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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.

Protocol Stipulation

1. The CIRB raised concerns that normal siblings would be exposed to pressure (real or self imposed) to participate in this research protocol for the direct benefit of their ill sibling. The board acknowledged that it would be difficult or impossible to separate this influence from the pressure to act as a bone marrow donor independent of the research. However, the CIRB suggests but does not require the use of a third party informed assent monitor to minimize potential influence, as well as the use of different doctors for the recipients and the donors. The board notes that the latter suggestion is already standard practice in many allogeneic stem cell transplant programs. No response is required.

Recipient Informed Consent Stipulations

1. Please change "Neupogen" to "filgrastim".
2. Please include the following wording in the first paragraph under "Why Is this Study Being Done?" to state: "Bone marrow transplant is recommended by many physicians for children with leukemia that have a high chance of relapse with chemotherapy alone. Bone marrow transplant is not recommended for all types of leukemia."
3. The CIRB notes that the "invitation" section (page 85) states: "After chemotherapy treatment, many doctors recommend high dose chemotherapy followed by a transplant of bone marrow cells from a donor, or SCT, for children and adolescents with leukemia. This is because SCT may be a better therapy than chemotherapy alone for most patients. This use of stem cell transplant is considered to be an accepted, standard treatment for children with leukemia who are in remission." This may be true for the patient population eligible for this trial, but for accuracy and completeness, please state "After chemotherapy treatment, many doctors recommend high dose chemotherapy followed by a transplant of bone marrow cells from a donor, or SCT, for children and adolescents with **high risk or relapsed** leukemia."
4. The CIRB notes that page 90 states "We will talk to males who have reached puberty about sperm banking." If appropriate please add " We will talk to females who have reached puberty about egg banking."
5. Please spell out GVHD on page 90 in the risks section.
6. The CIRB notes that page 90 (Risks) states that "Some of the common side effects include infection and GVHD" and that these risks are listed in Attachment #3 since they are treatment risks (as opposed to research risks). However, the next section (Risks of Study) states "Since receiving G-CSF bone marrow might result in receiving a higher stem cell dose, there may be an increased risk of GVHD." Therefore, it would appear that (increased) GVHD is a risk of the study *per se* and should be included in the body of the informed consent form instead of the attachment. Please revise accordingly.
7. Please include "a quicker recovery from the low blood counts after transplant" as a potential benefit along with the already included "a better chance of a getting rid of cancer for a long time."
8. The CIRB notes that the alternatives section states that instead of being in this study, patients may receive a standard stem cell transplant (Arm B of this study), but does not add that patients may also undergo G-CSF primed BM transplant off study. As Pulsipher and colleagues note "G-CSF-mobilized stem cell or G-CSF primed bone marrow harvest is an accepted practice at many pediatric transplant centers (Pediatr Blood Cancer 46:422, 2006). Please revise.
9. The CIRB notes that the optional research questions (page 93) include "blood may be kept for use in future research to learn about, treat or prevent cancer". Many other COG studies involving tissue banking also include an option for use in future research for other disease than cancer." Please revise if appropriate.

Donor Informed Consent Stipulations Only

1. Please change "Neupogen" to "filgrastim."
2. Please include the following wording in the first paragraph under "Why Is this Study Being Done?" to state: "Bone marrow transplant is recommended by many physicians for children with leukemia that have a high chance of relapse with chemotherapy alone. Bone marrow transplant is not recommended for all types of leukemia."
3. Since the use of G-CSF is an integral part of the research, please move the risks of G-CSF to the body of the informed consent form rather than an attachment.
4. The CIRB believes that older donors and parents of normal donors should be informed of the theoretical risks of leukemogenesis related to G-CSF. Therefore, please add the following to the Risks section of the Donor consent form: "Very rarely patients with abnormal white blood cells and

abnormal bone marrow have developed leukemia after years of treatment with G-CSF. We do not know if treatment with G-CSF was a contributing factor in the development of the leukemia. Also, when high doses of this drug are given to cells in test tubes it can cause some changes in the genes of those normal cells. We believe it is extremely unlikely that the short course of G-CSF as proposed in this study carries any risk of causing cancer."

