



Office for Human Research Protections
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[June 11, 2009]

Tim Wysocki, Ph.D., C.I.P.
Chair, Nemours Oncology Institutional Review Board
Nemours Foundation
10140 Centurion Parkway North
Jacksonville, Florida 32256

**Re: Secretary's Determination on the Research Protocol:
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
Principal Investigator: Eric Sandler, MD
NCI Grant No. PASCT0631#R02PAPP01**

Dear Dr. Wysocki:

We are writing on behalf of the Acting Assistant Secretary for Health (ASH), Department of Health and Human Services (HHS), and the Commissioner, Food and Drug Administration (FDA) regarding the above-referenced research protocol.

In October 2008 the Nemours Oncology institutional review board (IRB) forwarded the protocol to the Office for Human Research Protections (OHRP) and FDA for consideration pursuant to requirements of the HHS regulations at 45 CFR 46.407 and the FDA regulations at 21 CFR 50.54, for research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Review Process and Required Stipulations

Following receipt of the protocol, a notice was published in the *Federal Register* seeking public comments on the approvability of the protocol. On December 9, 2008 the Pediatric Advisory Committee, after receiving recommendations from the FDA Pediatric Ethics Subcommittee, reviewed and recommended that FDA and HHS approve the protocol under 46.407 and 50.54, subject to the following six stipulations:

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 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.

On May 26, 2009, Dr. Steven K. Galson, Acting ASH, based on the determination made by Dr. Joshua Sharfstein, former FDA Acting Commissioner, and the recommendation of Dr. Jerry Menikoff, OHRP Director, granted approval under 45 CFR 46.407 for the Department to support the research study, subject to the six stipulations listed above. The research protocol, if so modified, would be in conformance with FDA regulations at 21 CFR parts 50 and 56, and with HHS regulations at 45 CFR part 46, subparts A and D. The Acting ASH's decision memorandum is enclosed with this correspondence.

Implementation of the Protocol Revisions

Because this is a multi-site study and, as a condition of HHS approval, the six stipulations apply to all study locations, the following sequential steps will need to be completed before subject enrollment may begin at your institution:

1. The main study investigator will integrate the required changes into the protocol document and parental permission form.
2. The revised protocol and parental permission form will be reviewed by the National Cancer Institute's (NCI's) Pediatric Central IRB.
3. OHRP will review the revised protocol and parental permission form, with appropriate input from FDA, to ensure that the required stipulations have been satisfied.
4. The Nemours IRB (and the NCI Pediatric Central IRB) will be notified of the outcome of OHRP's review.

5. The amended protocol will be sent to the NCI Children's Oncology Group, to in turn forward the protocol to the local principal investigator at each institution engaged in the study.
6. The revised protocol and parental permission form will be submitted by the local principal investigator to the Nemours IRB for review and approval.
7. Upon approval by the Nemours IRB, subject enrollment may begin.

OHRP also has informed the National Institutes of Health of the Acting ASH's determination and what we see as the necessary next steps. If you have questions about this implementation process, please contact Edward E. Bartlett, Ph.D. at OHRP at 240-453-8249 or at Edward.bartlett@hhs.gov. FDA will also be available for assistance, as needed.

Thank you for your continuing commitment to the protection of human subjects.

Sincerely,

[/s/ Jerry Menikoff]

Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections
Office of Public Health and Science

[/s/ Dianne Murphy]

Dianne Murphy, M.D.
Director
Office of Pediatric Therapeutics
Food and Drug Administration

Enclosure

cc:

Dr. Eric Sandler, Nemours
Dr. Amy Patterson, NIH
Ms. Sarah Carr, NIH
Dr. Joanne Less, FDA
Dr. Robert Nelson, FDA
Dr. Sara Goldkind, FDA