Research with Children An Ethical and IRB Perspective

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Objectives

Understand the rationale behind the regulations governing research with children

Know the 4 categories of IRB approval of pediatric research

Be able to determine which category of approval is appropriate for a given research protocol.

Know the requirements for parental permission.

The Pediatric Research Dilemma

Vulnerable subjects to be protected from research?

Moral imperative to study safety and effectiveness of therapies in children.

The National Commission Report (1977)

Acknowledged the dilemma and affirmed the importance of conducting research with children.

The Commission has therefore sought to answer the following two questions:

- under what conditions is the participation of children in research ethically acceptable,
- under what conditions may such participation be authorized by the subjects and their parents.

Core Principles

Respect for Persons

Beneficence

Justice

Respect for Persons

Individuals should be treated as autonomous agents

Those with diminished autonomy must be provided with additional protections.

Respect for Persons

Parental permission

Provision of assent

"I don't need informed consent to give you a sponge bath."

Beneficence

Provision of benefit

Avoidance of harm

Justice

Requires the fair distribution of the burdens and benefits of research.

- "Given their dependent status and their diminished capacity to consent, it is important that children be protected against selection solely because of administrative convenience or because their illness or socioeconomic condition render them especially vulnerable."
- Research risks should be allocated to adults and older children whenever feasible

The regulations

The regulations establish:

- Scientific necessity and importance of the research
- Acceptable level of risk exposure
- Requirements for parental permission and child assent

Subpart D (HHS and FDA)

Research involving minors as participants must meet the criteria spelled out in Subpart D in addition to the Criteria for Approval (45 CFR 46.111, 21 CFR 56.111)

Definitions

Who is a child?

- Determined by state law.
- On NIH Bethesda Campus: Under age 18, minors that are married or are parents

Research

- A systematic investigation designed to develop or contribute to generalizable knowledge.

Minimal Risk

- Probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those that are ordinarily encountered in daily life, or during the performance of routine physical or psychological examinations or tests (of healthy children)(with prudent parents)
  - Consider age, disruption of normal routine, separation from parents or unusual discomforts.

National Commission Recommendations

Recommendations 3-6 form the basis for the current regulatory categories

- 46.404/50.51
  - minimal risk
- 46.405/50.52
  - > min risk but PDB
- 46.406/50.53
  - > min risk, but no PDB
- 46.407/50.54
  - Not otherwise approvable

Recommendations 7-10 address requirements for parental permission, 9 and 10 address wards of the state and institutionalized children.

Underpinnings

Risks must be low if there is no prospect of direct benefit (PDB).

- Data in support of the research must support either:
  - Acceptably low risk

  OR
  - Prospect of direct benefit

Children should not be placed at a disadvantage by being enrolled in a clinical trial.

- eg, exposure to excessive risk or failure to get necessary health care.

