Agency Guidance Snapshot: Research Involving Children as Subjects and Not Otherwise Approvable by an Institutional Review Board: Process for Referrals to Food and Drug Administration and Office for Human Research Protections *(Draft Guidance)*

*The Yale Human Research Protection Program (HRPP) has launched the "**Agency Guidance Snapshot**" series. The purpose of the Agency Guidance Snapshots is to highlight recent agency guidance from the Food and Drug Administration (FDA)[1], Office for Human Research Protections (OHRP)[2], and other federal agencies that specifically impacts Yale University and affiliate stakeholders who conduct or oversee **human subjects research.***

Please Note: Yale University does not expect any immediate changes to policies due to this guidance; however, this guidance will be taken into consideration as policies and procedures are reviewed and revised in the future. Yale University may have additional requirements related to the topics covered in this guidance. For more information, please refer to the following Yale University Human Research Protection Program (HRPP) documents located on the HRPP website (Policies, Procedures, Guidance, and Related Documents) and in the Yale HRPP IRES-IRB Library (IRES IRB LOGIN): **1)** Yale HRPP Policy and Standard Operating Procedure Manual; **2)** Yale HRPP Investigator Manual; **3)** Yale IRB Members and Chairs Manual**;** and **4)** HRPP Supplemental Guidance Manual. Please also refer to University Policies & Procedures and policies published by the various Yale University schools and departments.

Title of Document:	Research Involving Children as Subjects and Not Otherwise Approvable by an Institutional Review Board: Process for Referrals to Food and Drug Administration and Office for Human Research Protections *(Draft Guidance)*
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Stakeholders Impacted:	Investigators ☒ Sponsors ☒ Sponsor-Investigators ☒ IRB/HRPP Staff, Chairs, & Members ☒ Other ☐
Hyperlink to Document:	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/research-involving-children-subjects-and-not-otherwise-approvable-institutional-review-board-process

[1] FDA Guidance documents represent the Agency's current thinking on a particular subject. They do not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] This guidance, when finalized, will represent OHRP's current thinking on this topic and should be viewed as recommendations unless specific regulatory requirements are cited. The use of the word "must" in OHRP guidance means that something is required under the Department of Health and Human Services (HHS) regulations at 45 CFR part 46. The use of the word "should" in OHRP guidance means that something is recommended or suggested, but not required. An institution may use an alternative approach if the approach satisfies the requirements of the HHS regulations at 45 CFR part 46.

For any questions, please contact HRPP Assistant Directors
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Overview of Guidance Document:

This guidance is intended to assist institutional review boards (IRBs), institutions, investigators, and sponsors in understanding the processes used for review of research involving children as subjects that is not otherwise approvable by an IRB and has been referred to the Food and Drug Administration (FDA) under 21 CFR 50.54, the Office for Human Research Protections (OHRP) under 45 CFR 46.407, or both, for review.

Background on Subpart D (Protections for Children as Research Subjects)

- Department of Health and Human Services (HHS) issued 45 CFR part 46, subpart D, "Additional Protections for Children Involved as Subjects in Research," as a final rule on March 8, 1983. HHS's subpart D regulations apply to all research involving human subjects and conducted or supported by HHS.
- FDA issued 21 CFR part 50, subpart D, "Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products," as a final rule on February 26, 2013. FDA's subpart D regulations apply to clinical investigations regulated by FDA.
- FDA-regulated clinical investigations conducted or supported by HHS are subject to both sets of regulations.
- An IRB may only approve research involving children as subjects that satisfies the following applicable regulations (as well as requirements of all other applicable provisions of subpart D):
  - **21 CFR 50.51** and **45 CFR 46.404**: Research not involving greater than minimal risk.
  - **21 CFR 50.52** and **45 CFR 46.405**: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
  - **21 CFR 50.53** and 45 **CFR 46.406**: Research involving no more than a minor increase over minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

21 CFR 50.54 & 45 CFR 46.407 (Research on Children Not Otherwise Approvable by an IRB)

- If an IRB does not find that research involving children as subjects meets the regulatory requirements discussed above, **the research may proceed only if the following criteria in 21 CFR 50.54, 45 CFR 46.407, or both as applicable, are satisfied:**
  - The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; AND
  - The Commissioner of Food and Drugs, the Secretary of HHS, or both as applicable, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:
    - The research in fact satisfies 21 CFR 50.51, 50.52 or 50.53; 45 CFR 46.404, 46.405, or 46.406; or both sets of regulations as applicable, OR
    - The following three conditions are met:
      - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
      - The research 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.

Key Points for Researchers:

While researchers should understand the process for IRB review and referral of research involving children as subjects that is not otherwise approvable by an IRB, there is no specific action that needs to be taken on the part of the investigator during the IRB review and referral to FDA/OHRP process, other than complying with IRB determinations and requests, as applicable. For information on the IRB referral process to FDA/OHRP for research involving children as subjects that is not otherwise approvable by an IRB, please see the section below titled, "Key Points for IRB/HRPP Staff, Chairs, & Members."

