PREP PEDIATRIC RESEARCH ETHICS AND POLICY

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Ethical Inclusion of Children in Research

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Pritzker School of Law, *by courtesy*

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Motivation for pediatric research

Physical Parameter	Children	Effect
Surface area-to-body mass ratio	Higher	Higher heat absorption
Metabolic rate	Higher	Higher heat production
Height	Lower height. Body closer to the ground	Thermal impacts of long-wave heat fluxes of high surface temperatures
Skin	More sensitive	
Physical activity	Higher	Higher metabolic heat production
Heat loss	Dry convective compared to adults evaporative heat loss	
Thermoregulation	Inferior	
	Undeveloped sweat gland capacity	
	Lower sweat rate	
		Lower evaporation heat exchange
Adaptive behaviour	Less adaptive	Less knowledge for sun protection
Heat exchanges	Rapid	Establishment of heat stress condition in short time
Thermal perception	Inferior	

Figure depicting differences between adults and children in heat perception from Antoniadis DG, et al. Atmosphere 2020.

Great need to find the right interventions and dosages for children, given that children are not small adults.

- "The vast majority of drugs are not designed or developed for pediatric or infant populations."

Gleeson et al. Adv Drug Deliv. Rev. 2021

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Overview

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1. When to enroll children in research

2. Risks/benefits

3. Decision-making
    a. Assent
    b. Consent
    c. Dissent

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1. When to enroll children in research

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When to enroll children in research

- 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 study adults first

- 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 negative attention if something goes wrong in a pediatric trial

Reasons to enroll children sooner

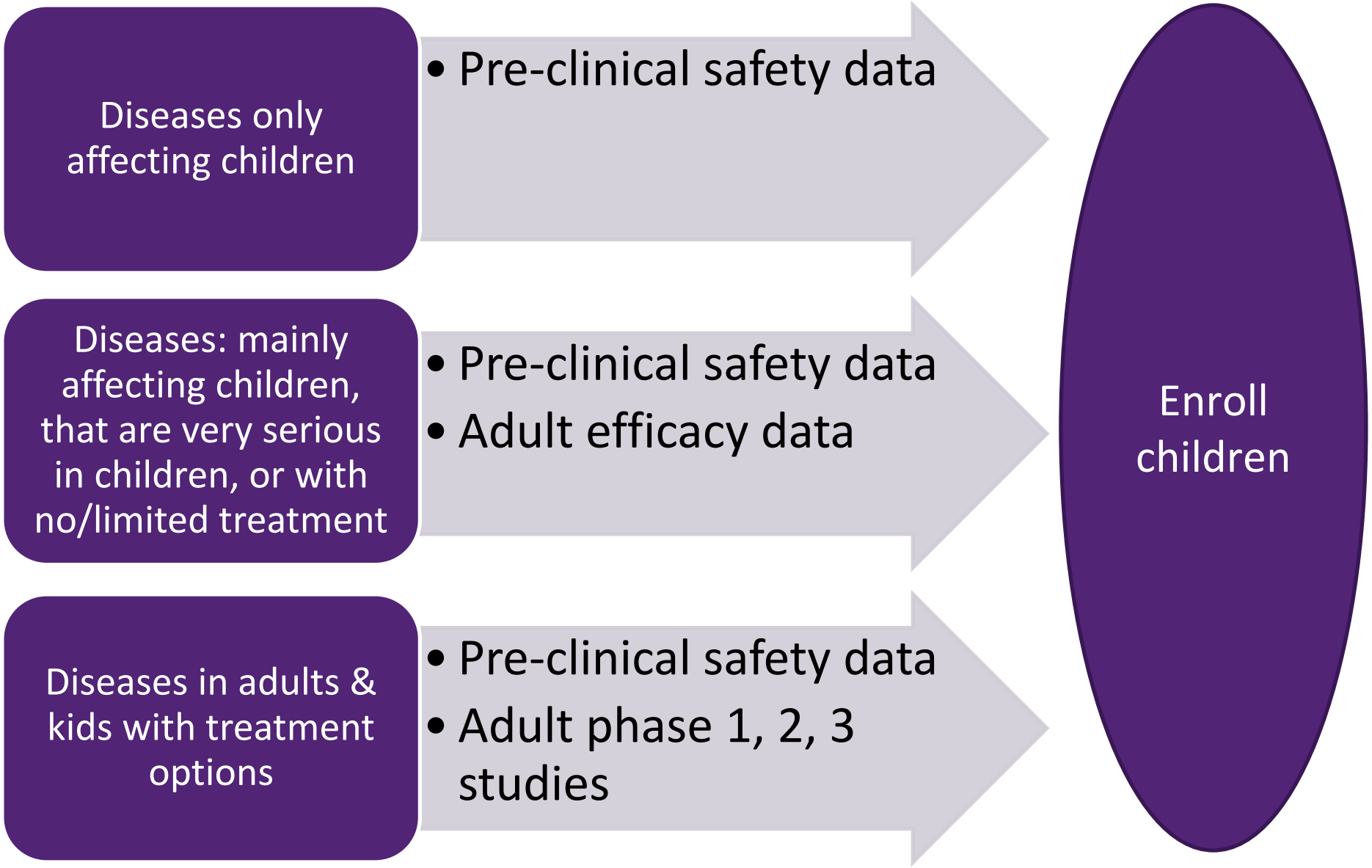
- Children can receive important benefits from research, especially if few alternatives
- Some diseases or conditions only affect children, or affect children differently
- Delay in pediatric testing may delay licensure or availability of the tested intervention

