

Stanley Manne Children's Research Institute™

Ethical Inclusion of Children in Research

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Ethical and Regulatory Aspects of Clinical Research

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Pritzker School of Law, *by courtesy*



Motivation for pediatric research

- Tremendous need to find the right treatments and dosages for children, given that children are not small adults.
- * Approximately 75% of drugs prescribed to children have not been tested in children, even for basic safety and efficacy.



Overview

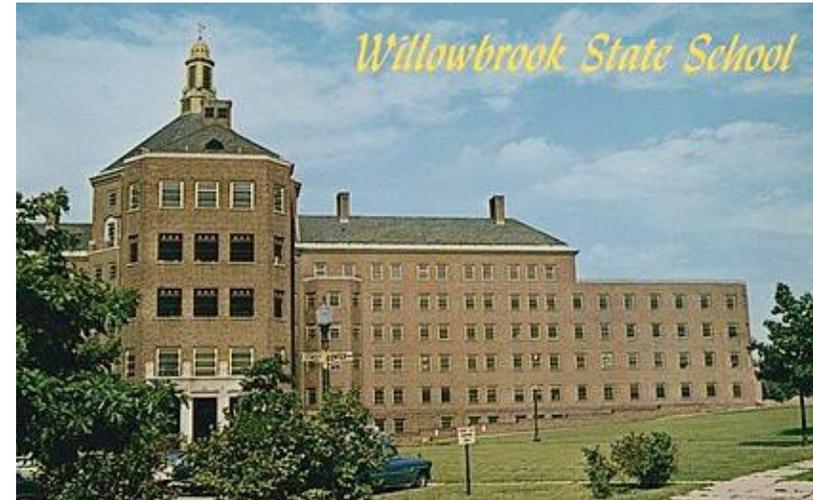
1. When to enroll children in research
2. Risks/benefits
3. Assent/consent

1. When to enroll children in research



When to enroll children in research: Missteps

- Many historical examples of children being enrolled in risky research before adults without good reason



When to enroll children in research: Missteps

- And there are also many examples of children being left behind



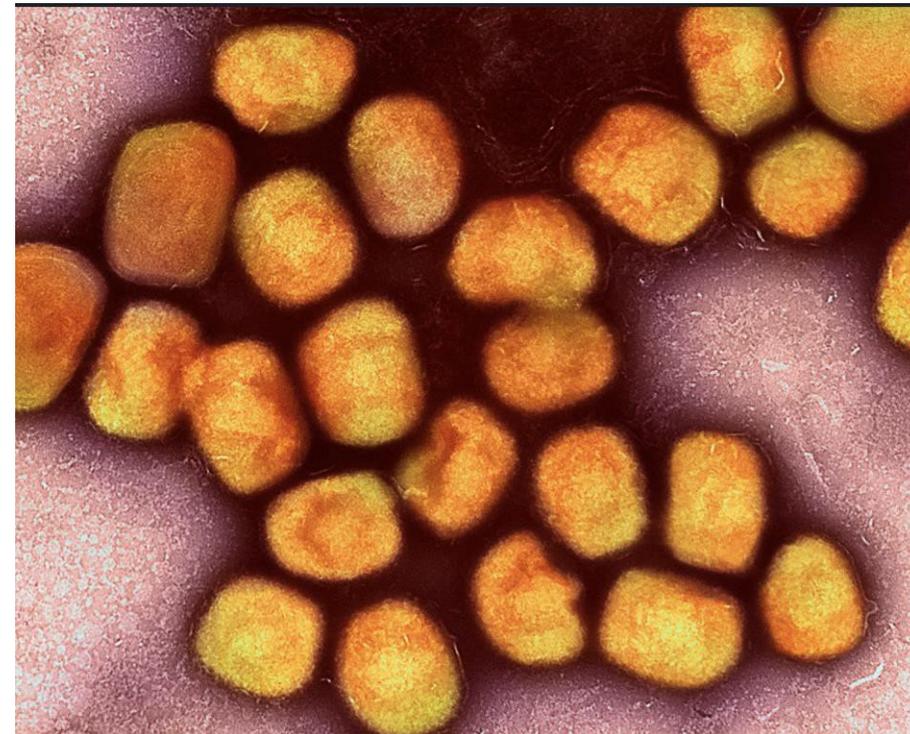
Enrolling Minors in COVID-19 Vaccine Trials

