of assumptions about the family which may or may not be true, and are often speculative in the absence of specific information about a given family.

The PES discussed the implications of this determination for the justification of sibling BM donation in the clinical setting. There was some concern that a finding of lack of direct benefit for the sibling BM donor would undermine the justification for children donating BM in the clinical setting. Two general points were made in response: (1) The argument that BM donation may be in the "best interest" of the sibling BM donor are based on the indirect benefits which might accrue to the sibling donor as a member of the family. The benefits under Subpart D must be a direct result of the research intervention (G-CSF), which is a narrower justification of the risks of BM donation in the research setting. (2) The ethical and legal underpinning of parental decision-making in the clinical setting is based on the lack of significant risk to the sibling BM donor, rather than the view that BM donation is in the sibling donor's "best interest." The lack of significant risk to the sibling BM donor places this decision within the discretionary decision-making authority we afford parents in balancing the competing interests of all family members, particularly the sibling BM donor and the sibling BM recipient. This perspective is supported by the view that the potential benefits of improved survival and/or decrease side effects for the BM recipient accrue to the entire family.

(3) If the G-CSF administration does <u>not</u> hold out a prospect of direct benefit to the sibling donors, are the risks of G-CSF administration appropriately considered to be no more than a minor increase over minimal risk? Is the intervention likely to yield generalizable knowledge about the sibling donors' disorder or condition that is of vital importance for the understanding or amelioration of [that] disorder or condition (21 CFR 50.53/45 CFR 46.406)? Does the intervention present experiences to the sibling donors that are reasonably commensurate with those inherent in their actual or expected medical,... psychological, [or] social... situations?

The focus of the PES discussion was on whether or not the sibling BM donors could be considered to have a disorder or condition. The PES came to consensus that the sibling BM donors do not have a disorder or condition in the context of this study. There was some discussion, but no agreement, on whether the sibling BM donors could be considered to have a condition in the context of other research protocols which would ask questions relevant to the health and welfare of the sibling BM donor (e.g., studying the psychological consequences after a clinical donation, reducing the need for transfusion after BM donation, and so forth). Concerning whether the sibling BM donors have a condition or disorder in this protocol, the PES comments included: (1) The fact that a child meets the inclusion criteria for a research protocol does not establish that the child has a condition. Merely being the sibling of someone with cancer is not a disorder or condition. This would be an expansion of the concept as proposed by The

National Commission in 1977. (2) The concept of condition should be linked to the understanding or amelioration of a negative state of the child that requires an intervention to prevent untoward consequences, rather than the circumstance of the child which is created by the choice of that child to be a BM donor. In effect, the condition is then being assigned by the investigators. (3) It is odd to consider how an external change creates a condition. The example that was mentioned: imagine performing HLA typing of one sibling prior to the other sibling getting being diagnosed with leukemia. Prior to the diagnosis of leukemia, the unaffected sibling would not have a condition. After the diagnosis, we would then need to conclude that the disorder of one sibling creates a condition in the other unaffected sibling.

The PES found it difficult to answer the questions about generalizable knowledge and commensurate experience, given the consensus that the sibling BM donors lacked a disorder or condition.

(4) If the G-CSF administration does hold out a prospect of direct benefit to the sibling donors, are the risks of G-CSF administration justified by this anticipated direct benefit? Is the relation of the anticipated benefit to the risk is at least as favorable to the sibling donors as that presented by available alternative approaches (21 CFR 50.52/45 CFR 46.405)?

The PES had a discussion of whether or not the potential benefits to the sibling BM donor justified the risks, and whether the relationship between the risks and potential benefits (if considered direct) were comparable to the available alternatives. There was no consensus on this aspect of 21 CFR 50.52 / 45 CFR 46.405, as the PES expressed a lack of clarity on how to approach this analysis given the prior discussion on the lack of direct benefit. Three comments are worth noting: (1) Regardless of whether or not the potential benefits are considered direct or indirect, it is uncertain how one would approach the type of balancing required under 21 CFR 50.52 / 45 CFR 46.405. (2) The balance of risks and potential benefits (even if indirect) are such that a "reasonable person" may decide to be a BM donor under the circumstances of this protocol. (3) The protocol under discussion is not being done to benefit the BM donor. To try to place the protocol under 21 CFR 50.52 / 45 CFR 46.405 is to stretch the concept of direct benefit beyond recognition. In this context there was some discussion of whether or not altruism could be construed as a potential benefit to the sibling BM donor. There was no consensus on this issue, although altruism as a motivation for BM donation is clearly not possible for children under about 6 years of age and the children selected for BM donation are, in a sense, being "drafted" and not volunteering.

