



MAYO CLINIC

Research Involving Children: Legal and Ethical Considerations

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Willowbrook Study

(New York, 1963-1966)

- Parents could admit children to state school for “mentally defective persons” if consented to research
- Study to understand disease; test ability of gamma globulin
- Children usually acquired disease due to conditions
- Intentionally fed infected stool or injected with purified virus

Jesse Gelsinger

- Teen with genetic enzyme deficiency at risk for accumulating toxic levels of ammonia
- High fatality rate but treatable with diet and medication
- UPenn gene therapy study offered “cure”
- 18 yo consented for self
- Died within 4 months of massive adverse reaction
- Conflict of interest; flawed consent

Grimes v Kennedy Krieger Institute

- Study of impact of lead abatement methods
- Children exposed to lead based paint and varying levels of lead dust
- Parents were consented but not told purpose
- Court determine study greater than minimal risk
- No therapeutic intent created duty to warn of dangers

782 A.2d 807 (Ct of Appeals, MD 2001)

Need for Information on Use in Children

- ~80% of listed medication labels disclaimed usage or lacked dosing information for children.
-PDR 1973* & 1991 Surveys
- Only 20-305 of FDA approved drugs have pediatric labeling.
-1094-1989* Survey, 1991-2001 Repeat Survey
- Only 38% of new drugs potentially useful in pediatrics were labeled for children on initial approval.
-1991-1997*, FDA statistics

***Source: AHLA presentation by Dianne Murphy, MD, "Off-Label Uses of Drugs and Devices in Children", 5/12/2009**

Off-Label Use

- The Federal Food Drug and Cosmetic Act does not regulate the practice of medicine

21 U.S.C. § 396

- Regulated products may be used “off-label”
 - MD well informed on use
 - Sound medical evidence
 - Scientific rationale
 - Records of product use and effects
- Document discussion/consent of patient/parents

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm>

REMS Interferes With Off-Label Use

- Risk Evaluation Management Strategy plans required by FDA for marketing
- 2007 FDA Act: ensure benefits of product outweighs the risk (>120 required)
 - Medication guide
 - Communication plan
 - Elements to assure safe use
 - Limited distribution system
 - Prescriber certification
 - Implementation System

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPat>

[ientsandProviders/ucm111350.htm](http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm)

Federal Regulations and Guidance

- Office of Human Research Protections (OHRP)
 - 45 CFR Part 46, Subpart D
 - OHRP Guidance

<http://www.hhs.gov/ohrp/policy/populations/children.html>

- Food and Drug Administration (FDA)
 - 21 CFR Part 50, Subpart D
 - FDA Consumer Advice

<http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048699.htm>

<http://www.hhs.gov/ohrp/policy/populations/children.html>

Applicability of Regulations

- OHRP
 - Federal funding or conducted
 - Scope of Assurance
 - Exemptions
- FDA
 - Clinical investigations regulated by FDA
 - Data submitted supporting an application

FDA Jurisdiction

- Foods, including dietary supplements, that bear a nutrient content claim or a health claim
- Infant formulas
- Food and color additives
- Drugs for human use
- Medical devices for human use,
- Biological products for human use
- Electronic products

Differences in OHRP and FDA Regulation

- OHRP
 - Exempts certain research
 - Waiver of informed consent
- FDA
 - No exemptions
 - Waiver of informed consent in emergency or research in emergency settings

OHRP Exemptions

- Educational settings
- Observation of public behavior, if investigator not interacting
- Public officials
- Existing data, records, specimens
- Approved by DHS or agency head
- Taste and food quality evaluation; consumer acceptance studies

OHRP Waiver of Consent in Private Research

- Emergency settings
- No greater than minimal risk; doesn't affect rights of subjects; could not practicably be conducted; subjects given information after participation, if appropriate
- If children are subjects
 - Consistent with state law
 - Other mechanisms to protect the child
 - Parental consent would place child at risk

45 CFR 46.408(c)

FDA Exception from Consent in Emergency

- Life-threatening situation
- Unable to communicate or obtain legally effective consent
- LAR not available
- No alternative equal or better at saving life

FDA Emergency Setting Exception from Informed Consent

- Life-threatening condition
- Consent not feasible
- Prospect of direct benefit
- Not practicable without waiver
- Time limited with efforts to obtain LAR consent
- IRB approval of consenting process
- Additional protections

Categories of Research Involving Children

- Not greater than minimal risk (404)
- >minimal risk; prospect of direct benefit to individual subject (405)
- >minimal risk; no direct benefit; generalizable knowledge (406)
- Not approvable but with opportunity to affect health or welfare of children in general (407)

Consent Standards

- One parent may consent for research that is minimal risk or with prospect of direct benefit to child subject
- Both parents, if available, must consent for greater than minimal risk with no prospect of direct benefit or if not otherwise approvable but opportunity to understand a serious problem affecting children

Research Involving Wards of the State or Public Agency

- Can be subject for minimal risk or studies involving potential for direct benefit (404, 405)
- If research is greater than minimal risk with no direct benefit then ward may participate only
 - Research is of status of wards
 - Conducted in setting where majority of children subjects are not wards
- Advocate appointed for each child in addition to guardian
 - Independent of researcher, agency or guardian

Regulatory Crosswalk

45 CFR	21 CFR
46.404	50.51
46.405	50.52
46.406	50.53
46.407	50.54
46.408	50.55
46.409	50.56

American Academy of Pediatrics Improve Communication

<http://aappolicy.aappublications.org/cgi/content/full/pediatrics;121/5/e1441>

Table 9

- Ensure the presence of a nurse
- Read the consent document with the parents, explicitly soliciting questions and allocating sufficient time to answer them
- Provide time to process the information, including taking the consent document home overnight
- Provide written and video explanations

American Academy of Pediatrics Improve Communication

<http://aappolicy.aappublications.org/cgi/content/full/pediatrics;121/5/e1441>

Table 9

- Provide information in the family's native language when possible
- Provide names and contact information for practitioners who can offer independent, competent second opinions
- Conduct a daily education conference to allow information to be incrementally processed

Case Discussion

Phase I Clinical Trial

Company proposes to Researcher a placebo controlled, randomized protocol to determine the safe dose for an investigational asthma drug. The drug has reached Phase III studies in an adult cohort but the data are not yet published.

What should an IRB consider in reviewing this study?

Study of ADHD Treatment on School Performance

Company A approaches Researcher proposing a study in which the researcher compares school achievement of two cohorts of children taking different drugs for ADHD. One drug is approved for the indication but one is used off-label for this purpose.

Can Researcher successfully obtain IRB approval for this study?

Emergency Treatment of Overdose

A child has received a 10x overdose of an approved chemotherapy drug. Unless an unapproved drug is administered within 12 hours of the administration of the chemotherapy the child has a >90% chance of death.

How does the hospital obtain the antidote?



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