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 using component analysis

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.

Core Principles

Principle of Scientific Necessity

- "IRBs should consider the scientific necessity of conducting a clinical investigation in children. It may be more efficient to consider scientific necessity prior to assessing risk and benefit under 21 CFR part 50, subpart D. Children should not be enrolled into a clinical investigation unless their participation is necessary to answer an important scientific and/or public health question directly relevant to the health and welfare of children *(emphasis added).* For example, for products that are being developed for use in adults and children, if effectiveness in adults can be extrapolated to children, then effectiveness studies in adults should be conducted to minimize the need to collect effectiveness data in children." *(draft FDA guidance)*

Two Central 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.

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
- Emancipated minors: **CONTACT OGC**

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 living in a safe environment with prudent parents)*
  - *"The standard of minimal risk should be interpreted as those risks encountered in the daily life of normal, average, healthy children living in safe environments and indexed to the experiences of children of the same age and developmental stage as the subject population"(FDA)*

Risk vs Benefit

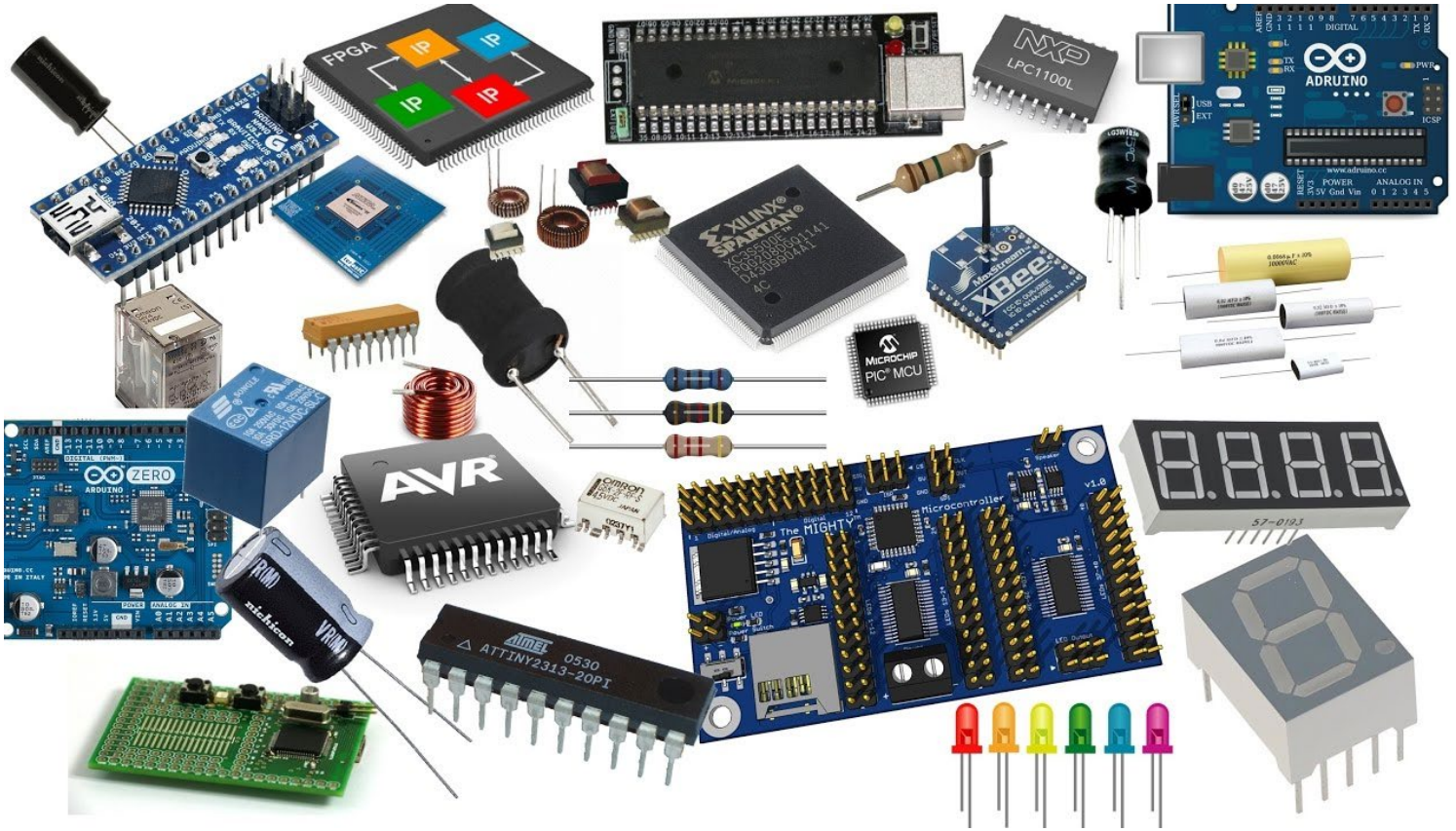
Adults:

