

October 1, 2008

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Food and Drug Administration
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(With copy via email)

Irene Stith-Coleman, PhD
Director, Division of Policy and Assurances
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(With copy via email)

RE: Request for National Panel Review under 45CFR46.407 and 21CFR50.54

The following study was submitted to and reviewed by the Nemours Oncology Institutional Review Board (IRB00005145) and determined not to be approvable under subpart D of the applicable federal regulations except upon the affirmative determination of a national review panel as described in 45CFR46.407 and 21CFR50.54:

Children's Oncology Group 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.

Funding Agency: National Cancer Institute

Reference Number: PASCT0631#R02PAPP01

Children's Oncology Group Principal Investigator: Stephan A. Grupp, MD, PhD

Nemours Principal Investigator: Eric Sandler, MD

Stated simply, the purpose of the study is to evaluate the effects, good and/or bad, on the child having a bone marrow transplant when G-CSF is given to a healthy sibling donor before the bone marrow donation (experimental treatment) compared to a standard bone marrow donation without administration of G-CSF to the donor (standard treatment).

Upon its initial review of the submitted protocol on July 2, 2008, the IRB deferred the study and requested additional information from the local investigator, Eric Sandler, MD, regarding potential risks to the sibling donors to whom G-CSF would be administered as well as correspondence from the Children's Oncology Group Central IRB regarding the regulatory basis of its approval of the protocol. This additional information would be utilized to inform the IRB in its determination regarding whether or not the use of G-CSF in otherwise apparently healthy matched siblings constitutes a minor, or slight, increase over minimal risk, thus resulting in a study eligible for approval as a 406/53 (providing the balance of the approvability criteria are met), or potentially requiring referral to the appropriate federal agencies under sections 507 and 54 of the applicable regulations. Copies of the salient component of the July 2, 2008 IRB minutes and IRB correspondence to the local Principal Investigator are attached for your review.

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The protocol was reconsidered at the IRB's convened meeting on September 3, 2008, including the additional documentation provided by the Children's Oncology Group through the local Principal Investigator. Again, the primary issue under consideration was the question of minor versus more than minor increase over minimal risk in a study that offered no prospect of direct benefit to the participants (the matched sibling donors, in this case). Of particular impact upon the board's decision was the opinion of a member who is also a pediatric hematologist / oncologist who expressed specific concern regarding the risk of leukemogenesis in genetically matched sibling donors, and the propriety of determining such risk as no more than a minor increase over minimal. The specific points offered by this member included:

- Siblings of patients with leukemia have a 2-to-5 fold increased annual incidence of leukemia (see Bennett et al). Other references are cited in Confer DL and Miller JP (2007) Long term safety of filgrastim (rhG-CSF) administration.
- Laboratory research suggests a leukemogenic potential of GCSF due to allele specific replication and aneuploidy (see Nagler et al reference).
 - a. Does a GCSF challenge unmask mutated recessive genes thus fulfilling the role of the second hit in Knudson's two-hit cancer initiation model?
 - b. GCSF could also provide the first hit, leaving the cell genome vulnerable to the second hit.
 - c. Loss of replication synchrony returned to baseline after a few months, but aneuploidy was seen in some donors up to 9 months after GCSF administration.
- Donor registries report no increased risk of cancer in GCSF mobilized stem cell donors
 - d. *But*, greater than 2000 normal donors will have to be followed for greater than 10 years to detect a 10-fold increase in leukemogenic risk.
 - e. Under reporting is an issue as many registries use volunteer surveys to collect data.
 - f. Data on GCSF risks specific to healthy sibling donors of recipients with hematologic malignancies is lacking.

(Note that the articles referred to in the comments immediately above are included as supplemental material with this communication.)

In addition to the above points, the IRB also considered the known risks of the administration of G-CSF to otherwise healthy individuals, particularly including injury to and potential rupture of the spleen. The IRB determined that the total risk to the donor G-CSF recipients constituted more than a minor increase over minimal risk. The IRB further determined that the research does present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. Copies of the minutes describing the IRB's discussion, and IRB correspondence with the local Principal Investigator are attached for your further review.

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The motion made and approved by majority (unanimous) vote of a duly constituted quorum is fully stated as follows:

Motion: The study intervention for the donor group constitutes more than a minor increase over minimal risk, with the likelihood that if done, it would yield vital information about the disorder or condition being studied. Therefore, the IRB determined that this is research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children per 45CFR46.407 and 21CFR50.54. The IRB will refer this study to the FDA via appropriate procedure for determination as to whether or not the study is approvable.

Official correspondence was subsequently sent to the local Principal Investigator (Eric Sandler, MD) informing him of the IRB's determination. In addition, the Nemours Institutional Official (Paul Garfinkel), who was present at the IRB meeting at which the determination was made, met with Dr. Sandler to discuss the implications of the board action, including the necessity of communicating the issue to the Children's Oncology Group. It was decided that Dr. Sandler would make that contact.

Therefore, in consideration of the determination of the Nemours Oncology IRB, this study is being referred to both DHHS and FDA for review under the guidance provided by both agencies regarding the implementation of the previously noted regulations.

An index of attachments and additional supplemental material germane to the IRB's determination immediately follows this cover correspondence.

Sincerely yours,

Tim Wysocki, PhD, CIP
Chair, Nemours Oncology Institutional Review Board

Attachments

cc: Eric Sandler, MD, Chief, Division of Hematology / Oncology
Paul Garfinkel, MSH, CIP (Institutional Official)
Children's Oncology Group
Vicky Funanage, PhD, Director of Biomedical Research
Roy Proujansky, MD, Executive Vice President and COO

Index of Attachments and Supplemental Material

1. Institutional and Protocol Information
2. Current Protocol Version
3. Parental Permission Form
4. Assent Forms
5. IRB Minutes - July 2, 2008 and September 3, 2008 meetings
6. Investigator Correspondence – July 3, 2008 and September 10, 2008
7. Correspondence from the COG CIRB
8. Journal Articles provided by COG
 - Blood 2007 110:4584-4587
 - Bone Marrow Transplantation 2005 35:361-367
 - Pediatr Blood Cancer 2006 46:422-433
9. Journal Articles provided by IRB
 - Pediatr Blood Cancer 2006 46:407-408
 - Experimental Hematology 2004 32:122-130
 - British Journal of Hematology 2006 135:642-650