Ethical guidance

- World Health Organization's Council for International Organizations of the Medical Sciences (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



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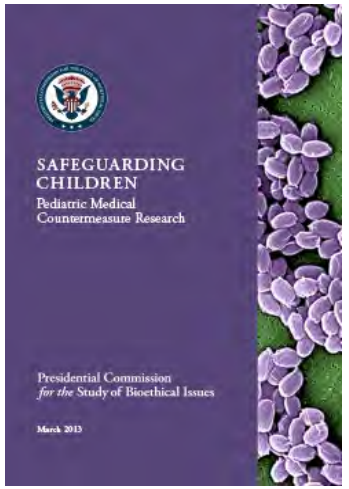
Confederation of European Specialists in Pediatrics, Eur. J. Pediatr. (2004) 163: 53-57.

Helpful, but….

- The recommendations don't focus directly on:
  - Risks/benefits,
  - Importance of the research, or
  - Differences between *prevention* and *treatment*

- May make more sense to focus on risk/benefit ratio of research given available alternatives

Age de-escalation



- Many groups recommend age de-escalation as additional protection for risky pediatric research

- Used in:
  - Research on treatments for malaria, cancer, flu
  - Vaccine trials on anthrax, typhoid, enterovirus, malaria, HPV, and COVID-19

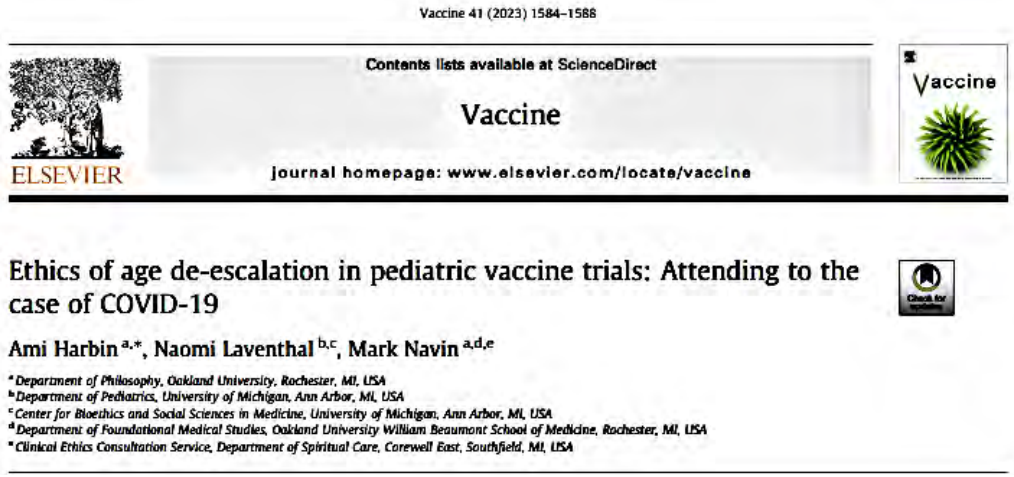
- Is age de-escalation always a useful safeguard?

