Key Ethical Issues in Research with Children

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Disclaimer

The views expressed in this talk are my own. They do not represent the position or policy of the NIH or US government.

Readings and Case

Smyth. Arch Dis Child 2007;92(10):835-7.

Wendler, Glantz. J Pediatrics 2007; 150:579–582.

Who is a Child?

- Legally and culturally who is a child varies from place to place. In the US, it is typically individuals under 18 years of age.
- Because children cannot consent, enrolling them in research raises important ethical issues.

Key Issues

1. Is the research valuable?
2. Is there a good reason to enroll children?
3. Prospect of benefit to participants?
4. Is non-beneficial pediatric research ethical?
5. What level of (net) risk is acceptable?
6. Parental permission
7. Pediatric assent and objections

#1: Is the Research Valuable?

Science and Ethics

- Some think the social value of trials is irrelevant to, or in tension with ethics.
- In fact, social value is a requirement of ethical research and is especially important for pediatric research.

Emanuel, Wendler, Grady. JAMA 2000; 283:2701-2711

Practice

- There is significant concern regarding the risks of pediatric clinical trials.
- In contrast, there may be insufficient concern regarding the value of the trials.
- Do not enroll children unless the research is valuable!

Study and Interventions

- Each research intervention included in the study should have social value.
- The study as a whole should have important social value.

Empirical Data (177 pairs; RR=95.2%; 13-18 yo)

- Vast majority of teens and parents felt that the adolescents were making an important contribution to help others.
- 80.8% of the adolescents felt proud to be participating in research to help others.

Wendler et al. Pediatrics 2012; 130:692-699

Key Questions

- How to determine prospectively whether a given study has important social value?
- How to decide which research to prioritize? Let scientists be scientists? Most common conditions? Most deadly?

#2: Reason to Enroll Children?

Compelling Reason Enroll Minors?

- Do not enroll children in research that can be conducted equally well with adults.
- Example: First study of a new drug for a condition that affects adults and children.
- When to initiate pediatric studies depends on the circumstances.

When Enroll Minors: New Agents

- Diseases with sufficient treatment: start pediatric trials of new agents after phase III in adults.
- Diseases without sufficient treatment: start pediatric trials of new agents after phase II in adults.

Confederation European Specialists in Peds. Eur J Pediatr 2004; 163: 53-57

Key Questions

- Is it acceptable to begin pediatric trials earlier for conditions without sufficient treatment and significant morbidity or mortality?
- What about studies of conditions that differ between adults and children (type 1 diabetes?)?

Not all Children are the Same

- Most teenagers (14-18 yo) are able to understand clinical research.

Ondrusek et al. J Med Ethics. 1998;24:158-165.

- These data suggest that research with teens raises less ethical concern than research with younger children.

Implementation

- When possible, enroll children over age 14 before younger children.
- For studies that raise greater concern: evaluate individual children to ensure they understand the study in question.

#3: Prospect of benefit to participants?

Components Analysis

- Clinical trials are composed of different elements or interventions.
- Evaluate the risk-benefit profile of each intervention, and then the risk-benefit profile of the entire study.

Prospect of Benefit

- Do the potential benefits for subjects of the intervention justify its risks?
- If yes, is the risk-benefit profile of the intervention at least as favorable as the available alternatives?

Wendler. J Peds 2008; 152:467

Key Question

- What does it mean for the potential benefits to justify the risks?
- Consider whether enrolling in the study and undergoing each intervention is in the child's clinical interests: If it is, the potential benefits justify the risks.

#4: Is Non-beneficial Pediatric Research Ethical?

Non-beneficial Pediatric Research

- The biggest disagreement for the US National Commission was whether non-beneficial pediatric research is ethical.
- This disagreement continues, with many people arguing that it is unethical to enroll children who cannot consent in 'non-beneficial' research.

Survey Data (N=100; RR=45%; N=89; RR=74%)

- Pediatricians and researchers: 47% in UK, 59% in Canada believe non-beneficial pediatric research is unethical.

  Sammons. Eur J Clin Pharmacol 2007;63:431-36

- Canadian medical students: 49% agree children "should only participate in trials from which they receive a direct benefit.

  Wang. J Pop Therapeutics Clin Pharm 2007;18:e10-e16

Charitable Activities

- Most agree that it can be acceptable to expose children to low risks to help others in daily life (charity car wash, collect money for hurricane victims).
- This suggests it can be acceptable to expose children to some risks to benefit others. Are research risks different?

