

Barry Anderson, a member of CTEP, requested a consultation with the Department of Clinical Bioethics to discuss a proposed phase III trial of G-CSF stimulated bone marrow versus conventional bone marrow as a stem cell source in matched sibling donor transplantation. He asked us for input on several ethical issues, discussed below, relating to the prospective donor siblings. We make three recommendations: the research should exclude siblings who would donate peripheral blood stem cells in the clinical setting; adding a third arm to the trial should be considered; and assent/consent should be required for all participants and sustained dissent should be respected. Below, we elaborate on these recommendations and discuss related issues.

(1) What are the risks? Under the federal regulations, research risks are those that individuals face above and beyond the risks they would face in the clinical setting. Based on the information provided, assuming that the research involves bone marrow harvesting techniques equivalent to those used in the clinical setting, the only risks for donors who would otherwise undergo bone marrow harvest in the clinical setting are those that go beyond the harvesting procedures; namely, the G-CSF treatment. If some donors would provide peripheral blood stem cells in the clinical setting, then the bone marrow harvesting procedures would count as research risks. Hence, to minimize the research risks, we recommend excluding sibling pairs where the donor would be donating peripheral blood stem cells.

(2) Trial design: Since donating peripheral blood stem cells exposes donors to less risk than bone marrow, we suggest that the researchers consider a three-arm trial, including a peripheral donation arm. If the peripheral arm could be designed to offer a reasonable risk-benefit profile for the recipient (perhaps involving T-cell depletion), then this suggested design would increase the value of the study by offering the potential to assess an approach that poses less risks and burdens to the donors.

(3) Assessing the research: In order for the trial to satisfy the regulations, it must be approvable in one of three categories (unless the group wants to consider submitting the protocol for possible 407 approval). The risks must be minimal (§ 404); the risks must be outweighed by the prospect for direct benefit to the donors (§405); or the risks are a minor increase over minimal risk and the research will yield generalizable knowledge about the donors' condition (§ 406). All the consultants agreed that the proposed research could be approved in one of these categories, although there was some disagreement on what would be the most appropriate category.

Some consultants thought the protocol could likely be approved as minimal risk. It was reported at the meeting that 80% of adults experience mild bone pain; 10% to 15% report moderate pain; and 50% to 60% report a headache from G-CSF. It was also reported that NSAIDs provide either major or mostly complete relief from those effects. These data suggest that it might be a minimal risk study, although we did not have sufficient data to assess the potential for long-term cancer risks.

Other consultants believe the protocol could be approved as prospect of direct benefit. In their view, the possible increased survival from the research intervention for

the recipient represents a direct benefit to the sibling donor. Their opinion on direct benefit accords with the OHRP's interpretation of the regulations. Others were concerned that the increased likelihood of sibling survival should not be construed as "direct," as understood in the federal regulations.

Finally, one consultant discussed the possibility that the donors do, in fact, have a medical condition under study. Therefore, if the risks are determined to be slightly more than minimal, the research could satisfy the requirements for minor increase over minimal risk. The research question is, "How can we improve the quality and quantity of stem cells that donors provide for their recipient siblings?" Thus, the status of the donors, as stem cell providers, is under study.

(4) Assent process: There was general agreement that assent should be required for donors over 7 years old. Sustained dissent from all kids should be respected, although sporadic or inconsistent dissent would not require the end of conversations or persuasion. One consultant stated that informed consent – not mere assent – should be required from each donor sibling between the ages of 14 and 18 unless he or she were unable to give consent.

Some consultants thought that kids' consent/assent should be assessed independently of the parents. Also, some felt that it would be helpful to have the assessment performed by a qualified clinician who is independent of the research team. However, some other consultants thought this would be unnecessary, particularly with younger children.

Finally, as part of the assent process, prospective donors should be informed that they may receive an injection that may cause some pain and discomfort to them, but may increase the chances that their siblings will get better. However, it will be important to explain that even if they decline research participation they may still donate in the clinical setting.