- 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



How to review: component analysis

Component analysis is required by the regulations!

- Each population must be considered separately
- Each intervention/procedure must be considered separately
  - "A research protocol, including a protocol studying a pediatric condition, may, and usually does, include multiple research-related interventions or procedures, some that offer *prospect of direct benefit* and some that do not. Any intervention or procedure conducted solely for research purposes and not needed for clinical management or routine clinical care should be evaluated separately to determine whether it offers *prospect of direct benefit* to the enrolled child (known as a "component analysis" of risk). If a specific intervention or procedure does not offer *prospect of direct benefit*, the risk of the intervention or procedure should be limited to a *minor increase over minimal risk,* and meet the other conditions outlined under 21 CFR 50.53 unless the protocol is referred for review, as per 21 CFR 50.54 (see section III.F)."
  - "Failure to carefully evaluate the different components of a clinical investigation may result in an intervention or procedure that does not offer *prospect of direct benefit* exceeding the allowable ceiling of a *minor increase over minimal risk"*

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!

Component Analysis

Identify the populations being enrolled

- Affected children
- Healthy children
- Consider age ranges

Identify each specific intervention/procedure

- Separate drug and placebo
- All interventions/procedures should be considered.
  - Questionnaires, blood draws, biopsy, administration of study drug etc.

Component analysis

For each intervention/procedure determine if there is a prospect of direct benefit.

- If yes, explicitly identify what the benefit is and that it is at least as great as available alternatives

For each intervention, determine the risk level

- Risk: minimal, no more than a minor increase over minimal, > minimal

Do this for each minor population in the study.

Figure out the approval category for the intervention (or that it is not approvable)

Figure out the parent signature requirement

- Overall study is based on the highest individual requirement.

Component analysis

Intervention/procedure	PDB? If yes, identify benefit	Risk (min, > min, minor increase over min)	Approval category	Parent sigs
Insert intervention/procedure here				

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 living in a safe environment with prudent parents)

Examples

- Chart review
- Questionnaires
- Non-contrast MRI (within accepted SAR)
- Blood draws (depending on volume, frequency and child's 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.
- *"Prospect of direct benefit should result from the research intervention or procedure being studied (e.g., the investigational drug or medical device) and not from ancillary interventions or procedures, such as physical exams done as part of the trial" (FDA)*

What is direct benefit?

Tangible, positive outcome that may be experienced by the individual as a result of the research intervention

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, or
- would result in detection of a treatable condition that would not otherwise have been detected

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). Animal data may be sufficient, if adult data is unlikely to establish efficacy in children (certain progressive diseases that begin in childhood).
- *"When evaluating if an intervention or procedure offers a prospect of direct benefit, the IRB should consider whether the evidence establishing proof of concept about a potential beneficial effect is sufficient, and whether the proposed dose (particularly for drugs) and duration of exposure to the intervention or procedure are adequate to offer a potential clinical benefit to the individual child." (FDA)*

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 investigational drug
- Surgical procedure
- Medical device

Who can be enrolled?
- Minors with, or at risk for the disease or condition under study
- 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.

