Welcome from the Office for Human Research Protections

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U.S. Food and Drug Administration
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Overview of the Subpart D Expert Panel Process

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Today's Focus

- Referred Protocol
  - 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.
- Referring IRB
  - Nemours Oncology Institutional Review Board

IRB Referrals under Subpart D

- If an IRB does not believe that research [clinical investigation] involving children as subjects meets the requirements of §46.404 [50.51], §46.405 [50.52], or §46.406 [50.53], HHS will conduct or fund research and/or the FDA-regulated clinical investigation may proceed only if:
  - The IRB finds [and documents] that the research [clinical investigation] presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
  - The Secretary [and/or Commissioner of Food and Drugs], after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines that the research [clinical investigation] can proceed under either §46.404 [50.51], §46.405 [50.52], §46.406 [50.53], or §46.407 [50.54].

References to 45 CFR 46, Subpart D; 21 CFR 50, Subpart D

Charter

- The Pediatric Advisory Committee (PAC) advises and makes recommendations to the FDA Commissioner regarding… research involving children as subjects as specified in 21 CFR 50.54.
- PAC advises and makes recommendations to the Secretary directly or… through the Commissioner on research involving children as subjects that is conducted or supported by DHHS as specified in 45 CFR 46.407.
- A permanent Pediatric Ethics Subcommittee (PES) of the PAC advises and makes recommendations to the PAC on… IRB referrals related to clinical investigations involving children as subjects as specified in 21 CFR 50.54, and IRB referrals that involve both FDA regulated products under 21 CFR 50.54 and research involving children as subjects that is conducted or supported by DHHS as specified in 45 CFR 46.407.
- The PES will consist of two or more members of the parent PAC and additional experts (e.g., science, medicine, education, ethics and law) to address specific issues within their respective areas of expertise.

http://www.fda.gov/oc/advisory/OCPedsCharter2008.html 5

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Guidance

- Food and Drug Administration
  - Guidance for Clinical Investigators, Institutional Review Boards and Sponsors Process for Handling Referrals to FDA under 21 CFR 50.54.
    - Federal Register (Dec. 22, 2006, Volume 71, pp. 77034-77035)
    - http://www.fda.gov/OHRMS/DOCKETS/98fr/06d-0172-gdl0002.pdf
- Office for Human Research Protections (OHRP)
  - Children Involved as Subjects in Research: Guidance on the HHS 45 CFR 46.407 ("407") Review Process.
    - Date: May 26, 2005
    - http://www.hhs.gov/ohrp/children/Guidance_407Process.pdf

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Joint FDA/OHRP Review

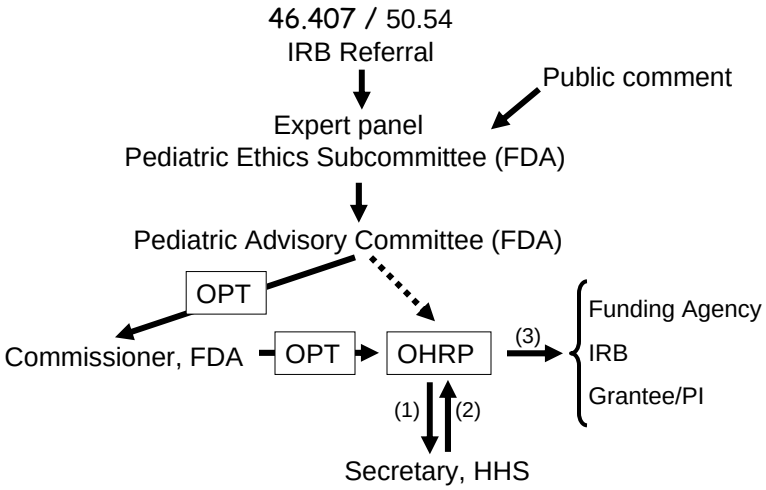
- Protocols meeting the conditions of 45 CFR 46.407 also may be subject to Food and Drug Administration (FDA) regulations under 21 CFR 50.54 if the protocols involve a clinical investigation of an FDA-regulated product.
    - http://www.hhs.gov/ohrp/children/Guidance_407Process.pdf

Joint FDA/OHRP Review Process

- FDA will issue a Federal Register notice about its schedule for review and receipt of public comments.
- In cooperation with OHRP, FDA will convene the PES of its PAC to review the protocol.
- The PES will transmit a consensus report to the FDA PAC, which will then make its final recommendations to the FDA Commissioner.
- PAC recommendations will be transmitted to the FDA Commissioner through the Office of Pediatric Therapeutics (OPT), which will comment on the recommendations in an accompanying transmittal memorandum.
- OPT will forward the Commissioner's determination to OHRP.
- OHRP will send a transmittal memo with its recommendation, the Commissioner's determination, and all supporting documents, including the recommendations of the PAC and summary of the Subcommittee meeting, to the Secretary for a determination as to whether the clinical investigation may be conducted or supported by HHS.

http://www.fda.gov/OHRMS/DOCKETS/98fr/06d-0172-gdl0002.pdf;
http://www.hhs.gov/ohrp/children/Guidance_407Process.pdf

OHRP/FDA Joint Review



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Overview of Subpart D Analysis, and Questions for Panel

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Risk of G-CSF?