Risk vs Benefit

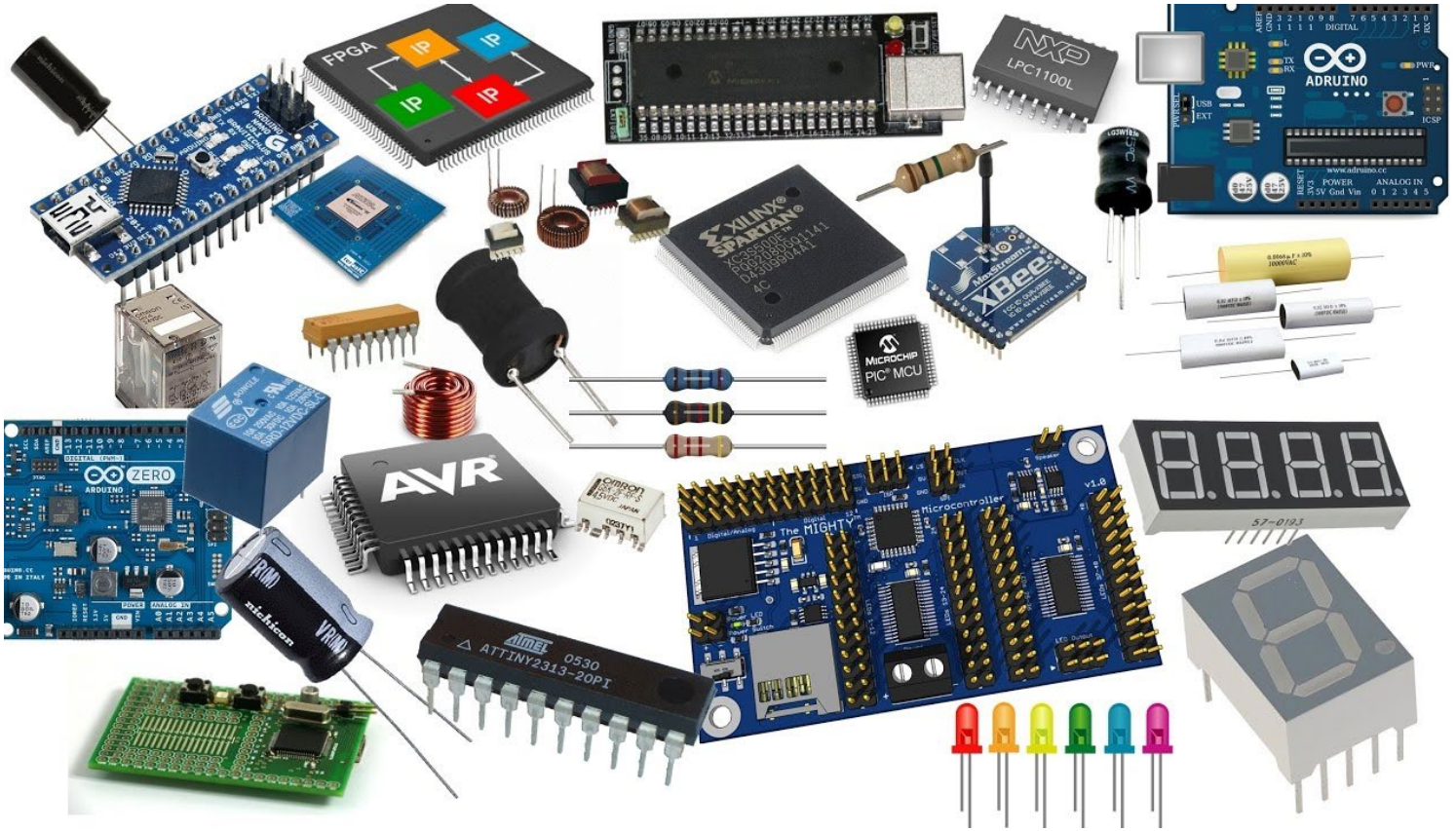
Adults:

- Risks balanced against either direct benefit or importance of anticipated knowledge

Children:

- Investigations that pose more than low risk CANNOT be justified by the importance of the anticipated knowledge.
- If risk is more than low, there MUST BE a prospect of direct benefit. The benefit must be comparable to available alternatives.

Component Analysis



Analyzing risk: Component analysis

Allowable risk exposure for an intervention or procedure not offering PDB must be restricted to low risk, therefore

Individual research interventions and procedures must be assessed for both

- Prospect of direct benefit
- Level of risk

Component Analysis

NO PACKAGE DEAL!

46.404/50.51

§46.404 Research not involving greater than minimal risk.

- HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in §46.408.

46.404/50.51-minimal risk

Minimal risk (absolute standard)

- The risk of everyday life (normal healthy kids with prudent parents)

Examples

- Chart review
- Questionnaires
- Non-contrast MRI
- Blood draws (depending on volume, frequency and childs age, weight and condition)

Who can be enrolled?

- Healthy or affected child

Parental Permission/Assent?

- 1 or 2 parents
- Assent required unless waived

46.405/50.52

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

HHS will conduct or fund research in which the IRB finds that 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, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:

- (a) The risk is justified by the anticipated benefit to the subjects;
- (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.

What flavor of benefit?

Direct

- arising from the research intervention

Collateral

- Arising from the other aspects of the protocol

Aspirational

- Social value of the scientific knowledge

Direct benefit

A benefit is direct if:

- It accrues to the individual research participant
- Is a result from the specific research intervention or procedure, and not from ancillary benefits.

Based on the “structure” of the intervention, NOT the investigators intent or protocol’s objective.

What is direct benefit?

Tangible, positive outcome that may be experienced by the individual

No package deal!

Placebo does not offer benefit

What is not direct benefit?

Most diagnostic and monitoring procedures (blood draw, CT scan, biopsies etc) unless that information is critical for assessing the safety of another intervention that does offer PDB.

Diagnostic/monitoring procedures that might alter clinical care of the patient unless that procedure is routinely performed for the same purpose in clinical practice and will alter care.

More frequent visits to the doctor

Getting medications for free

What is prospect of benefit?

Level of evidence to support PDB is less than that to establish efficacy

- Based on evidence (eg adult/animal data)

Whether the intervention offers PDB is separate from whether that PDB is of sufficient probability, magnitude and type to justify risks, given overall clinical context.

- Risk/benefit calculus
- Should be at least as good as clinically available alternatives.

The other 2 factors

Justification of risk

- Scientifically sound expectation of success
- Risks of an intervention can only be justified by the benefits to be expected from that same intervention or procedure (no package deal).
- Can include possibility of avoiding greater harm from the disease

Available alternative approaches

- Enrollment in a trial should not place child at a disadvantage
- Does available mean all?