Key Points for IRB/HRPP Staff, Chairs, & Members:

Referral and Meeting Procedures

Once the IRB has determined that research involving children as subjects meets the criteria found in 21 CFR 50.54, 45 CFR 46.407, or both as applicable, the IRB must submit an electronic referral to FDA and/or OHRP as soon as possible, and include:

- The IRB's explanation of why the clinical investigation or proposed research does not meet the standard subpart D requirements (for FDA/OHRP, as applicable);
- The IRB's finding that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- The research protocol, investigator's name, current informed consent documents/parental permissions forms, and, if being used, the assent form(s) and/or a description of the assent process;
- Other informative supporting documents, such as the IRB minutes, correspondence between the IRB and the investigator, investigational product labeling, the investigator's brochure (IB), and the IRB's assessment of investigator qualifications and research site adequacy;
- IRB names and contact information (also include institution name for OHRP referrals);
- **For FDA referrals only**: IND or IDE numbers assigned by FDA, if applicable and known;
- **For OHRP referrals only**: HHS application number (if applicable) and name of the HHS division conducting or supporting the research.

For FDA-regulated research, after a referral is accepted by FDA, the relevant FDA office will prepare for presentation of the clinical investigation to a joint meeting of FDA's Pediatric Advisory Committee (PAC) and the Pediatric Ethics Subcommittee (PES). FDA will schedule the meeting based on the urgency of the request.

For HHS-regulated research, Review of referrals to OHRP will be conducted by an expert panel comprised of individuals selected for their expertise relevant to the specific referral. OHRP will post referral materials in a public docket, including a notice that the panelists' individual recommendations will be publicly posted in the established docket after the expert panel meeting.

The agencies encourage the IRB, the sponsor (if appropriate), and the investigator(s) to attend the meeting to assist the members in understanding the clinical investigation or proposed research and provide an opportunity for the members to ask questions regarding the basis for the referral.

Final Determinations

FDA	OHRP
Recommendations: • For PAC/PES meetings, after deliberation and discussion of the clinical investigation, the PAC/PES will vote on whether to recommend that the proposed clinical investigation may proceed under 21 CFR 50.51, 50.52, 50.53 or 50.54. The PAC/PES members will not write individual recommendations.	**Recommendations:** • For OHRP expert panel meetings, after deliberation and discussion of the proposed research, each panel member will write an individual recommendation discussing whether the research meets the criteria of 45 CFR 46.407(b)(1) or (2). OHRP will post the individual panel member recommendations in the docket. The public may provide comments in the docket for 30 days after the date of the expert panel meeting.
Final Determinations: • After the meeting, FDA staff will develop and send a memorandum that outlines the recommendation(s), as well as relevant supporting documents, to the FDA Commissioner. The memorandum will request the Commissioner make a final determination as to whether, and if so, under which provisions of subpart D, the clinical investigation may proceed. • After the Commissioner has made a final determination, FDA intends to forward the determination to the IRB and post the final determination on the FDA website within 90 days of the PAC/PES meeting or as soon as practicable thereafter.	**Final Determinations:** • After the OHRP expert panel meeting, OHRP will develop a recommendation for the Assistant Secretary for Health (ASH). After review of the relevant materials and OHRP's recommendation, the ASH, on behalf of the HHS Secretary, will make the final determination regarding whether the research may proceed under 45 CFR 46.404, 46.405, 46.406, or 46.407. • OHRP will inform the referring institution and/or IRB chair, the investigator, and the HHS division supporting or conducting the research of the ASH's determination and post its recommendation to the ASH and the ASH's final determination in the established docket within 90 days of the expert panel meeting or as soon as practicable thereafter.

Special Considerations

- For research that FDA and OHRP determine is both HHS-conducted or supported and FDA-regulated, FDA and OHRP generally intend to conduct a joint review of the research and will follow the process for FDA-only assessment of referrals.
- For multisite research regulated by FDA and conducted under an IND or IDE, if an IRB makes a referral under 21 CFR 50.54, FDA will determine whether the clinical investigation may proceed or will be placed on clinical hold. If FDA concludes that a clinical hold is appropriate, the agency generally intends to apply that clinical hold to all sites, regardless of whether IRBs other than the one that referred the protocol have approved the protocol.
- For multisite research regulated by OHRP, that does not require, or is excepted from the requirement for, single IRB review under 45 CFR 46.114, the HHS division supporting or

conducting the research may consider the implications of the 45 CFR 46.407 review process on the conduct of the research at other HHS supported sites and whether, if consistent with applicable law, to delay or suspend subject enrollment at these other sites pending the outcome of the review.

For more related information, please see the following links to additional resources:

- FDA Website – Regulatory Information
- HHS Website - Office for Human Research Protections
- CITI Program - FDA Draft Guidance on Research Involving Children as Subjects
- WCG IRB - Current Process for Reviewing Research Involving Children as Subjects That is Not Otherwise Approvable by an IRB

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