

# **Ethics of Research with Children**

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# Overview

- Conceptualize pediatric research within the ethically acceptable and scientifically sound pediatric research within the framework described by Drs. Emanuel, Wendler, Grady, and Killen.
- Discuss some of the “up front” considerations that inform ethically appropriate and scientifically sound pediatric research.
- Orientation is towards judicious inclusion of children in research.

# Ethical Framework

Emanuel, Wendler, Grady, JAMA May 24/31, 2000;283(20):2701-11.

Emanuel, Wendler, Killen, Grady, JID March 1, 2004; 189:930- 7.

- Scientific/social value
- Scientific validity
- Fair subject selection
- Favorable risk/benefit ratio
  - Risk minimization
- Independent review
- Informed consent
- Respect for enrolled subjects (e.g., opportunity to withdraw, privacy protection)
- Collaborative partnerships (e.g., community, researchers, health policy makers)

## **Scientific/social value**

*Emanuel, Wendler, Grady*

- “Clinical research evaluates a diagnostic or therapeutic intervention that could lead to improvements in health or well-being [for the subject] or increases knowledge [for public health or other individuals with the disorder or condition under study].

# Scientific/social value

- Although multi-site pediatric oncology research dates back to the 1950's, children have long been identified as “therapeutic orphans” (Harry Shirley, M.D., 1963). [General orientation towards exclusion of children from research to **protect them from research-related risks**]
- 1977, National Commission issued *Report and Recommendations on Research Involving Children* (basis for current federal regulatory structure).
- 1970's-early 2000's: American Academy of Pediatrics through published guidances, FDA through regulations, and Congress through legislation sought to encourage pediatric research.
- **But . . .**
- Roberts, et. al., “Pediatric Drug Labeling: Improving the Safety and Efficacy of Pediatric Therapeutics,” JAMA August 20, 2003; 290(7):905-11:
  - “Only 1/3 of drugs used to treat children have been studied adequately in the population in which they are being used and have appropriate use information on the product label.
  - “For the other 2/3 of drugs, information regarding safety and efficacy for pediatric patients is insufficient or absent.”
  - As a result, children were **exposed to medication risks** in the clinical setting, that is, from off-label use. [n=1]

## Scientific/social value

- Major changes in laws and regulations governing FDA drug approvals in children:
  - FDA Regulations, Additional Safeguards for Children in Clinical Investigations, 2001
  - “Carrot and stick” approach to encouraging/requiring pediatric research
  - Best Pharmaceuticals for Children Act, 2002
  - Pediatric Research Equity Act, 2003
  - National recognition of the critical importance of pediatric research is coupled with a consensus that children are a vulnerable group in need of additional protections.

## Scientific validity

- Emanuel, Wendler, Grady: “To be valuable, clinical research must be conducted in a **methodologically rigorous** manner.”
- 21 CFR 314.126(a): “The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease placebo effect, or biased observation.”
- 21 CFR 314.126(a): “Reports of **adequate and well-controlled** investigations provide the primary basis for determining whether there is ‘substantial evidence’ to support the claims . . . .”

# Scientific Validity

*21 CFR 314.126(b)(1) & (b)(2)*

- A study design must use a valid comparison with a control to provide a quantitative assessment of drug effect:
  - Placebo concurrent control
  - Dose-comparison concurrent control
  - No treatment concurrent control
  - Active treatment concurrent control
  - Historical control



## Scientific validity

- Pediatric studies must conform to the same scientific rigor as studies enrolling adults.
- (From a regulatory standpoint, placebo-controlled studies are not the only acceptable study design.)
- A key question is whether it is necessary to enroll children in research to meet the objectives of the research, and if so, when along the development trajectory children should be enrolled?

## Scientific validity

- Pediatric studies pose scientific, ethical, practical, regulatory and legal challenges.
- Avail yourself of early input from FDA-regulated clinical investigations involving children.
- Guidance for Industry:
  - Formal Meetings Between Sponsors or Applicants, 2009 (related to the development and review of drug or biological products)
  - Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff, 2014

## **Fair subject selection**

*Emanuel, Wendler and Grady*

- “Scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects.”

# Scientific necessity

- Derived from the requirement for equitable subject selection
- Children should not be enrolled in research unless their participation is necessary to answer an important scientific question about their health or other children with the disorder/condition.
- Hierarchical enrollment, if possible:
  - Subjects capable of informed consent, i.e., most adults, should be enrolled prior to children. Children capable of assent should be enrolled prior to children who cannot assent.
  - There may be a trade-off between enrolling a less vulnerable population and obtaining the most useful and interpretable data. This needs to be adjudicated on a case-by-case basis.
- Enrolling children in research partly depends on:
  - Disease characteristics under study;
  - Whether the disease/condition occurs in adults and how its manifestation compares to that in children;
  - Ability to obtain useful and interpretable data;
  - Scientific objectives of the research.