Kevin Mintz, PhD, E Jardas, BS, [...], and David Wendler, PhD

[Additional article information](#)

Abstract

It is widely agreed that an effective response to the coronavirus disease 2019 pandemic needs to include a vaccine that is safe and effective for minors. However, many current vaccine trials have no plans for when to enroll minors. Others have recently proposed enrolling minors as young as 12 years old. This lack of a systematic approach raises 2 concerns. Waiting too long to enroll minors could unjustly deny minors and their families the benefits of a vaccine and has the potential to delay an effective response to the pandemic by a year or longer. At the same time, enrolling minors too soon runs the risk of exposing them to excessive risks. With these concerns in mind, in the present



When to enroll children in research: How to think about it

- First question: Who is a child?
- Legally and culturally, who is a child varies from place to place
- Typical definition: Children are too young to give their own consent legally

Reasons to first study adults

- Children generally more vulnerable to harm than adults; better not to expose them to unknown risks
- Children cannot give their own consent and protect their own interests
- Greater potential for litigation or controversy if something goes wrong in a pediatric trial

Reasons to enroll children sooner

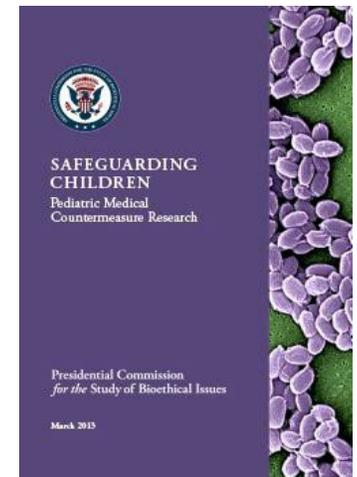
- Children can receive important benefits from research, especially if few alternatives
- Some diseases or conditions only affect children, or affect children differently
- Delay in pediatric testing may delay licensure or availability of the tested intervention

