Protecting the people who volunteer to participate in research

Compliance Strategies for Clinical Trials

Children in Research

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Compliance Strategies for Clinical Trials

- Fundamental Question:
- Know the nature of your research portfolio
- Who is doing the research?
- Who is funding the research?
- Where is the research being conducted?
- How are the subjects being recruited?

Compliance Strategies for Clinical Trials

- Research involving Children
- What are the regulatory issues
- What are the strategies for ensuring compliance with the regulatory requirements

Research Involving Children

- FUNDING FROM THE US GOVERNMENT
- Department of Health and Human Services
- 45 CFR Part 46, Subpart D
- specific to DHHS
- applicability to other funded research through MPA
- Department of Education

Research Involving Children

- Other regulations:
- (1) FDA Interim Final Rule on Children;
- (2) 1998 Pediatric Rule;
- (3) FDA Modernization Act of 1997;
- (4) ICH Guidelines;
- (5) FDA Information sheets: “Guidance for Institutional Review Boards and Clinical Investigators”.

Research Involving Children
FDA Interim Final Rule

- FDA Interim Final Rule on Research Involving Children
- Issued because of the Children's Health Act of 2000
- Effective April 30, 2001
- Adopts Subpart D with some deviations and some explanatory text

FDA Interim Rule on Research Involving Children

- Definition of guardian
- DSMBs for research involving children where greater than minimal risk; prospect of direct benefit; may not be able to assess risks ahead of time with new drugs;
- Should placebo controlled trials be permitted;
- What is a minor increase above minimal risk;
- when appropriate to waive assent;
- no waiver of parental consent permitted;
- wards may participate.

Research Involving Children
FDA Pediatric Rule

- 1998 Pediatric Rule (63 FR 66632)
- , December 2, 1998
- Requires manufacturers to assess the safety and effectiveness of certain drug and biological products in pediatric patients.
- Establishes presumption that children will be included in research.
- Rationale: absence of pediatric labeling information posed significant risks for children.

Research Involving Children
FDA Modernization Act

- FDA Modernization Act (Public Law 105-115)
- creates economic incentives for manufacturers to conduct pediatric studies on drugs for which exclusivity or patent protection is available under the Drug Price Competition and Patent Term Restoration Act or the Orphan Drug Act.
- Manufacturer requests pediatric studies + FDA requested that the manufacturer conduct studies = 6 months of additional marketing exclusivity.

Research Involving Children
ICH Guidelines

- ICH Guidelines
- E11 Clinical Investigation of Medicinal Products in the Pediatric Population

Research Involving Children
FDA Information Sheets

- FDA pediatric website
- http://www.fda.gov/cder/pediatric

Overview of the DHHS regulations relating to research involving children

Subpart D

Research Involving Children

- Exemptions: one of the six exemptions does not apply to research involving children.
- 46.401(b) “…the exemption at 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.”

Research Involving Children: Definitions

- Children
- Assent
- Permission
- Parent
- Guardian
- no definition of minimal risk

Research Involving Children: 45 CFR 46.404

Research not involving greater than minimal risk.

- IRB must find that adequate provisions are made for soliciting the (i) assent of the children and the (ii) permission of their parents or guardians, as set forth in 46.408.

45 CFR 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

- More than minimal risk to children is presented by
  (i) an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or
  (ii) by a monitoring procedure that is likely to contribute to the subject's well-being if:
- risk is justified by the anticipated benefit;
- relation of anticipated benefit to risk is as favorable as alternatives;
- assent and permission of parents sought.

45 CFR 46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects disorder or condition.

- Risk is minor increase over minimal risk
- research presents situations reasonably equal to to those inherent in their actual situations;
- research likely to yield generalizable knowledge about disorder or condition
- adequate provisions for getting assent and permission.

45 CFR 46.406

- Greater than minimal risk + no prospect of direct benefit
- Must find existence of a disorder or condition

45 CFR 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

- IRB finds research cannot meet other requirements;
- IRB makes certain findings;
- Secretary HHS consults with a panel of experts

45 CFR 46.408 Requirements for permission by parents or guardians and for assent by children.

- (a) Solicitation of assent;
- (b) Adequate provision for soliciting permission;
- (c) Waiver where permission not reasonable;
- (d) Permission documented;
- (e) If IRB determines assent required; must also determine whether and how will be documented.

45 CFR 46.408
Assent not required

- Assent of children not necessary where IRB finds:
- children are not capable of providing assent;
- intervention holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research.

45 CFR 46.408 Permission of Parents

- One parent ok for research under 404; 405
- Both parents required to consent for research under 406 and 407 unless one parent is deceased; unknown; incompetent, or not reasonably available or when only one parent has legal responsibility for the care and custody of the child.

45 CFR 46.408
Waiver of Parental Permission

- IRB may waive need for parental permission where parental permission is not reasonable (for example, neglected or abused children).
- Supercedes waiver criteria of Common Rule. The Common Rule is stricter and only permits a waiver with minimal risk research.
- Waiver of parental permission in the childrens regulations can be made regardless of the degree of risk.

Compliance Strategies for Clinical Trials

- Stage: Research involving children.
- Issue: How do you know its being done properly?

Compliance Strategies for Clinical Trials

- Can you answer the fundamental questions?
- Who is conducting the research?
- Who is paying for the research?
- Where is the research being conducted?
- What is the nature of the research?
- What education and training has been provided?
- Are there policy and procedure manuals that identify how the IRB will review research involving children?

Compliance Strategies for Clinical Trials

- Is there an investigator manual?
- Are the forms informative and adequate?
- How is the IRB recording minutes of meetings?
- Is there adequate documentation in the minutes?
- If you are using a central IRB, how are you auditing or assessing their continuing ability to review your research?

Compliance Strategies for Clinical Trials: The investment

- Adequate Funding
- Education and Training
- IRB assessments
- Review of documents
- Random audits of IRB files
- Random audits of investigator files
- Consent Monitors
- Data Safety Monitoring Boards

Compliance issues in the news

- conflicts of interest (ownership of stock in pacemaker inserted in children)
- IRB determinations of minimal risk (NICHD Trial)
- use of vulnerable populations (economically disadvantaged children)
- recruiting strategies (explaining research vs available treatments)
- placebos (greater than minimal risk, no prospect of direct benefit)
- Legally authorized representative vs guardian or surrogate (parental consent for medical treatment vs. research)

Conclusion