- The IRB referral focused on the question of the risk of G-CSF administration to the matched sibling donors.
- The options available under Subpart D are:
  - Minimal Risk (46.404; 50.51)
  - Minor Increase Over Minimal Risk (46.406; 50.53)
  - Greater than a Minor Increase over Minimal Risk (46.405; 50.52)
  - Referral for federal panel review (46.407; 50.54)

Minimal Risk

- Any clinical investigation… in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians.

21 CFR 50.51; 45 CFR 46.404

Minimal Risk

- Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

21 CFR 56.102(i); 45 CFR 46.102(i) 13

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Criteria for IRB approval of research

- All of the following requirements must be satisfied:
  - Risks to subjects are minimized: (i) By using procedures consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) when appropriate, by using procedures already being performed for diagnostic or treatment purposes.
  - Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.
  - Selection of subjects is equitable.
  - Informed consent will be sought and appropriately documented.
  - Where appropriate, adequate provision for monitoring the data collected to ensure the safety of subjects.
  - Where appropriate, adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

21 CFR 56.111(a); 45 CFR 46.111(a) 14

Minor Increase over Minimal Risk

- Any clinical investigation in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject may enroll children as subjects only if the
  - Risk represents a minor increase over minimal risk;
  - Presents experiences to subjects reasonably commensurate with those inherent in their actual or expected medical, …psychological, [or] social… situations;
  - Likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of [that] disorder or condition; and
  - Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

21 CFR 50.53; 45 CFR 46.406

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Disorder or Condition

IOM Recommendation 4.3 (2004)

1. a specific (or a set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that …
2. an established body of scientific evidence or clinical knowledge has shown to …
3. negatively affect children's health and well-being or to increase their risk of developing a health problem in the future.

Does not represent FDA, OHRP or HHS policy.

Greater than Minimal Risk

- Any clinical investigation… in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject may involve children as subjects only if the
  - Risk is justified by the anticipated benefit to the subjects;
  - Relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
  - Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

21 CFR 50.52; 45 CFR 46.405

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Questions for the Panel - 1

- What are the risks of G-CSF administration?
- If these risks are appropriately considered to be minimal risk, have the general criteria for IRB approval been met?
- If not, are there additional stipulations that the panel would recommend?

Questions for the Panel - 2

- If the risks of G-CSF administration to the sibling donors are more than minimal risk, does the intervention offer the prospect of direct benefit to the sibling donors?
- In answering this question, you should consider the range of potential benefits to the sibling donors (including contributing to the improved health of the recipient). You should also consider whether any potential benefits are the direct result of the research intervention.

Questions for the Panel - 3

- If the G-CSF administration does not hold out a prospect of direct benefit to the sibling donors…
  - Are the risks of G-CSF administration appropriately considered to be no more than a minor increase over minimal risk?
  - Is the intervention likely to yield generalizable knowledge about the sibling donors' disorder or condition that is of vital importance for the understanding or amelioration of [that] disorder or condition?
  - Does the intervention present experiences to the sibling donors that are reasonably commensurate with those inherent in their actual or expected medical,… psychological, [or] social… situations?

Questions for the Panel - 4

- If the G-CSF administration does hold out a prospect of direct benefit to the sibling donors, are
  - The risks of G-CSF administration justified by this anticipated direct benefit?
  - Is the relation of the anticipated benefit to the risk is at least as favorable to the sibling donors as that presented by available alternative approaches?

Required Findings under 50.54/46.407

- Either the research [clinical investigation] in fact satisfies the conditions of §46.404 [50.51], §46.405 [50.52], or §46.406 [50.53], as applicable, or
- All of the following conditions are met:
  - The research [clinical investigation] presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
  - The research [clinical investigation] will be conducted in accordance with sound ethical principles; and
  - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in §46.408 [50.55].

21 CFR 50.54; 45 CFR 46.407

Questions for the Panel - 5

- If the research does not satisfy the conditions of either §46.404 [50.51], §46.405 [50.52], or §46.406 [50.53]…
  - Does the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children?
  - Will the research be conducted in accordance with sound ethical principles?
  - Are adequate provisions made for soliciting the assent of children and the permission of their parents or guardians?

Summary of Key Questions

- What is the risk of G-CSF administration?
- Does administration of G-CSF to the sibling donors offer a prospect of direct benefit?
- Do sibling donors have a disorder or condition?

Panel Discussion

- The panel should determine whether or not the research is approvable (with/without modifications) under a Subpart D category.
- The panel should provide reasons for this determination.
- The panel is not functioning as an IRB, but to provide a recommendation to Commissioner FDA / Secretary HHS.
- Any requested modifications should be divided clearly between “stipulations” (i.e., required for approval) and “recommendations” (i.e., not required for approval).