What is a minor increase over minimal risk?

A slight increase over minimal risk that poses no significant threat to the child's overall health or well-being.

Any potential harms with the intervention or procedure should be expected to be transient and reversible and the probability for severe pain, discomfort, or harm should be extremely small or nonexistent.

Consider the setting and the experience level of the investigator when making an assessment as to whether an intervention or procedure meets criteria as

What else?

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

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

> *"For children to be exposed to the level of risk described in 21 CFR 50.53, the children should either have or be at risk for the specific disorder or condition that will be studied in the clinical investigation. Objective or empiric data should support that the condition proposed for study has the potential to negatively impact the child's health and well-being or increase the risk of developing a health problem in the future, as well as that collection of the data will enhance understanding towards prevention, diagnosis, improvement, or treatment of the condition."*

- Institute of Medicine (2004); *Committee on Clinical Research Involving Children, Ethical Conduct of Clinical Research Involving Children*; Field MJ, Behrman RE, editors. Washington DC: National Academies Press. Recommendation 4.3. Available at https://www.ncbi.nlm.nih.gov/books/NBK25542/ (accessed April 29, 2022).

46.406/50.53

>minimal but no PDB

- No more than a minor increase over minimal

Examples

- CT
- MRI with contrast
- Superficial LN bx
- BM Bx
- Non-therapeutic, procedural sedation administered by experienced personnel (consider cumulative risk if more than one)

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
- Administration of placebo to kids via a central venous catheter.

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.

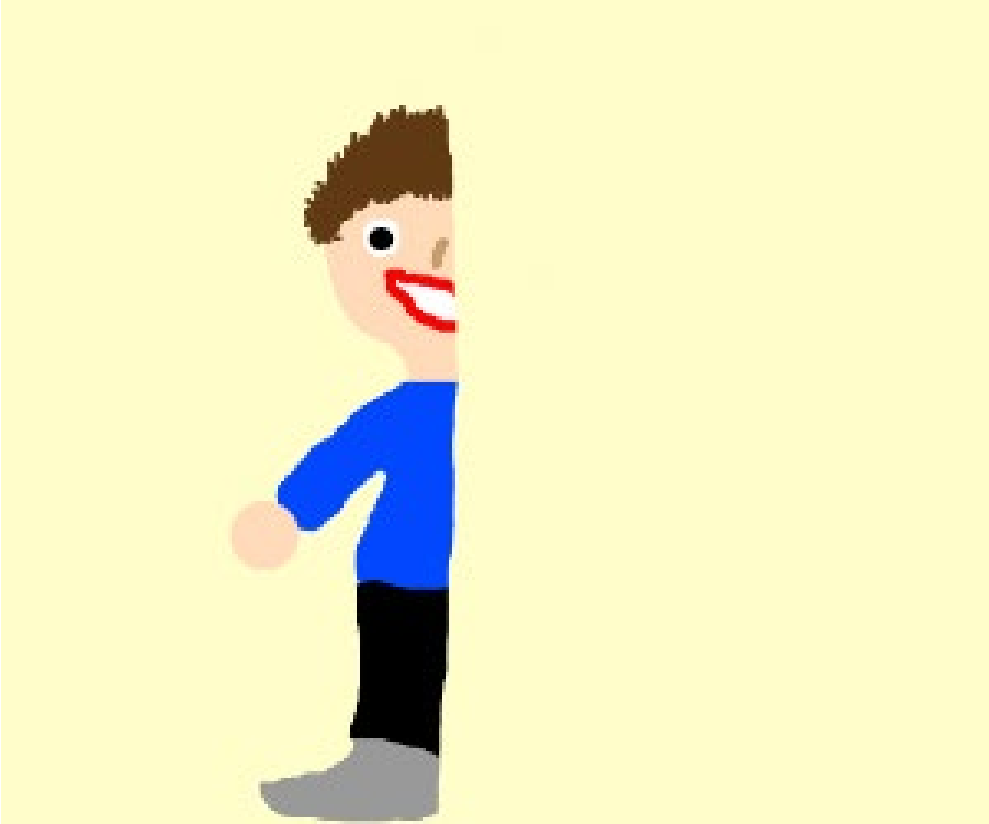
What is not reasonably available?