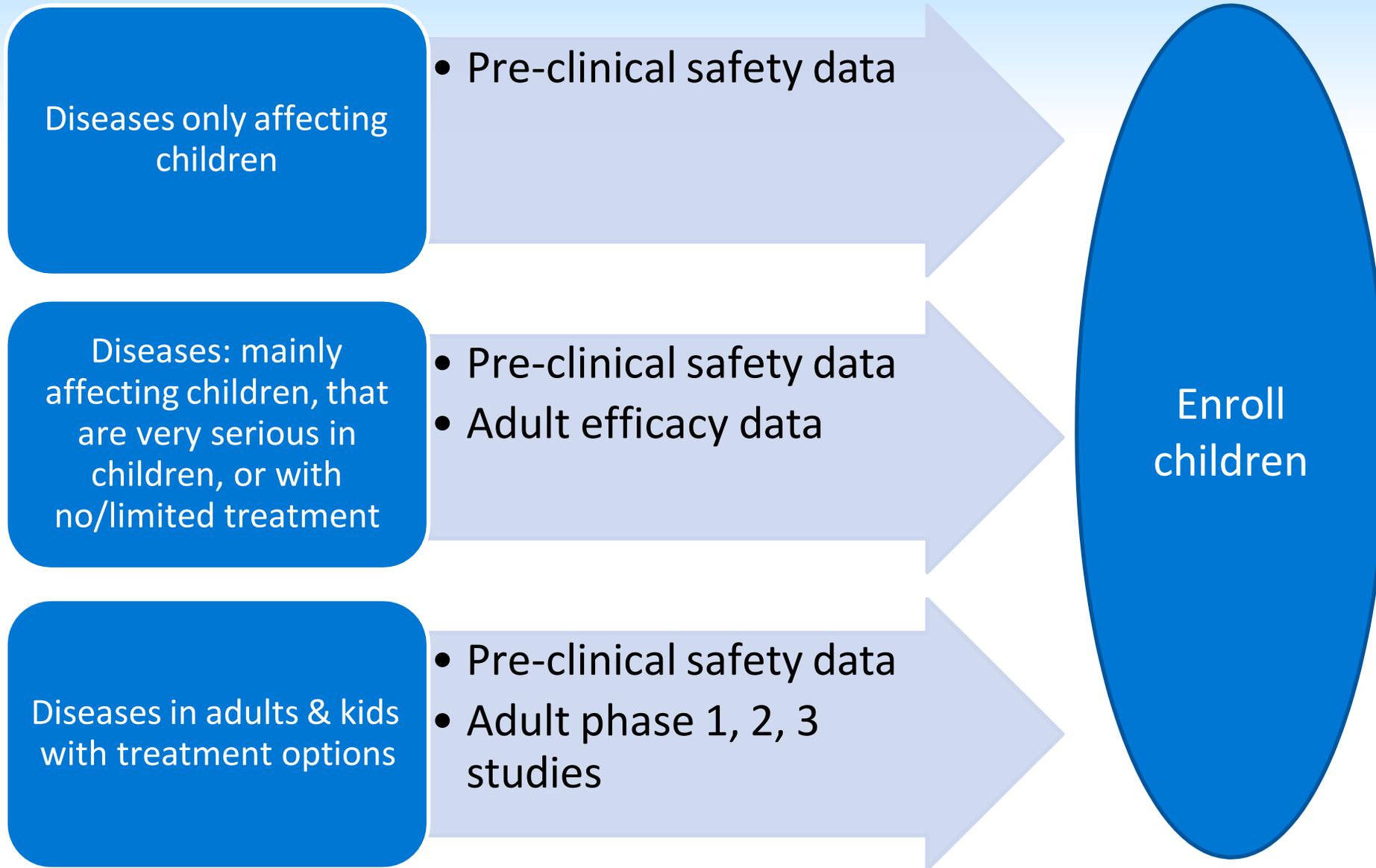
Ethical guidance

- CIOMS (2016): Adults first in all cases
- Declaration of Helsinki (2013): People who can't consent should not be in research unless:
 - Prospect of direct benefit or
 - Research is designed to promote health of the group, involves minimal risk/burden, cannot be performed with people who can consent

Age de-escalation

- Many groups recommend age de-escalation as additional protection for risky pediatric research
- Open questions about whether it is always an appropriate protection
 - E.g., FDA decision about emergency use authorization of COVID vaccines to children under 5





Confederation of European Specialists in Pediatrics, Eur. J. Pediatr. (2004) 163: 53-57.

Helpful, but....

- Fails to incorporate public health considerations for vaccinating children
- Don't focus directly on the risks/benefits, importance of the research, or differences between prevention and treatment
- In regulations and ethical analysis, may make more sense to focus on risk/benefit of research, given available alternatives

2. Risks and benefits



International regulatory frameworks

- Most regulations, including the Council of Europe, Uganda, CIOMS, British MRC, Canada Tri-Council, Australia and South African MRC, permit pediatric research:
 1. That offers a prospect of benefit, or
 2. That poses “minimal” risk



U.S. Federal Regulations: 4 categories of protection

U.S. Federal Regulations: 45 C.F.R. 46, Subpart D

1. Minimal risk
2. Prospect of direct benefit that outweighs risk
3. Minor increase over minimal risk, no prospect of direct benefit
4. Anything else that is approved by special panel

Definitions

- Minimal risk: risks of daily life, or of routine exams or tests
- No definition for a “minor increase over” minimal risk in regulations

Survey of U.S. IRB Chairpersons (%; N=188)

Procedures performed in healthy 11 year olds

		MR	> MR
10 cc Blood Draw	?		?
MRI		?	?
Survey Sexual Activity		?	?
Allergy Skin Testing		?	?
Lumbar Puncture	?		?

Survey of U.S. IRB Chairpersons (%; N=188)

	MR	> MR	
10 cc Blood Draw	8	18	
MRI	48	44	
Survey Sexual Activity	4	4	
Allergy Skin Testing	2	7	
Lumbar Puncture	2	9	

The need for data

- Review committees should not assess the risks of pediatric research using just their own personal judgments.
- Instead, review committees need data on the risks of research procedures and on the risks of daily life, and to compare the two.

