TO: Acting Assistant Secretary for Health
FROM: Director, Office for Human Research Protections
SUBJECT: Recommendation for Approval of HHS Support for Research Involving Children--ACTION

ISSUE

This document provides a recommendation by the Office for Human Research Protections (OHRP) that the Department of Health and Human Services (HHS) approve with required stipulations the proposed research protocol entitled “COG Protocol 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.”

In making this recommendation, OHRP has reviewed the proposed research, considered the opinions of experts in pertinent disciplines, and reviewed all public comments received. In addition, OHRP has considered the position of the Food and Drug Administration (FDA) as detailed in the memorandum signed by the Acting Commissioner on May 11, 2009 (Tab A). The Nemours institutional review board (IRB) referred this protocol to OHRP on October 1, 2008, for consideration under 45 CFR 46.407 of the HHS regulations for the protection of human subjects.

DISCUSSION

Regulatory Background

All human subjects research studies that are conducted or supported by HHS that are not otherwise exempt under 45 CFR 46.101(b) and that propose to involve children as subjects require IRB review and approval in accordance with the provisions of HHS regulations at 45 CFR part 46, subpart D (Additional Protections for Children Involved as Subjects in Research), as well as basic protections required under subpart A (Federal Policy for the Protection of Human Subjects).
The HHS regulations at 45 CFR part 46, subpart D require that an IRB consider whether the proposed research involving children as subjects meets the requirements of any of the following regulatory categories:

- 45 CFR 46.404 -- Research not involving greater than minimal risk
- 45 CFR 46.405 -- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual
- 45 CFR 46.406 -- Research involving a minor increase over minimal risk and no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject’s disorder or condition

If the IRB does not believe that the proposed research meets the requirements of 45 CFR 46.404, 46.405, or 46.406, and is found to be suitable for review under the procedure provided in 45 CFR 46.407 (research not otherwise approvable which presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children), the research may proceed only if the following conditions are met:

(a) The IRB finds and documents 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; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:

(1) that the research in fact satisfies the condition of 45 CFR 46.404, 46.405, or 46.406, or

(2) that the following conditions are met:

   (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

   (ii) the research will be conducted in accordance with sound ethical principles; and

   (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardian, as set forth in 45 CFR 46.408.

Under FDA’s Interim Final Rule, effective April 30, 2001 (21 CFR part 50, subpart D), the FDA adopted similar regulations (21 CFR 50.51, 50.52, 50.53, and 50.54) requiring IRB review to provide additional safeguards for children enrolled in research regulated by the FDA.
In cases where FDA regulations apply, OHRP has delegated its authority to the FDA to convene the required panel of experts to review and to advise the Secretary of Health and Human Services on the proposed research. In order to conduct the expert panel review, the FDA utilizes the Pediatric Ethics Subcommittee (PES) of the established Pediatric Advisory Committee (PAC). OHRP works in close collaboration with the FDA in all aspects of the review including the selection of experts to participate on the PES.

At its meeting the PES develops recommendations to be forwarded to the PAC, which then makes its recommendations to the FDA Commissioner. The recommendations of the PAC and the approval decision by the FDA Commissioner are then reviewed by OHRP which makes final recommendations to the Secretary, who has delegated the approval authority to the Assistant Secretary for Health (ASH).

**Overview of Study Hypothesis and Design**

For pediatric patients with leukemia who require allogeneic stem cell transplantation, the current standard of care involves using bone marrow or peripheral blood stem cells harvested from donors who have not received any interventions to stimulate the bone marrow. Administration of filgrastim (G-CSF) to bone marrow donors prior to the harvesting of bone marrow (hereinafter referred to as G-CSF-stimulated bone marrow) has been shown in adults to increase marrow cellularity, thus leading to improved engraftment in adult recipients. However, the safety and effectiveness of G-CSF-stimulated bone marrow for children with leukemia undergoing allogeneic bone marrow transplantation are unknown.