Age de-escalation

- Although young children had lower risks from COVID-19 infection than many other groups, there were 651 deaths & 2,370 cases of MIS-C in children <5

- Due to use of age de-escalation, COVID-19 vaccines for children <5 were not available during Omicron surge in December 2021, had largest increase in hospitalization rates at that time

- Particularly problematic if there is an unduly narrow conception of the risks/benefits for children to be involved in research, as for COVID-19 vaccines



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Ethics of age de-escalation in pediatric vaccine trials: Attending to the case of COVID-19

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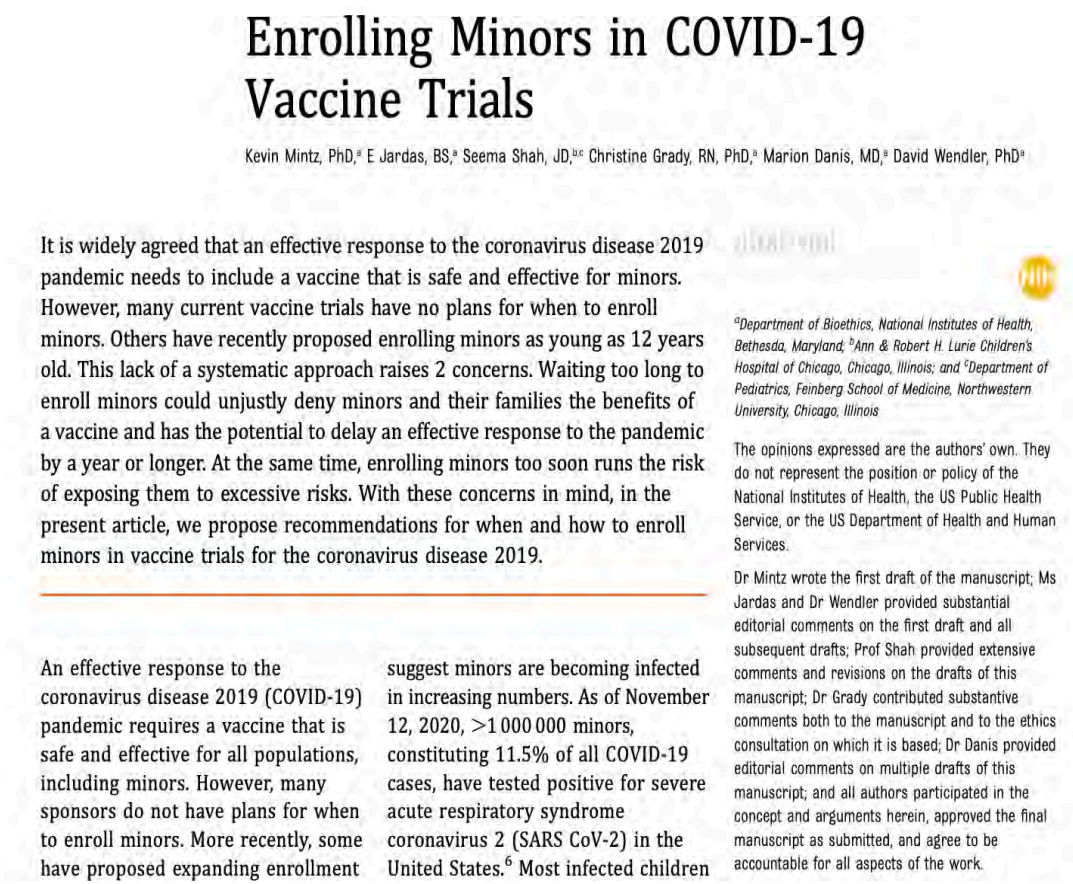
When to Enroll Children in Vaccine Trials during COVID-19

- In the COVID pandemic, children were often an afterthought in research and policy decisions
- Need to learn from this and do better by children in future pandemics



Enrolling Minors in COVID-19 Vaccine Trials

Kevin Mintz, PhD,[a] E Jardas, BS,[a] Seema Shah, JD,[b,c] Christine Grady, RN, PhD,[a] Marion Danis, MD,[a] David Wendler, PhD[a]

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 article, we propose recommendations for when and how to enroll minors in vaccine trials for the coronavirus disease 2019.

An effective response to the coronavirus disease 2019 (COVID-19) pandemic requires a vaccine that is safe and effective for all populations, including minors. However, many sponsors do not have plans for when to enroll minors. More recently, some have proposed expanding enrollment

suggest minors are becoming infected in increasing numbers. As of November 12, 2020, >1 000 000 minors, constituting 11.5% of all COVID-19 cases, have tested positive for severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) in the United States.[6] Most infected children

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The opinions expressed are the authors' own. They do not represent the position or policy of the National Institutes of Health, the US Public Health Service, or the US Department of Health and Human Services.