46.405/50.52

> minimal risk with PDB
- Risk justified by benefit
- Benefit at least as good as available alternatives

Examples
- Administration of drug
- Surgical procedure
- Medical device

Who can be enrolled?
- Minors with condition
- Healthy? What would be direct benefit to a healthy kid?

Parental Permission/Assent
- 1 or 2 parents
- Assent required unless waived by the IRB

46.406/50.53

§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 subject's disorder or condition.

HHS will conduct or fund research in which the IRB finds that 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, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

- (a) The risk represents a minor increase over minimal risk;
- (b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
- (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- (d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in §46.408.

3 special conditions

Risk is no more than a minor increase over minimal.

Experience is reasonably commensurate with the subjects actual or expected experience.

Is likely to yield generalizable knowledge about the subjects disorder or condition.

46.406/50.53

>minimal but no PDB
- No more than a minor increase over minimal

Examples
- CT
- MRI with contrast
- Skin biopsy
- BM Bx
- Procedural sedation administered by experienced personnel

Who can be enrolled
- Only children with/at risk for the condition under study
- NO HEALTHY CHILDREN

Parental permission/Assent
- 2 parents
- Assent required unless waived by IRB

Not otherwise approvable

If the IRB is unable to determine that the research meets the requirements of previous categories

- IRB determines that the research presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children.
- Referred to a national panel to determine that it either meets other criteria or that research is justified by the importance of the knowledge sought and would not contravene the principles of respect for persons, beneficence and justice

46.407/50.54

§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.

HHS will conduct or fund research that the IRB does not believe meets the requirements of §46.404, §46.405, or §46.406 only if:

- (a) 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
- (b) the Secretary, 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, has determined either:
- (1) that the research in fact satisfies the conditions of §46.404, §46.405, or §46.406, as applicable, or (2) the following:
- (i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- (ii) the research will be conducted in accordance with sound ethical principles;
- (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in §46.408.

46.407/50.54

Majority reviewed under 46.407 to date have been for interventions that are > minimal to children lacking a disorder or a condition (healthy controls), or more than minor increase over minimal with no PDB.

- Metabolic studies in normal children
- Bronchoscopy in CF kids
- Administration of GnRH to healthy

Parental Permission

404/405 (50.51/50.52)

- 1 or 2 parents

406 (50.53)

- 2 parents

When does 2 mean 1?

…both parents must give their permission 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.

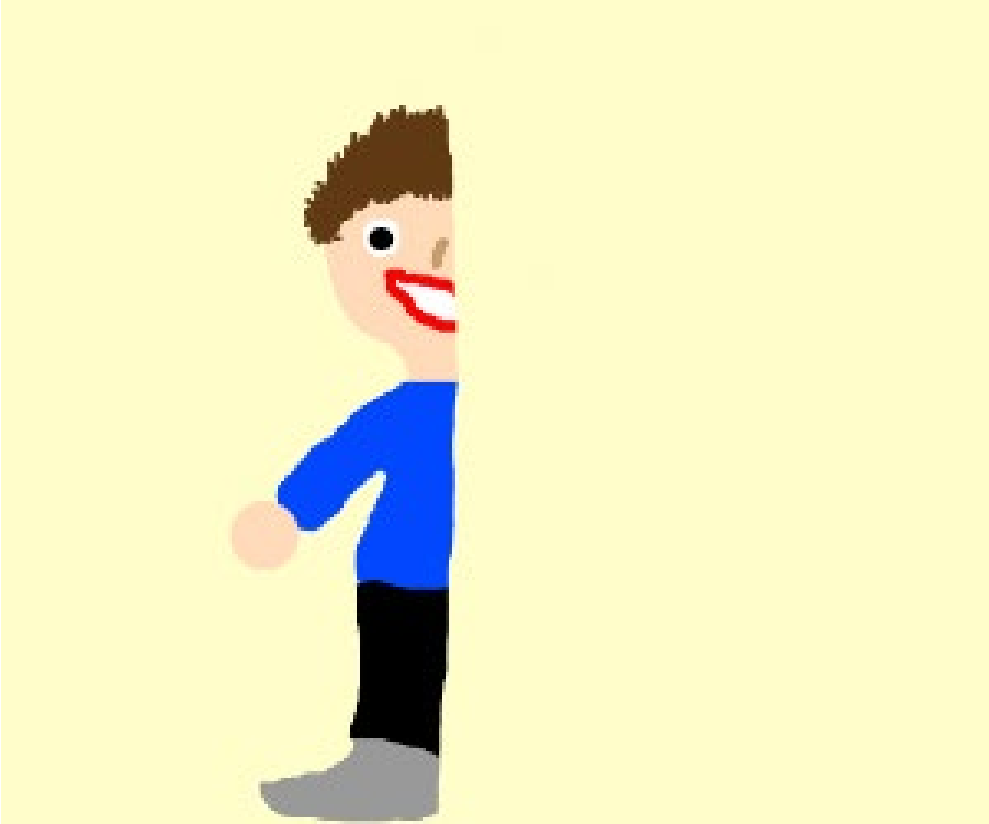
What is not reasonably available?