The major hypothesis of this Phase III trial is that G-CSF-stimulated bone marrow will improve event-free survival in children with leukemia undergoing allogeneic bone marrow transplantation. The study uses a prospective, randomized design involving control and experimental groups, with each group consisting of sibling-donors and sibling-recipients:

1. **Controls (usual care):**
   a. Healthy donors who undergo a standard bone marrow harvest
   b. Sibling-recipients who receive the bone marrow transplant

2. **Experimental group:**
   a. Healthy donors who receive G-CSF for five days and then undergo a bone marrow harvest
   b. Sibling-recipients who receive the G-CSF-stimulated bone marrow transplant

The major study endpoints are treatment-related mortality at 100 days, rates of graft failure, and rates of graft versus host disease. Sibling-recipient assessments occur at 1, 6, and 12 months, with possible yearly monitoring for 10 years. The study involves a total of 830 subjects, half of whom are sibling-donors and half are sibling-recipients.

The protocol includes two optional companion studies:

1. RD Safe to evaluate short- and long-term risks to donors
2. A biology study to assess cellular immune response and store the subjects’ blood for future unspecific research
Protocol Referral

The key regulatory issue centers around the appropriate approval category required to enroll normal healthy children into the experimental donor group that is administered the G-CSF.

The protocol was reviewed by the Pediatric Central IRB (CIRB) of the National Cancer Institute (NCI). On October 26, 2006 the CIRB determined the inclusion of normal siblings in the experimental group met the criteria for 45 CFR 46.406, research involving greater than minimal risk and no prospect of direct benefit, but likely to yield generalizable knowledge about the subject’s condition (Tab B).

The protocol was activated by the NCI-sponsored Children’s Oncology Group in December 2007 and subsequently submitted to the IRBs at approximately 30 institutions. These IRBs approved the protocol, and subject enrollments subsequently commenced.

One of the institutions expected to participate in this protocol was the Nemours Foundation in Jacksonville, Florida. The Nemours Foundation Oncology IRB discussed the protocol and determined that the study could not be approved under 45 CFR 46.404, 46.405, or 46.406. The Nemours Foundation Oncology IRB further determined that, as required under 45 CFR 46.407, the study presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. Accordingly, the Nemours Foundation Oncology IRB referred the protocol to FDA and OHRP on October 1, 2008 for a determination under 21 CFR 50.54 and 45 CFR 46.407.

Following consultation between OHRP and NIH, the principal investigator for this multi-site study agreed to suspend subject enrollment at all study sites pending the outcome of the 45 CFR 46.407/21 CFR 50.54 process.

Public Review and Comment

On November 14, 2008, a Federal Register Notice was published soliciting public review and comment, for a period of 18 days. Documents related to the protocol were made available on the OHRP website (www.hhs.gov/ohrp/children/gcsf.html), including the proposed protocol, parental permission documents, subject assent documents, and IRB deliberations on the proposed protocol. These documents were also made available on the FDA website (www.fda.gov/ohrms/dockets/ac/oc08.html#pac), and a docket was established on the FDA website for the submission of public comments.

In response to the Federal Register notice, two comments were received, the second of which was not related to the proposed protocol:

1. A letter from Dennis Confer of the National Marrow Donor Program, highlighting a letter published in the British Journal of Hematology indicating there is no evidence of long-term risk among healthy adult donors who receive G-CSF.
2. A letter from the American Mothers Organization questioning the procedures of the PES and expressing concerns about the problem of autism.
Both letters were read into the meeting transcript. All comments and concerns were addressed by the PES with recommendations forwarded to the PAC.

**Review by FDA Panel of Experts**

On December 9, 2008, the PES of FDA’s PAC held a public meeting to discuss the protocol. The PES consisted of 4 members and 7 voting consultants who brought multiple specialties and perspectives to the discussion. The Subcommittee consisted of 4 pediatric ethicists, 4 oncologists, 1 cardiologist, and 2 patient-consumer representatives. Additionally, there was an opportunity for public comment both prior to the public meeting via the FDA docket and at the meeting itself. After substantial discussion and the opportunity for public comment the PES forwarded to the PAC a recommendation that the protocol be approved providing 4 stipulations were met.