2nd parent does not have to be physically present

- Electronic means OK

When does 1 mean 2?

Joint custody



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)

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

- Assent waived (very young)
- Oral Assent (young)
- Written Assent
  - Age-appropriate document
  - Actual consent (15 and up?)

Examples

A pediatric cancer study involving:

- Administration of an investigational drug (efficacious in adults for same condition)
- Frequent monitoring of blood levels of the drug, which may require placement of a central line.
- A peripheral LN biopsy procedure after several cycles of treatment for future unspecified research.

Component analysis

- Drug
  - PDB: Yes, drug is efficacious in adults
  - Risk: > minimal due to known adverse effects
- Blood draws
  - PDB? Maybe, if monitoring is necessary to safely administer drug. No, if just for determining PK
  - Risk? Depending on volume and route of drawing, could be minimal, or possibly minor increase.
- Placement of central line
  - PDB: possibly if necessary for safe administration of the drug.
  - Risk: > minimal
- Research biopsy
  - PDB: no, if solely for research purposes
  - Risk: depends on site and potential complications.

Intervention	?PDB	Risk	Approval category	Parent signature
Investigational drug	Yes, possible amelioration of disease	GTMR due to possible AE	405/50.52	1
Blood draw (peripheral vein)	Yes, titration of drug to avoid toxicity	Minimal	404/50.51	1
Placement of central line	Yes, allows for safe administration of drug	GTMR	405/50.52	1
Research biopsy of peripheral LN	No	minor increase over minimal	406/50.53	2

Example 2

A randomized, placebo-controlled study of an investigational drug for treatment of migraines.

Interventions include:

- Oral administration of drug or placebo
- MRI with contrast
- Lumbar puncture to determine changes in a biomarker

Component analysis

Administration of drug

- PDB?
  - Possibly, depends on data, dosing regimen etc
- Risk?
  - almost always > MR for investigational therapies
    - Route of administration (po, iv etc)
    - Known safety data

Administration of placebo

- PDB?
  - Placebo can never impart PDB.
- Risk?
  - Minimal for oral placebo
  - Will known effective therapy be withheld, and if so, what is risk?

Component analysis

MRI and LP?

- Is there PDB?
- What is the risk?

Is it approvable? Under what?

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

Intervention	?PDB	Risk	Approval category	Parent signature
Administration of drug	Yes, relief of migraine	GTMR as investigational drug	405/50.52	1
Administration of placebo	No	Minimal risk	404/50.51	1
MRI with contrast	No	Minor increase over minimal	406/50.53	2
LP	No	Minor increase over minimal	406/50.53	2

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

2 minor populations
- Recipients
  - Affected children with immunodeficiency
- Donors
  - Healthy children

Procedures
- Recipients
  - Conditioning chemo regimen
  - Infusion of donor cells
  - Lots of labs
  - Lots of imaging
  - Post txp IS
- Donor
  - labs
  - Stem cell/Bone Marrow Harvest
  - Aliquot of cells for future lab research

Recipients

GTMR with prospect of direct benefit

approvable under 46.405/50.52

Solution for donors

Separate clinical from research

- Donors are not being studied
- But must be in a protocol at NIH

Minor donors are healthy children therefore any research must be minimal risk

- Only research intervention is analysis of an aliquot of collected cells

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

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