Research and Charitable Activity

(N=177 pairs; response rate=95.2%; 13-18 yo)

View	Teens	Parents
Equally willing	128 (72.3%)	155 (87.5%)
Prefer Research	26 (14.7%)	10 (5.5%)
Prefer Charitable Activity	21 (11.9%)	6 (3.4%)

Wendler et al. Pediatrics 2012; 130:692-699

Implications

- These data support the view that non-beneficial pediatric research can be acceptable when it has important social value, and net risks are sufficiently low.
- Make subjects into participants!

#5: What Level of Net Risk is Acceptable?

Absolute Risks

- It is difficult to evaluate absolute risks.
- Is a risk of 1 in 7,312 of a child experiencing a bone fracture acceptable?
- Many regulations direct IRBs/RECs to compare the risks of research to the risks children face in activities in daily life.

Minimal Risk: Definition

"Minimal risk means that the probability and magnitude of 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"

45CFR46

Problem

- The risks of many activities in daily life are acceptable because they offer potential benefits to participants (e.g. surfing)
- These risks do not provide a standard for evaluating the risks of non-beneficial research.

Wendler. Hastings Cen Rep 2005; 35:37-43

Charitable Participation Standard

Proposal: Compare risks of non-beneficial interventions to the risks of appropriate activities designed to benefit *others*

Examples: Weeding neighbor's garden; car wash; Putting child in car to drive neighbor

Wendler, Glantz. J Peds 2007; 150:579-582

#6: Parental permission

Require Parental Permission?

- Typically, children should be enrolled in research only when a parent (guardian) gives their permission.
- Parental permission can be waived when the IRB/REC determines it is not an appropriate safeguard (e.g. minimal risk research or research on child abuse).

Number of Parents

- Permission of one parent is typically sufficient for research that poses minimal risk or offer a prospect of benefit.
- For more controversial research, may require the permission of both parents (if available).

#7: Pediatric Assent and Objections

US Regulations

- With a few exceptions, most regulations require the assent of children who are capable of providing assent.
- In making this determination, IRBs should take into account the "age, maturity and psychological state of the children."

Assent

- Prospective and explicit agreement of a child to a proposal to do something or have something done to them.
- To be able to assent, individuals must have some understanding of their circumstances, the proposal, and the future.

Objections

- Objections involve statements or other forms of communication that one does not like what one is doing or experiencing.
- Objecting to what is happening does not require understanding and may result from not understanding.

Current Debate

- Wide disagreement over age or level of maturity at which children can assent.
- Some argue assent should be obtained from 3 year olds. Others argue assent is inappropriate because parents should decide for their children.

The Age Threshold

- Many groups, including U.S. National Commission and American Academy of Pediatrics, argue children become capable of assent at age 7.
- US COG group argues investigators should solicit the views of all children older than toddlers, and require assent from children older than age 9.

Respect for Autonomy

- Asking for a child's view and then ignoring it because they do not understand is problematic.
- This suggests that assent should be required when children are able to understand, typically age 14.

Non-Maleficence

- Children should not be exposed to greater than minor distress or risk.
- This implies that the sustained objections of *all* children should be respected, at least in the context of non-beneficial research.

Implementation

- Provide age appropriate information.
- Assent required: Ask if willing to participate.
- Assent not required: Ask if any questions or concerns. Proceed while monitoring the child. If objections, stop, assess, and address.

Together or Separate?

	My choice	Maybe/ No
Parent/family member in room	17	10
Alone in room	24	3

Of the participants who stated it was not or may not have been their choice: All stated they were glad they participated, except two who stated 2 "maybe" glad.

[N=70, RR=74%,11-19 yo, mean 13.7 yo, mostly AA males]

Together or Separate?

- 64 child/parent pairs randomized to either joint or separate consent/assent process.
- No difference in willingness to participate. However, significantly greater knowledge of the trial in parents and older children who were separated.

Annett et al. http://dx.doi.org/10.1080/23294515.2016.1251507

Information

- It is important to have a plan and to explain to parents and children what information will be shared with the other party.
- Child tells researchers he hates his parents? Says she sometimes does not go to school? Pregnancy test positive?

Summary

- Pediatric research raises important ethical issues.
- Data and analysis can help to protect children in a way that does not block valuable and appropriate research.

Apharesis Case

Non-beneficial research acceptable?
Net-risks low enough?
Parental permission sufficient?
Assent required?
Encouragement acceptable?
Payment appropriate?