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March 25, 2008

Memo to: BMT Center PIs and CRAs

Subject: ASCT0631

The study design of ASCT0631 is innovative and includes the donor of the bone marrow as a research subject in addition to the recipient. The ASCT0631 study design was piloted in 9 pediatric centers, all of which approved the use of G-CSF in normal donors. This use of G-CSF is standard of care for donor mobilization of PBSC across the country, including the 20% of siblings donors who donated PBSC in a recent Pediatric Blood and Marrow Transplant Consortium (PBMTC) review (Pulsipher et al., BMT). Our pilot study is in now press in Blood (see Frangoul, et al., Blood).

This study design was discussed extensively with and approved by the COG Scientific Council, BioEthics, the Myeloid Disease Committee, CTEP and the Pediatric Central IRB. In addition, the COG and PBMTC published 2 papers on the issues of use of G-CSF in normal donors (Pulsipher et al. and Schultz et al, PBC).

In my opinion, by far the most useful document to inform your IRB's deliberations is the detailed and thoughtful Pediatric Central IRB review, which outlined the rationale for approval as they saw it. The approval portion of the letter is quoted in its entirety to present this analysis, with Pediatric CIRB permission, below.

As transplanters, we argue that minor sibling donation provides direct benefit to the donor, in that the transplant reduces the likelihood of their sibling dying, which would otherwise have substantial and negative effects on the donor both directly and indirectly because of the impact on the parents. However, as you will see, the Pediatric Central IRB chose to approve the study as a minor increase over minimal risk, approved under 45 CFR 46.406.

Please let me know how I can help you in getting this important study approved at your institution, and thanks so much for your help with ASCT0631 and the COG SCT research agenda.

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Sincerely yours,

A handwritten signature in black ink, appearing to read 'S. Grupp', written in a cursive style.

Stephan A Grupp, MD PhD  
Chair, Stem Cell Transplant Discipline  
Children's Oncology Group

**Full text of Pediatric CIRB approval letter:**

November 8, 2006

Stephan A. Grupp, M.D, PhD  
Children's Hospital of Philadelphia  
Division of Pediatric Oncology, ARC 902  
3615 Civic Center Blvd  
Philadelphia, PA 19104

**Re: CIRB Approval Pending Modification to Initial Review**

**ASCT0631**, "A Phase III Randomized Trial of G-CSF Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source In Matched Sibling Donor Transplantation." (Protocol Version Date 09/11/06)

Dear Dr. Grupp,

At the full board meeting of the Pediatric NCI Central IRB (CIRB) held on October 26, 2006, the Board reviewed the above referenced protocol (protocol and informed consent version 09/11/06) and voted to **approve pending modifications**, as stipulated below.

The CIRB determined that involvement of children with leukemia (the stem cell recipients) satisfies the requirements of 45 CFR 46.405, and 21 CFR 50.52, research/clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects with the permission of at least one parent required for the recipient.

The CIRB then considered the involvement of normal children as bone marrow donors, and made the following findings:

1. Are the donors research subjects?

The CIRB found that the incorporation of research questions and corresponding modifications into the stem cell procurement process means that the stem cell donor should be considered a research subject. For example, the randomization of donors to two different methods of stem cell procurement (e.g., with and without G-CSF) clearly meets the definition of research as "a systematic investigation . . . designed to develop or contribute to generalizable knowledge." In addition, the stem cell donor is a research subject since the investigator "obtains data through intervention or interaction with the individual." Under these conditions, the procedure for stem cell donation (assuming the donor is a child) must satisfy the requirements of 45 CFR 46 subpart D.

2. Does the research constitute no more than minimal risk to the donors?

Subpart A [45 CFR 46.102(i)] states "minimal risk means that 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."

According to SACHRP (and consistent with proposals from the IOM and NHRPAC) the definition of minimal risk at 45 CFR 46.102(i) when applied to subpart D should be interpreted as those risks encountered by normal, average, healthy children living in safe environments in daily life or during the performance or routine physical or psychological examinations or tests. Further, according to SACHRP, research procedures involving children can be approved as minimal risk if the probability and magnitude of harm are equivalent to risks of daily life or routine examinations with respect to (a) duration, (b) cumulative characteristics, and (c) reversibility of harm.