On December 9, 2008, the PAC met to review the PES recommendations. Following discussion, the PAC recommended the protocol be approved and expanded on the PES recommendations, outlining six stipulations to be met.

On May 11, 2009, the FDA [Acting] Commissioner approved the research under 21 CFR 50.54(b) with the six required stipulations recommended by the FDA Office of Pediatric Therapeutics. (Tab A).

**OHRP FINDINGS AND RECOMMENDATIONS**

OHRP has reviewed the research protocol and other related documents, considered the recommendations provided by the PAC, reviewed the comments received from the public, and considered the position of the FDA as outlined in the memorandum from the Acting FDA Commissioner. Additionally, OHRP has considered the relevant requirements set forth in 45 CFR part 46, subparts A and D.

OHRP concurs with FDA’s decision that the research study is approvable under 21 CFR 50.54, with the six required stipulations outlined below, and finds that the research study is approvable under 45 CFR 46.407. In finding that the research study can be approved under 45 CFR 46.407,

OHRP is not concluding that the other IRBs that previously found the research to be approvable under 45 CFR 46.405 or 45 CFR 46.406 were out of compliance with 45 CFR part 46, subpart D.

OHRP acknowledges that the application of subpart D to protocols involving the administration of experimental interventions and/or procedures to healthy sibling bone marrow donors has and will continue to raise important questions. OHRP’s recommendation for approval of this specific protocol under 45 CFR 46.407 should not be seen as establishing a precedent for future protocols involving healthy siblings as bone marrow donors, nor as a precedent for how the provisions of 45 CFR 46.405 and 46.406 should be interpreted with regard to such future protocols. OHRP welcomes further discussion of these issues as future protocols are developed and reviewed.
Stipulations of Approval

Under this 45 CFR 46.407 approval of the research study, the following six stipulations must be satisfied before the research may be reinitiated. In order to ensure uniform implementation of the research study across all institutions, the stipulations must be satisfied by all institutions engaged in the research:

1. Donor Exclusion Criterion Section 3.2.5.3, revise as follows: Donors who are found to be at increased risk for bone marrow donation following G-CSF administration due to a pre-existing medical condition, as determined by an independent physician.

2. Donor Exclusion Criterion Section 3.2.5.5, revise as follows: The presence of an uncontrolled infection should be expanded to any child who has an active infection, especially pulmonary, as well as (a) splenomegaly or a history of splenic injury, or (b) an active or recent pulmonary disease or condition as determined by a physician separate from the research team.

3. Section 9.2, Off Study Criteria: Strengthen the DSMB safety monitoring for the sibling bone marrow donor by adding other suspension criteria (in addition to death) such as splenic rupture, acute lung injury, or a hematological malignancy.

4. Section 3.0 Study Enrollment and Patient Eligibility: Each research site should appoint an independent person to function as an advocate for the potential sibling donor. The advocate should participate in the research decision in a meaningful way, acting on behalf of the potential sibling donor.

5. Parental permission form for bone marrow donors who receive G-CSF, page 6: The last two bullet points that pertain to ARDS and leukemia should also indicate that these conditions are potentially life-threatening.

6. Donor Eligibility Criteria 3.2.4, insert an additional inclusion criterion: All things being equal, preference should go to an older sibling donor.

RECOMMENDATIONS

1. HHS should support the proposed research protocol entitled “COG Protocol 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” with stipulated revisions as outlined above.

2. This decision should be made available to the public via appropriate methods, such as placement on the OHRP website.
DECISION

1. HHS should support the proposed research protocol entitled “COG Protocol 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” with stipulated revisions as outlined above.

   Approved [/s/ Steve K. Galson]   Disapproved __________________   Date [5/22/09]

2. This decision should be made available to the public via appropriate methods, such as placement on the OHRP website.

   Approved [/s/ Steve K. Galson]   Disapproved __________________   Date [5/22/09]

   [/s/ Jerry Menikoff]
   
   Jerry Menikoff, M.D., Ph.D.

2 Attachments:
   Tab A - Memorandum signed by FDA Acting Commissioner
   Tab B - CIRB Approval Letter dated November 8, 2006