Summary of Children Regulations:
IRB Review of Research Involving Children

Department of Health and Human Services (HHS) 45 CFR Part 46 Subpart D
Food and Drug Administration (FDA) 21 CFR Part 50 Subpart D

OHRP/HHS and FDA have regulations governing conduct of research involving children. The IRB must review research/clinical investigations involving children as subjects covered by Subpart D and approve only those protocols that satisfy the criteria and conditions described below.

Additional requirements may apply when research with children is supported by or involves other federal agencies (e.g., Department of Education, Environmental Protection Agency).

These regulations can be grouped into 5 categories:

- Definitions;
- 4 Risk/Benefit Categories with Conditions;
- Assent: Capacity, Documentation, Waiver;
- Permission Requirements;
- Wards: Conditions/Advocate.

Definitions

[FDA 21 CFR 50.3(s) & DHHS 45 CFR 46.402]

"Minimal Risk"
The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

"Guardian"
Individual who is Authorized Under State and Local Law to Consent on Behalf of a Child to General Medical Care

"Permission"
The agreement of parent(s) or guardian to the participation of their child or ward in research or a clinical investigation.

"Assent"
A child's affirmative agreement to participate in a clinical investigation. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Risk/Benefit Categories

The IRB must review research/clinical investigations involving children as subjects covered by this Subpart D and approve only those clinical investigations that satisfy the criteria described in Categories 1, 2, and 3. Should the research fall under Category 4, a report must be sent to the applicable federal agency for review and the IRB may not independently approve the research.

Risk/Benefit Category 1: Not Greater than Minimal Risk
(46.404 and 50.51)

The IRB must find that:

1. Adequate provisions have been made for soliciting the assent of the children as set forth in 46.408 and 50.55;

2. Adequate provisions have been made for soliciting the permission of their parents or guardians as set forth in 46.408 and 50.55 (Permission of one parent is sufficient, if approved by the IRB.).

Risk/Benefit Category 2: Greater than Minimal Risk, but Prospect of Direct Benefit to Individual Subjects (46.405 and 50.52)
IRB must find that:

1. Risk is justified by anticipated benefit;

2. Relation of the benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches;

3. Adequate provisions are made for soliciting assent of children and permission of their parents or guardians (Permission of one parent is sufficient, if approved by the IRB.).

Risk/Benefit Category 3: Greater than Minimal Risk, No Prospect of Direct Benefit to Individual Subjects, but Likely to Yield Generalizable Knowledge about the Subject's Disorder or Condition (46.406 and 50.53)

IRB must find that:

1. Risk represents a minor increase over minimal risk;

2. The intervention or procedure presents experiences to the subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations;

3. The procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for understanding or amelioration of the subjects' disorder;

4. Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians; (except under specific circumstances, permission must be obtained from both parents).

Risk/Benefit Category 4: Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (46.407 and 50.54). To approve requires:

1. IRB finds the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem.

2. Review by the HHS Secretary or FDA Commission after consultation with a panel of experts and public comment.

FDA Expectations in Applying Categories in Placebo Controlled Studies:

Upon final adoption of FDA Subpart D, FDA provided interpretation of category assessment relative to placebo-controlled studies. FDA has indicated that administration of a placebo would not meet Category 2 (21 CFR 50.52) because it would not offer a prospect of direct benefit. In addition, the FDA does not consider the concept of enhanced safety monitoring or follow up provided to subjects in a placebo arm to constitute a prospect of direct benefit.

FDA expects the IRB to conduct a component analysis of each arm of a placebo-controlled trial. The placebo arm of a pediatric clinical trial should be categorized under either Category 1, 3, or 4.

Assent Requirements: FDA and DHHS

[FDA 21 CFR 50.55 & DHHS 45 CFR 46.408]

Assent is required if Children are capable of Assent

To Determine if a Child is Capable of Assent, the IRB must Consider:

1. Age
2. Maturity
3. Psychological State
4. All Children or
5. Each Child

Assent is NOT required IF:

1. Capability Limited/Cannot Reasonably be Consulted OR
2. Prospect of Direct Benefit Important to Health/Well-being and Available Only in Context of Investigation OR

3. No More than Minimal Risk and Will Not adversely Affect Rights and Welfare and Could Not Practicably be Carried Out When Appropriate, provided pertinent information after participation

Assent Documentation:

IRB Must Determine Whether and How Assent Must Be Documented.

Parental Permission

[FDA 21 CFR 50.55 & DHHS 45 CFR 46.408]

IRB Must Determine that Provisions are in Place to Solicit and Document Permission of Each Child's Parent(s) or Guardian in accord with basic elements of informed consent (i.e. FDA 21 CFR 50.25 & 50.27; DHHS 45 CFR 46.116 & 46.117).

When the IRB requires Both Parents' Permission (e.g., Research Categories 3 & 4), Only One Parent's Permission is Needed if One Parent is:

- Deceased;
- Unknown;
- Incompetent;
- Not Reasonably Available;
- Only one Parent has Legal Responsibility for the Care and Custody of the Child.

Waiver of Parental Permission

DHHS 46.408 – Parental Permission May be Waived if:

- Research Protocol Designed for Conditions or Research Protocol Designed for Subject Population for which Parental/Guardian Permission is not a Reasonable Request to Protect Subjects and
- Provided an appropriate mechanism for protecting children is substituted and
- Waiver not inconsistent with Federal, State, or Local Law.

DHHS 46.116 – Parental Permission May Be Waived if:

- Research is No More Than Minimal Risk and
- Rights and Welfare – Not Adversely Affected and
- Research Could Not be Practicably Conducted Without Waiver and
- Subjects Provided With Pertinent Information After Participation, if Applicable

FDA 50.24 –Does not allow Waiver of Parental or Guardian Permission for studies that are greater than minimal risk, with exception of Emergency research (21 CFR 50.54)

IRB Review of Research with Wards of the State

[FDA 21 CFR 50.56 DHHS 45 CFR 46.409]

IRB must determine that the research meets the following categories:

1. Related to Status as Wards OR
2. Conducted in Schools, Hospitals, or Similar Settings in Which Majority of Children Involved are NOT wards

Required Safeguard:

1. An Advocate must be appointed for Each Child

Advocate:

1. Serves in Addition to Guardian or In Loco Parents
2. May Serve for More than One Child
3. Must Have Background and Expertise and Serve Throughout the Study
4. Cannot be Associated with Study, Investigator, or Guardian Organization