## Scientific necessity

- Consider the ability to extrapolate efficacy from adults with supporting PK, dose-response, safety studies in children if the course of the disease and the drug effects are sufficiently similar in adults and pediatric patients.

## **Favorable risk/benefit ratio**

*Emanuel, Wendler, Grady*

- Potential benefits are enhanced
- Risks to subjects are justified in relation to the benefits
- Risks are minimized, as possible

# **Additional Safeguards for Children in Clinical Investigations**

*21 CFR 50, Subpart D, 45 CFR 46, Subpart D*

- 50.51, 46.404: Not involving greater than minimal risk
- 50.52, 46.405: Involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects
- 50.53, 46.406: 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

## **Basic regulatory framework (based on recommendations of the National Commission)**

- Absent a prospect of direct therapeutic benefit to the enrolled children, their risk exposure must be minimal or a minor increase over minimal risk, or;
- The research risks must be justified by anticipated direct benefits to the children; the relation of the anticipated benefits to the risks is at least as favorable as any available alternatives, or;
- The prospective research can be referred to a federal expert panel for public deliberation.



# Additional Safeguards for Children in Clinical Investigations

*21 CFR 50, Subpart D, 45 CFR 46, Subpart D*

- 50.54, 46/407: Clinical investigation not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children
- Process for Handling Referrals to FDA under 21 CFR 50.54
  - <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127605.pdf>

## **Minimal risk**

*21 CFR 50.3(k), 45 CFR 46.102(i)*

- The probability and magnitude of the harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

## Many of the key terms in Subpart D have no regulatory definitions

- Minor increase over minimal risk
  - Greater than minimal risk
  - More than minimal risk
  - Disorder or condition
  - Reasonably commensurate
  - Vital importance
- 
- Debate and variability in the implementation of Subpart D continues.
  - Given the recommendations of NHRPAC, SACHRP, the IOM, and many others, progress has been made.

## Understanding risk

- Risk should be assessed in terms of:
  - Cumulative (types of interventions, times repeated)
  - Magnitude
  - Probability
  - Frequency
  - Severity
  - Duration
  - Age-graded
  - Special population (recognizing the heterogeneity of the pediatric population)
  - Equivalence to the daily lives or experiences in routine physical or psychological examinations
  - Commensurability/comparability to experiences already familiar to the children being studied
- If there is a dearth of clinical data, it will be difficult to assess risks to children from an investigational product.

# Understanding risk

- SACHRP and IOM: The definition of minimal risk should be in relation to a normal, average, healthy child living in a safe environment. (Uniform standard)
- Freedman, et. al.: “The concept, ‘risks of every day life,’ has normative as well as descriptive force . . .”
- Identification and quantification of risks (Wendler, Emanuel)
- Risks a “scrupulous parent” would assume (Nelson, Rossi)

## Benefits

- Directly to the individual child
  - The placebo arm of a trial cannot be considered to confer the prospect of direct benefit.
- To other children with a similar disease/condition through accrued knowledge
- To public health
- Collateral (bundled interventions that offer a benefit but are unrelated to the research intervention under study, e.g., access to medical care, monitoring). These interventions should not be considered when assessing the risk benefit ratio of the research.

# Independent review

- Emanuel, Wendler, Grady: Unaffiliated individuals must review the research and approve, amend or terminate it.
  - Diminish conflicts of interest
  - Improve accountability
  - Fulfill a fiduciary responsibility
- Many entities that oversee research (e.g., IRB, ERC, DMC, granting agency, scientific review committee, endpoint adjudication committee)
- Pediatric expertise should be included, either through membership or as an ad hoc consultant (See, for example, 21 CFR 56.107(a), 45 CFR 46.107(a))

## **Informed consent (parental permission and assent)**

- Emanuel, Wendler, Grady: “Provision of information to subjects about purpose of the research, its procedures, potential risks, benefits and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate.”
- Ongoing process throughout the life-cycle of the study; more than a signature on a form.



## Parental permission and assent

- If a child is to be enrolled in research, a parent(s) or guardian must provide permission, with the assent of the child when appropriate.
- Subpart D has specific requirements regarding parental permission and assent.
- FDA and HHS hold parental permission processes to the same ethical and regulatory standards as informed consent processes for adults with intact decisional capacity.

