



## DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

November 18, 2008

Robert "Skip" Nelson, M.D., Ph.D.  
Pediatric Ethicist, Office of Pediatric Therapeutics  
Office of the Commissioner  
Food and Drug Administration  
U.S. Food and Drug Administration · 5600 Fishers Lane  
Rockville, MD 20857

Irene Stith-Coleman, Ph.D.  
Director, Division of Policy and Assurances  
Office for Human Research Protections  
1101 Wootton Parkway, Suite 200  
Rockville, MD 20852

Dear Dr. Nelson and Dr. Stith-Coleman:

Thank you for the opportunity to provide information and background materials to the FDA Pediatric Ethics Subcommittee and Pediatric Advisory Committee to further inform the deliberations of these groups on December 9, 2008. These meetings will discuss a referral by an Institutional Review Board (IRB) of a clinical investigation (ASCT0631) entitled "Children's Oncology Group Protocol ASCT0631: A Phase III Randomized Trial of Granulocyte Colony Stimulating Factor (G-CSF) Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source in Matched Sibling Donor Transplantation."

The ASCT0631 clinical trial was developed by the Children's Oncology Group (COG), and it was reviewed by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI) and by the NCI Pediatric Central IRB. Throughout the review process following protocol submission by COG, there was recognition of the complex safety and ethical issues associated with research involving sibling donors. The background materials reflect the careful consideration given to these issues at each of the steps in the review process. The steps, in brief, were as follows:

- Submitted with the ASCT0631 protocol was a document entitled "Pediatric bone marrow donation and the potential risks/benefits of G-CSF administration to the donor" that was prepared by the COG Stem Cell Transplant Committee (first attachment).
- As part of the CTEP review process, an NIH Bioethics Consult was requested (see second attachment). All of the consultants who participated in the Bioethics Consult agreed that the proposed research could be approved without § 407 review, although there was not unanimity as to the most appropriate category (i.e., § 404, § 405, or § 406).
- CTEP also requested and received information from OHRP about its position concerning research involving pediatric stem cell donors (see third attachment). Either § 405 or § 407 mechanisms were described as potential pathways for approval, depending upon protocol-specific circumstances.

- The NCI Pediatric Central IRB reviewed the ASCT0631 clinical trial and provided a thorough review of the various issues related to the involvement of normal children as bone marrow donors in the trial (see fourth attachment). The Board provided rationale for considering sibling donors to have a “condition” and found that the inclusion of normal child donors satisfied the requirements of 45 CFR 46.406 and 21 CFR 50.53.
- Finally, during the protocol review process, members of the COG Stem Cell Transplant Committee and the Pediatric Blood and Marrow Transplant Consortium published two relevant articles concerning the participation of sibling donors in research involving the administration of G-CSF. These publications are also enclosed.

The ASCT0631 protocol was activated by COG in December 2007. At the time of the hold pending the outcome of the 407 process, the protocol had been approved by IRBs of 31 COG member institutions. A total of 14 subjects at 11 different sites had been enrolled.

We hope that these materials will be helpful to members of the Pediatric Ethics Subcommittee and the Pediatric Advisory Committee. If there is additional information that we can provide for Committee members, please let us know.

Sincerely,



Malcolm A. Smith, MD, PhD  
Associate Branch Chief, Pediatrics  
Cancer Therapy Evaluation Program, NCI