

From: Carome, Michael (HHS/OS)  
Sent: Monday, January 23, 2006 3:13 PM  
To: Anderson, Barry (NIH/NCI) [E]  
Subject: RE: Consult question

Barry,

The following, with slight modification, is the complete text of OHRP's response to Dr. Alan Sandler back in 2003 regarding this same issue. The one addition is the paragraph that is marked with \*\* at the beginning. I hope this helps. Let me know if you have further questions.

Mike

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Department of Health and Human Services (HHS) regulations at 45 CFR 46.102(f) define a human subject as a living individual about whom an investigator conducting research obtains (i) data through intervention or interaction with the individual, or (ii) identifiable private information. Where a research protocol involves a stem cell transplant procedure, both the donors and the recipients in most cases would be human subjects.

OHRP believes that the level of risk that such research presents to the donor subject depends on whether the stem cell transplant procedure is an accepted standard clinical intervention for the disease under investigation and, as a result, would occur regardless of the research, or whether it is part of the research. For example:

Scenario (a): When stem cell transplant is an accepted standard clinical intervention for the disease under investigation and the donor would be donating stem cells regardless of the research (e.g., the objective of the research protocol is to determine whether an investigational agent administered to the recipient enhances engraftment of the stem cells in patients undergoing stem cell transplant for a type of lymphoma), the donors generally become research subjects because the investigators obtain identifiable private information about them. Under such circumstances, the stem cell collection procedure would not be considered part of the research for the donors, the risks of the stem cell collection procedure would not be considered risks of the research for the donors, and an IRB may find the research to involve no more than minimal risk, presuming there are appropriate safeguards to protect the confidentiality of the private information about the donors.

Scenario (b): When stem cell transplant is not an accepted standard clinical intervention for the disease under investigation and the donor would not be donating the stem cells outside the context the research (e.g., the objective of the research protocol is to determine the safety and efficacy of stem cell transplantation for disease X), the donors become subjects because the investigators are intervening with them through the stem cell harvest procedure. Under these circumstances, the stem cell collection procedure would be considered part of the research for the donors, and the risks of the harvest procedure would be considered risks of the research for the donors.

When reviewing research involving stem cell transplants, the IRB must ensure that the criteria for approval of research under HHS regulations at 45 CFR 46.111 are satisfied with respect to both the donor and recipient subjects.

When either the donor or recipient subjects are children, the provisions of requirements of subpart D of 45 CFR Part 46 must also be satisfied for the child subjects.

Donor subjects who are adults may participate in any research, regardless of the level of risk or potential benefit, as long as the research satisfies the criteria under HHS regulations at 45 CFR 46.111.

Donor subjects who are children may participate in stem cell transplantation research, so long as the IRB finds that the research satisfies the requirements of Subpart D in addition to the requirements of 45 CFR 46.111.

With respect to scenario (a) above, OHRP believes that an IRB reasonably may find that with respect to the donor subjects who are children, the research does not involve greater than minimal risk and is permissible under HHS regulations under 45 CFR 46.404.

With respect to scenario (b), presuming that the stem cell harvest procedure involves greater than minimal risk to the donor subjects, OHRP believes that an IRB would be limited to approving the research under the conditions of 45 CFR 46.405 or 46.407. In order to approve such research under 45 CFR 46.405, the IRB would have to find that, with respect to the donors: (a) the risk is justified by the anticipated benefit to the subjects; (b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternatives; and (c) adequate provisions are made for soliciting the assent of the children and permission of the parents or guardians, as set forth in 45 CFR 46.408.

In assessing benefits to the donors under scenario (b), OHRP would not recommend that IRBs focus on the prospect of feeling "altruism" as the sole prospect for direct benefit for the individual subjects. Otherwise, altruism could be used to justify much research involving children and to by-pass the protections intended under HHS regulations under 45 CFR 46.406 and 46.407. However, with respect to stem cell transplant research involving donors who are children, depending on the specifics of the research, an IRB might conclude that, if the recipient is a family member, there is a prospect for tangible direct benefits to the donors, such as improved family dynamics and psychosocial relationships that could result from improving the health of a family member who has a life-threatening or other serious illness, and therefore could find the research to be permissible under HHS regulations at 45 CFR 46.405. In approving such research, the IRB would have to find, among other things, that the risk to the donors is justified by these anticipated benefits to the donor (see 45 CFR 46.405(a)).

\*\*For some stem cell transplant research involving children donors with recipients who are family members of the donors, an IRB might conclude that the research does NOT hold out the prospect of direct benefit to the individual donor subject or that, even if there is the prospect of direct benefit, the risk the subjects is NOT justified by the anticipated benefit to the donor subjects or the relation of the anticipated benefit to risk is NOT at least as favorable to the donor subjects as that presented by available alternatives (i.e., not being a donor). Under these circumstances, the research could only be conducted or supported by HHS if the provisions of 45 CFR 46.407 are satisfied.

In assessing the risks of such research, the IRB should carefully consider both the physical and psychological risks of the harvest procedure itself, as well as the psychological risks to the donor that can result from failure of the transplant.