2nd parent does not have to be physically present

- Electronic means OK

When does 1 mean 2?

Joint custody (?only at the NIH)



Waiver of parental permission

Waiver of informed consent criteria must be met (46.116 (c) or (d)

IRB determines that a research protocol is designed to study conditions in children or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the parental permission requirements provided that an appropriate mechanism is in place to protect the children, and provided that the waiver is not inconsistent with federal, state, or local law (45 CFR 46.408(c)).

Research related to certain conditions in adolescents for which they may legally receive treatment without parental consent (for example contraceptive or STI research)

- Not considered minors in this case, and subpart D doesn't apply

Research designed to understand the needs of neglected or abused children.

Research involving children whose parents are legally or functionally incompetent.

Assent

Assent is always required, unless waived by the IRB

Requirement for assent may be waived if:

- Capability is so limited that the child cannot be consulted or
- Prospect of direct benefit important to the child's health available only within the research context
- Minimal risk research that could not otherwise be conducted.

Assent is an affirmative statement

- Failure to object cannot be taken as assent.

General guidelines

- < 5 y.o. assent waived
- 6-12 oral assent process
- ≥ 13 written assent
- 15-17 may be able to sign same document as parent

Examples

A pediatric cancer study involving:

- Administration of an investigational drug
- Frequent monitoring of blood levels of the drug, which may require placement of a central line.
- A biopsy procedure after several cycles of treatment for future unspecified research.

Component analysis

- Drug: > min risk with PDB
- Blood draws: it depends.
  - Peripheral sticks, w/in volume guidelines…MR
  - Central line…>MR, is their PDB?
- Research biopsy
  - Most likely > MR without PDB

Example 2

A randomized, placebo controlled study of a new medication for children with migraines.

Interventions include:

- Administration of drug or placebo
- MRI
- Lumbar puncture to determine changes in a biomarker

Component analysis

Administration of drug

- PDB?
  - Possibly, depends on data
    - If yes, allowable risk may be more than a minor increase over minimal
    - If no, must be no more than a minor increase over minimal

Administration of placebo

- PDB?
  - Placebo can never impart PDB.
  - Will known effective therapy be withheld, and if so, what is risk?
  - Risk must be no more than minor increase over minimal.

Component analysis

MRI and LP?

- Risk: Minimal or > minimal?

Is it approvable? Under what?

- 404: min risk
- 405: > min risk, PDB
- 406: minor increase over min risk, no PDB
- 407: not otherwise approvable

Example 3

Bone marrow transplant study for immunodeficiency disease

Recipients get std conditioning regimen and either related donor or MUD txp

- Age >5

Related donors

- Healthy individuals age > 5
- BM or SC harvest procedure
- Extra blood for research purposes

Component analysis

Recipients

- Conditioning chemo
- Lots of labs
- Lots of imaging
- Txp
- What if a research biopsy?

Donors

- BM or SC harvest procedure
- Aliquot of cells for research
- What if given a drug to mobilize cells for harvest?

Solution

Separate clinical from research

Research must be minimal risk

Protocol/consent must describe only the research

Clinical care consents for clinical procedures

Example 4

Protocol to develop and validate a GnRH agonist test to facilitate in the differentiation of disorders of puberty

Protocol involves:

- enrollment of affected children and normal, healthy children
- Administration of a single SQ dose of leuprolide
- serial blood draws through an IV (150-240 cc)
- X-rays for bone age

Component analysis

is it approvable?

- 404: min risk
- 405: > min risk, PDB
- 406: minor increase over min risk, no PDB
- 407: not otherwise approvable

Must assess risks & benefits of each population separately

- Affected
- Normal healthy

References

Ethical Considerations in Conducting Pediatric Research Michelle Roth-Cline, Jason Gerson, Patricia Bright, Catherine S. Lee and Robert M. Nelson H.W. Seyberth et al. (eds.), Pediatric Clinical Pharmacology, Handbook of Experimental Pharmacology 205, DOI 10.1007/978-3-642-20195-0_11, # Springer-Verlag Berlin Heidelberg 20

Report and recommendations: Research Involving Children, The National Commission for the protection of human subjects in biomedical and behavioral research; http://videocast.nih.gov/pdf/ohrp_research_involving_children.pdf

Material from 2012 PRIMR course . Research Involving Children: Framing and Applying Additional Protections. Skip Nelson, Steven Joffe and Susan Kornetsky.