# Assent

- Assent means the child's affirmative agreement to take part in the research, not just the failure to object.
- American Academy of Pediatrics has stated that, "assent should be obtained from any child 7 years of age or older . . ."
- Subpart D: In determining whether children are capable of providing assent, the IRB must take into account:
  - Age
  - Maturity
  - Psychological state
- *Important exception*: The assent of children is not a necessary condition for proceeding with research if the intervention or procedure involved in the research holds out the 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. 21 CFR 50.55(c)(2), 45 CFR 46.408(a)
- Developmentally appropriate process and forms (if used)
  - Assent should not consist of a child signing the parental permission form
- Laws (state and international) governing the definition of "child", mature minor, emancipated minor vary, requiring additional awareness when conducting multi-site or multi-national pediatric research
- IOM Recommendation 5.6: ". . . create an assent processes that consider and respect the child and the family as a unit as well as individually . . ."

## **Respect for potential and enrolled subjects**

- Emanuel, Wendler, Grady: “Individuals must continue to be treated with respect from the time they are approached throughout their participation and even after their participation ends.” (e.g., right to withdraw, respect for privacy, provision of new information)
- Poses challenges as research becomes more complex:
  - How, for example, should informed consent be addressed for future use of stored biospecimens when pediatric research subjects reach the age of majority?

## Collaborative partnerships

- This ethical principle was originally described by Emanuel, Wendler, Killen and Grady in the context of research in developing countries.
  - “Develop partnership with researchers, makers of health policies and the community”
  - “Involve partners in sharing responsibilities for determining the importance of health problem, assessing the value of research, planning, conducting, and overseeing research, and integrating research into the health-care system.”

## Collaborative partnerships

- Important concept that should be applied broadly. For example, partnering with disease-based advocacy groups and foundations to help inform:
  - Study design (e.g., would a placebo-control be acceptable?)
  - Study endpoints and long-term outcomes (e.g., what symptoms or outcomes are of greatest concern?)
  - Risk-Benefit ratio (what risks are tolerable to you?)
  - Storage of biospecimens for future research
  - Importance of natural history studies
  - Best methods for recruitment and retention

# In conclusion . . .

- General consensus about the critical importance of pediatric research
- Shifted paradigm from exclusion to judicious inclusion:
  - FDA's Office of Pediatric Therapeutics, New Pediatric Labeling Information Database lists 526 pediatric studies done between 1998-2004. Many of them have an accompanying labeling change.
  - <http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase&displayAll=true>
- Ethics have evolved from paternalism and nonmaleficence to justice (in receiving adequately evaluated therapies) and beneficence.
- Nonetheless, protectionism appropriately persists, as does the debate about how to best protect children in research.
- On an optimistic note, the more pediatric research is conducted in a scientifically sound and ethically acceptable manner, the more sophisticated we can become in designing such research and the more we can hone our ethical judgment about when and how children should be included as research subjects.

## **Suggested references pertaining to scientific validity and/or necessity**

- Final Guidance, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998
- ICE E-9, Statistical Principles for Clinical Trials
- ICH E-10, Choice of Control Group in Clinical Trials
- ICH E-11, Clinical Trials in Pediatric Population
- Draft Guidance, Adaptive Design Clinical Trials for Drugs & Biologics, 2010
- Draft Guidance, Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs & Biological Products, 2012

## Additional references

- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Research Involving Children (Washington, DC: Government Printing Office, DHEW publication no. (OS) 77-0004) 1977.
- National Human Research Protections Advisory Committee:
  - <http://www.hhs.gov/ohrp/archive/nhrpac/nhrpac.htm>
- NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects, 1998
  - <http://grants.nih.gov/grants/guide/notice-files/not98-024.html>
- Field & Behrman Editors, Ethical Conduct of Clinical Research Involving Children, Institute of Medicine of the National Academies, The National Academies Press, Washington, D.C., 2004.
- SACHRP, Subcommittee on Research Involving Children:
  - <http://www.hhs.gov/ohrp/sachrp/subcommittees/index.html>



## Additional references

- American Academy of Pediatrics Committee on Drugs, Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations, Pediatrics July 1977;60(1):91-101.
- American Academy of Pediatrics Committee on Drugs, Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations, Pediatrics February 2, 1995; 95(2):286-94.
- American Academy of Pediatrics Committee on Bioethics, Informed Consent, Parental Permission, and Assent in Pediatric Practice, Pediatrics February 2, 1995; 95(2):314-7.
- Society for Adolescent Medicine, Guidelines for Adolescent Health Research: A Position Paper of the Society for Adolescent Medicine, Journal of Adolescent Health November 2003; 33:396-409.

# Thank you

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