(5) If the research does not satisfy the conditions of either §46.404 [50.51], §46.405 [50.52], or §46.406 [50.53], does the research present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children (21 CFR 50.54/45 CFR 46.407)? Will the research be conducted in accordance with sound ethical principles? Are adequate provisions made for soliciting the assent of children and the permission of their parents or guardians?

The PES reached the consensus view that the research does present a reasonable opportunity to understand, prevent, or alleviate of a serious problem affecting the health of children with leukemia who require a BM transplantation. The research may significantly reduce mortality

and reduce GVHD for the BM recipients, and may alter clinical practice for sibling BM donors (although this is more speculative).

The PES determined that the protocol could be conducted in accord with sound ethical principles (with one dissenting vote). Two of the ethical principles which were specifically identified, with required modifications to the protocol as noted below, were: (1) the minimization of research risk; and (2) the importance of assuring informed and voluntary parental permission and child assent (if appropriate). The PES discussed the potential conflict faced by parents when making a decision which places one child at risk for the sake of another. The stipulations which are recommended by the PES for the protocol to proceed were formulated to address these two ethical principles.

Summary of Subcommittee Determinations

(1) The research risks that should be considered when evaluating the inclusion of the healthy sibling donors is the incremental research risks of the G-CSF administration.
(2) The risks of G-CSF administration are more than a minor increase over minimal risk. Thus the protocol cannot be approved (for the healthy sibling donors) using 21 CFR 50.51 / 45 CFR 46.404 or 21 CFR 50.53 / 45 CFR 46.406.
(3) There are benefits to the donor (although some panel members thought these benefits somewhat speculative), but these should be considered indirect. Thus the protocol cannot be approved using 21 CFR 50.52 / 45 CFR 46.405.
(4) The donors do not have a condition with respect to this protocol. Thus, in addition to the risk of G-CSF administration, the lack of a condition means that the inclusion of healthy sibling donors cannot be approved using 21 CFR 50.53 / 45 CFR 46.406.
(5) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.
(6) The research can be conducted in accord with sound ethical principles (with one dissenting vote), assuming the following changes (below) are made to the protocol and consent documents.
(7) The inclusion of healthy sibling donors in this research protocol can be approved using 21 CFR 50.54 / 45 CFR 46.407.

Stipulations (required for approval)

(1) All donors with any increased risk for BM donation (not simply high risk) should be excluded. For example, the presence of an uncontrolled infection as an exclusion criterion should be altered to any child with an active infection, especially pulmonary.
(2) Last two bullet points in the parental informed permission document (ARDS, leukemia) should indicate that they are potentially life-threatening.
(3) Each research site should appoint an independent person to function as an advocate for the potential sibling donor.
(4) All things being equal, preference should go to an older sibling donor.

Recommendations (preferred but not required for approval)

None.

Vote:
The vote was 9 in favor and 2 against the motion of recommending approval under 21 CFR 50.54 / 45 CFR 46.407 with the above stipulations. One no vote was based on a disagreement with the stipulation regarding the requirement for a donor advocate. If this was altered to a recommendation rather than a stipulation, the individual would have voted in favor of the motion. A second no vote was based on one committee member who did not believe the study was conducted in accord with sound ethical principles due to the general concern over placing the BM donor sibling at additional risk for the benefit of the recipient.

The meeting adjourned at approximately 3:00 p.m. on December 9th, 2008.

Please see transcript for details

I certify that I attended the December 9th, 2008 meeting of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.

Carlos Peña, Ph.D., M.S.
Executive Secretary

Jeffrey R. Botkin, M.D., M.P.H.
Chair