3. Parental consent & child assent



Parental consent & child assent

- Children should be enrolled in research only with the permission of their legal guardian, typically their parents.
- Most guidelines allow waiver of parental consent in some cases (e.g., not a protection, laws permitting independent minor consent)

Parental consent/permission

- In U.S., regulations require that both parents give consent in riskier, non-beneficial research.
- Note permission is distinct from consent

Maternal views of HIV vaccine trials in Nairobi

97% willing to vaccinate infant if safe

91% willing to participate in research study

76% of women w/regular sexual partner thought partner approval required (62% though partner would approve)

64% willing to enroll in HIV-1 vaccine trial

Concerns about HIV vaccine trials

Side effects (75%)

Partner objection (34%)

Fear of discrimination (10%)

Fear of HIV acquisition through vaccine (8%)

Fear of false HIV results (5%)

Child assent

- The U.S. Federal regulations require that IRBs make provisions for assent from children who are capable.
- Assent is: “Affirmative agreement to participate in research, not just failure to object.”
- Or, agreement based on the child understanding as much as she is capable, even though child cannot understand enough to give valid consent.

Why do we require assent?

- Assent can serve different functions:
 - Control
 - Preparation for what they will have to do
 - E.g., overnight hospital stay
 - Respect for growing autonomy



Respectful assent process

1. Inform
2. Engage (questions and concerns)
3. Assent
4. Dissent (monitor discomfort, problems, objections)

Who can assent?

- Most guidelines do not specify which children are capable of assent.
- The U.S. Federal regulations stipulate only that:
 - The determination of assent should take into account the age, maturity and psychological state of the children.

Age as a proxy for decision-making

- Many use the rule of 7s.
- But individual children may have very different capacity for decision-making, depending on various factors.
 - E.g., chronically ill children

IRB practice

- Approximately half of IRB chairs required investigators to use a particular method.
 - Of these, 80% used an age cut-off (majority used age 7).
- The rest left it up to the investigators.

A. Whittle, S. Shah, B. Wilfond, G. Gensler, D. Wendler, Institutional Review Board Practices Regarding Assent in Pediatric Research, 113 Pediatrics 1747 (2004).

Can children give assent or consent?

- Children might become legally able to consent during the course of a study.
- Also, as children grow, they develop capacities to reason and understand.
- CIOMS: If children become capable of giving independent informed consent during the research, researchers should get their consent to continuing participation at that time.
- Debate about what to do in research with stored samples.

Can children give assent or consent?

- Studies of adolescent willingness to participate in HIV vaccine trial: mixed results
- One study of simplified assent form: 56% answered all questions correctly
- Adolescents have difficulty with randomization & false positive HIV tests
- Adolescents understand concept of placebo & clinical trials

Lee S, et al. JME 2013; Alexander AB, et al. Vaccine 2015

Can children give assent or consent?

- Some jurisdictions allow minors to legally consent to treatment based on status, maturity, or their conditions, may apply to research in some cases
- E.g., laws based on concern about adolescents failing to receive needed treatment because would reveal sexual risk behaviors

Dissent

- Many guidelines mention that a child's dissent should be respected, or that a child and parents have the right to withdraw at any time.
- How can we tell when a child is dissenting from research?

Dissent

- Age probably matters:
 - Crying infant
 - Recalcitrant 2 year old
 - Clear-thinking teenager
- Should respect sustained dissent by a child who understands what he/she is doing.
 - Children may have opinions about procedures (e.g., MRIs) that they have had before.
- May not want to force children to undergo research procedures.

Dissent

- Dissent is different from distress.
 - Dissent may reflect desire for control, or to express developing autonomy
 - Distress is when a child is experiencing psychological harm from research participation (e.g., child very scared of injections)

Dissent

- Importantly, can override dissent or distress if:
 - A child can obtain benefit from the research that she cannot obtain otherwise, and
 - Harms of proceeding are outweighed by that benefit

Summary

- Research with children requires balancing protection of individuals with need for data about treating children as a group
- Most guidelines strike this balance by allowing children to participate in research that benefits them, and minimal risk research if no prospect of benefit

Summary

- Consideration should be given to enrolling children in certain types of research earlier when avoiding delay is especially important
- To ensure earlier inclusion is ethical, important to ensure there is a solid justification and develop respectful permission & assent process

Thank you!