5. Since the stem cell harvest is part of standard care and not research, please move the risks to the attachment rather than the body of the informed consent form.
6. Please revise the third paragraph of the Invitation on page 107 to state: "You are being asked to participate in this study because you have agreed to donate bone marrow for transplantation to your sibling. The bone marrow contains stem cells. If you chose to be part of this study, you will be given a drug called G-CSF (filgrastim). The purpose of this study is to find out if G-CSF will increase the number of stem cells in the bone marrow. We also want to find out if people who get bone marrow transplants from donors who had G-CSF do better."
7. Please delete reference to PBSC on page 108, as this is not applicable to the subject.
8. Please clarify how the companion study works and what role it plays in the study when it is first mentioned on page 108.

Donor Assent Form Stipulations

1. The CIRB notes that the Donor assent form states "If you don't want to be in this research study, no one will be upset with you." This may or may not be the case. The CIRB suggests substituting "If you don't want to be in this research study, you don't have to be" or ""If you don't want to be in this research study, the doctor won't be upset with you."
2. The CIRB notes that the Donor assent form states "Years from now, when the study is all done, you will be able to find out from your doctor what was learned." This may or may not be the case. The CIRB suggest substituting "Years from now, when the study is all done, you may be able to find out from your doctor what was learned."
3. Though the Donor assent must be written at an age-appropriate level, it should not downplay the risks of G-CSF or lump them in with the risks associated with the BM donation. Please list the risks of the G-CSF treatments first and make them more complete.
4. Please indicate that G-CSF will be given by a shot under the skin each day for 5 days.
5. Please make it clear that "Normally, we don't give people G-CSF before they donate their bone marrow" in the introduction.
6. Please revise the statement, "Only if you choose to be in the study, the doctor or nurse will look you over from head to toe..." on the second page of the assent as this will occur if they are not participating in the study.
7. Please modify the sentence "However, you may be able to help your brother or sister, who needs the bone marrow transplant" to state: "Giving you the G-CSF before we give your brother or sister your bone marrow might make your bone marrow work better, but we are not sure if this is true yet. This is why we are doing this study."

Please be aware that the inclusion of Study Chair or Cooperative Group initiated changes, other than those made in response to CIRB stipulations or recommendations, or minor editorial/administrative changes in accordance with NCI CTEP policy, may result in delay of CIRB approval. Therefore, the CIRB recommends that you only respond to the CIRB stipulations and recommendations in order to facilitate a prompt review by the CIRB.

Your response to this review will be promptly considered upon receipt. The CIRB requests a response to these issues within 60 days of the date of the letter. If the concerns of the Board have been adequately addressed, the protocol and informed consent document may receive approval through CIRB expedited review procedures. If the response requires full Board review, the response will be placed on the agenda

for review at the next available full Board meeting of the CIRB. Please note that your responses to this letter will be posted on the NCI-CIRB website for access to local sites providing them a complete CIRB review.

The Central IRB (CIRB) of the National Cancer Institute (NCI) meets the requirements in 21 CFR 56 (Rev.), 45 CFR 46 (Rev.) and ICH (E6) GCP guidelines.

All communications should be sent to the CIRB Coordinator or the CIRB Administrator. They are located in the Central IRB Initiative Office at One Research Court, Suite 200 in Rockville, Maryland 20850. For general questions regarding the NCI Central IRB, please contact the Help Desk at 888-657-3711.

Sincerely,

A handwritten signature in black ink that reads "Bruce Gordon MD". The signature is written in a cursive style with a long horizontal line extending to the right.

Bruce Gordon, M.D.
Chair
NCI Pediatric Central IRB

cc:
Robert Castleberry, M.D.
Judy Everett, RN
Barry Anderson, M.D., Ph.D.
Anita Khayat, Ph.D.
Greg Reaman, M.D.
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