Key Ethical Issues in Pediatric Research

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5 Key Ethical Issues

- Importance of pediatric research
- Is ‘net-risk’ pediatric research ethical?
- Evaluating risks
- Assent
- Compensation

Importance of Pediatric Research

Background

- Informed consent is one of the key ethical safeguards for clinical research.

- To protect individuals who cannot consent, some regulations and guidelines prohibit their enrollment.

Implications

- This approach offers individuals important protection from exploitation and excessive risks.

- However, it also bars individuals who cannot consent from research that might benefit them and undermines research on conditions which affect them.

Current Situation

- Up to 2/3 of interventions used in children have not been systematically evaluated in them.

- But: children are not just little adults.

The Need

- To improve pediatric care, it is critical to conduct pediatric research.

- This raises the need for ethical guidance to ensure pediatric research is conducted appropriately.

Is Net-Risk Pediatric Research Ethical?

Prospect of Benefit

It is widely agreed that pediatric research can be ethical when it has important social value and it offers participants a prospect of benefit:

- The potential benefits for participants justify the risks.
- The risk-benefit profile is at least as favorable as the available alternatives.

Wendler. J Peds 2008; 152:467

‘Net-risk’ Pediatric Research

- The biggest disagreement for the US National Commission was whether it is ethical to enroll children in research when the risks exceed the potential benefits to participants (e.g. purely research blood draw or biopsy).

- This debate continues.

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

Assessment

- US and many other regulations try to address this concern by stipulating that the net risks of pediatric research should not be significantly greater than the risks ordinarily encountered in daily life.

- Yet, many risks in daily life are accepted because the activities benefit the participants (e.g. snow skiing).

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

Charitable Activities

- Compare risks of research to risks of activities designed to benefit others.

- Charity car wash, charity basketball game, shoveling neighbor's sidewalk.

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

- Are the risks of clinical research and charitable activities ethically similar?

Research versus Charitable Activity

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

US Public

- The US public considers net-risk pediatric research appropriate when it has important social value and the risks are not excessive.

- Higher risks supported for research with greater social value.

Schupmann et al. Pediatrics 2022;149(1):e2021052687

Why?

Wendler. The Ethics of Pediatric Research, 2010

Evaluating Risks

Belmont Report

- "Systematic, nonarbitrary analysis of risks and benefits should be emulated insofar as possible."

- "The nature, probability and magnitude of risk should be distinguished with as much clarity as possible."

- "Assessment of risks and benefits requires careful arrayal of relevant data.

Pediatric IRB Chairpersons

(N=188; response rate=84%)

	Minimal Risk (MR)	Minor Inc over MR	> Minor Inc over MR
10 cc Blood Draw	81%	17%	1%
Allergy Skin Testing	23%	43%	27%
Lumbar Puncture	6%	32%	56%

Shah, Whittle, Wilfond, Gensler, Wendler. *JAMA* 2004; 291:476-482

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

Misinterpretation #1

- Whether a procedure is minimal risk does not depend on whether children ordinarily encounter the procedure in daily life.

- Example: Reiki

- Instead: compare the level of research risks (probability of magnitude and harm) to the level of risks in daily life.

Misinterpretation #2

- Whether a procedure is minimal risk does not depend on whether it poses any chance at all of significant harm.

- Instead, the chances of significant harm must be very low.

SERR

To do better, we need to go beyond intuitions:

1) Data on the risks of the research procedure
2) Data on the risks of charitable activities
3) A way to compare the two

Rid, Emanuel, Wendler. JAMA 2010; 304:1472–1479

Pediatric Assent

US Regulations

- Require the affirmative agreement (assent) of children who are capable of providing it.

- In making this determination, IRBs should take into account the “age, maturity and psychological state of the 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 (rule of 7s?).

- US COG group argues investigators should solicit the views of all children older than toddlers, and require assent from children older than age 9.

(Old) IRB Practice

- 54% of U.S. IRBs leave the decision of which children are capable of assent to the judgement of the investigators.

- The remainder use an age cutoff: 22% use age seven; 9% use age 5 or 6; 18% use age 8-12.

Whittle, et al. Pediatrics 2004; 113:1747-1752

Appropriate Respect

- Asking children to make decisions they do not understand is problematic.

  Wendler Shah. doi: 10.1162/1526516033226143 82

- This suggests assent should be required when children are able to understand research, typically ages 12-14.

  Hein et al. doi: 10.1186/s12910-015-0067-z

Informing and Consenting/Assenting

- US regulations and many IRBs tether together informing individuals and obtaining their agreement.
- One result: all information individuals need is provided in the consent form (e.g. Tuesday 2pm).
- Another result: If individuals are not being asked for consent or assent they are not given any information.

Implementation

- Provide age appropriate information to all children, whether they are being asked for assent or not.
- If assent required: Ask if willing to participate.
- If assent not required: Ask if any questions or concerns. Proceed while monitoring the child. If objections, stop, assess, and address.

Compensation

Concerns

- "Rather than advising parents to keep children away from pesticides, the government is paying them to poison their children" (The Rutherford Institute).

- "Parents, whether improperly enticed by trinkets, food stamps, money or other items, have no right to place children in nontherapeutic research." (*Grimes v KKI*)

Isolating the Concern

- Many objections to payment for pediatric research reflect concerns about the research.

- IRBS need to make sure the research is appropriate: valuable, acceptable risks, etc.

Ensure Appropriate Risks

- If the inclusion/exclusion criteria don't ensure acceptable risks for all participants, require individualized assessment.

- Is payment for children's participation problematic in research that meets the ethical conditions?

5 Types of Payment

- Reimbursement (for expenses)
- Compensation (for burdens, risks, injury)
- Appreciation (for contribution)
- Incentives (to enroll and continue to participate)
- Profit sharing

Wendler et al. J Peds 2002; 141(2):166-171

Some Payments Obligatory?

- Reimbursement and compensation remove barriers to research enrollment.
- Also, subjects should not have to bear costs to contribute to the social good.
- Hence, reimbursement and compensation may be obligatory.

Reason for Incentives

- In some cases, removing barriers through reimbursement and compensation does not yield sufficient enrollment.
- In these cases, there are ethical reasons to facilitate socially valuable research.
- Incentives can be a means to promote this goal.

Concerns over Incentives

- Payment beyond costs raises the potential for parents to make money off children's enrollment.
- Assuming the research is ethical, small incentives to parents can promote valuable research without raising concern of exploitation.
- AAP: 'token' payments to parents (1995); 'minimal' payments (2010)

IRB Safeguards

- Assuming the research is appropriate: some incentives to parents can be acceptable.
- Consider potential for idiosyncratic risks or concerns.
- Develop ways to ensure payments for minors go to minors (e.g. gift cards).

Summary

- Pediatric research has important social value.
- It also raises important ethical concerns.
- Careful IRB evaluation and involvement of ethical researchers offers a way to permit valuable research while addressing the ethical concerns.