The CIRB carefully considered the supporting information provided by the investigators with regard to the real and theoretical risks associated with G-CSF administration. Based on the definition and clarifications provided the CIRB was not convinced that the probability and magnitude of harm associated with administration of G-CSF to a normal donor are equivalent to risks encountered by normal, average, healthy children living in safe environments in daily life or during the performance or routine physical or psychological examinations or tests with respect to (a) duration, (b) cumulative characteristics, and (c) reversibility of harm. Consequently, the CIRB could not classify this research as "minimal risk",

Therefore, in consideration of #2 above (not minimal risk), inclusion of these subjects did not satisfy the requirements of 45 CFR 46.404.

### 3. Is there direct benefit?

The CIRB was not convinced that there was a direct benefit to the child donors accruing from participation in this trial. The IOM pointed out that a "direct benefit is a tangible positive outcome (e.g., cure of disease, relief of pain, and increased mobility) that may be experienced by an individual." The CIRB notes that the administration of G-CSF to the child stem cell donor does not create a reasonable prospect of added direct benefit to the child donor, and that often quoted benefits (such as increased self-esteem, continued companionship of the surviving recipient, avoidance of possible guilt) are speculative, and the data are limited and mixed.

Therefore, in consideration of #3 above (the absence of direct benefit to the donor), inclusion of these subjects did not satisfy the requirements of 45 CFR 46.405.

### 4. Does the research constitute only a minor increase over minimal risk?

According to the IOM recommendations, a minor increase over minimal risk means "a slight increase in the potential for harm or discomfort beyond minimal risk." The CIRB considered the most dramatic theoretical risk of use of G-CSF, that is, the risk of leukemogenesis. While the board considered that this was a significant harm it also decided that the probability of the occurrence of this harm was so small as to make the potential for harm only a slight increase over minimal.

### 5. Does the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations?

In applying the commensurate criteria IRBs should determine that the research interventions or procedures are reasonably similar to those procedures and interventions that children with the condition or disorder as a class have or are expected to experience. According to the National Commission, the requirement of commensurability of experience should assist children who can assent to make a knowledgeable decision about their participation in research, based on some familiarity with the procedure and its effects. More generally, commensurability is intended to assure that participation in research will be closer to the ordinary experiences of the subjects.

The CIRB found that a subcutaneous injection (the immediate and relevant risk to the child donor) falls within the ordinary experiences of the subjects, since the donor has certainly undergone several phlebotomies (as preparation for bone marrow donation) and has probably seen his/her sibling undergo phlebotomy and injections. Therefore, the board found that the intervention or procedure presented experiences to subjects that are reasonably commensurate.

### 6. Does the normal donor have a disease or condition?

The IOM recommends that the term condition should be interpreted as referring to a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific or clinical evidence has shown to negatively affect children's health and well-being or to increase their risk of developing a health problem in the future.

SACHRP notes that healthy children can have a condition. Research with no prospect of direct benefit that can answer a question of vital importance to understanding or ameliorating a condition of healthy children that can only be answered if healthy children are involved in the research

The CIRB notes that the subject was a suitably matched sibling of a child with leukemia and was going to be asked, or had already agreed to undergo a surgical procedure to provide bone marrow for transplantation. The board further noted that being a bone marrow donor would expose the child to risks that could negatively effect their health and well-being (that is, general anesthesia, bone marrow harvest, possibility of blood transfusion). Therefore, after debate, the board concluded that the donor had a "condition."

7. Is the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition?

The CIRB considered that results from this study would likely provide guidance to physicians in the future regarding the utility of G-CSF in bone marrow harvest. One reasonable outcome of this study could be recognition that a smaller harvest volume is possible with G-CSF mobilized bone marrow, while providing equivalent number of progenitor cells to the donor. Therefore, future children with the "condition" of being marrow donors could be exposed to less risk associated with harvest. Consequently, the CIRB was satisfied that the research is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition.

Therefore, in consideration of #4, 5, 6 and 7 above (minor increase over minimal risk, commensurate, presence of a condition, and vital importance), the board found that the inclusion of normal child donors satisfied the requirements of 45 CFR 46.406 and 21 CFR 50.53, provided adequate provisions are made by the local IRBs for soliciting assent of the children and permission of their parents or guardians.