Dr Mintz wrote the first draft of the manuscript; Ms Jardas and Dr Wendler provided substantial editorial comments on the first draft and all subsequent drafts; Prof Shah provided extensive comments and revisions on the drafts of this manuscript; Dr Grady contributed substantive comments both to the manuscript and to the ethics consultation on which it is based; Dr Danis provided editorial comments on multiple drafts of this manuscript; and all authors participated in the concept and arguments herein, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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2. Risks and benefits

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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

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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

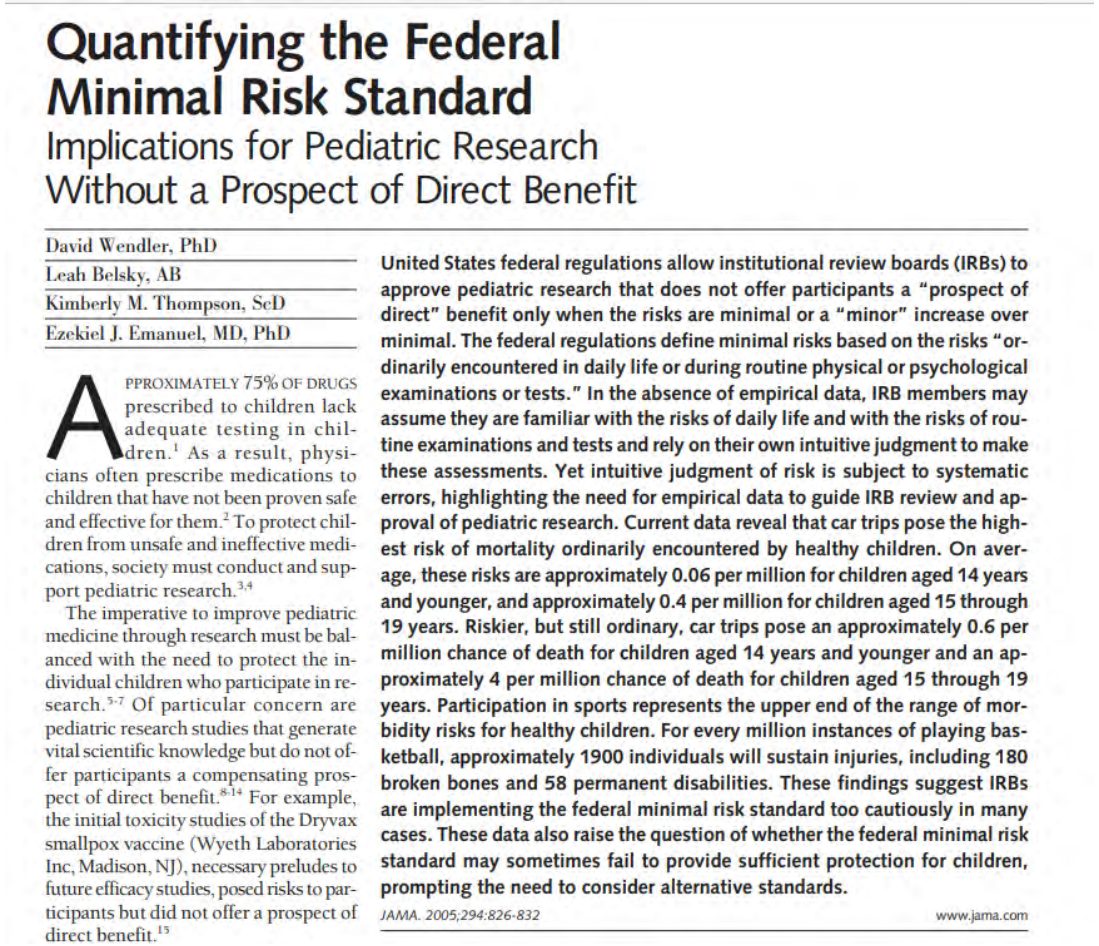
Survey of U.S. IRB Chairpersons (%; N=188)

	MR	> MR
10 cc Blood Draw	81	18
MRI	48	44
Survey Sexual Activity	44	48
Allergy Skin Testing	23	70
Lumbar Puncture	2	94

S. Shah, A. Whittle, B. Wilfond, G. Gensler, D. Wendler, 291 JAMA 476 (2004).

The need for data

- Review committees who assess risks based on intuition and judgment may:
  - Inaccurately estimate risk, and/or
  - Incorporate bias into their judgments
- Better to use data on the risks of research procedures and on the risks of daily life and compare the two.



Quantifying the Federal Minimal Risk Standard

Implications for Pediatric Research Without a Prospect of Direct Benefit

David Wendler, PhD
Leah Belsky, AB
Kimberly M. Thompson, ScD
Ezekiel J. Emanuel, MD, PhD

APPROXIMATELY 75% OF DRUGS prescribed to children lack adequate testing in children.[1] As a result, physicians often prescribe medications to children that have not been proven safe and effective for them.[2] To protect children from unsafe and ineffective medications, society must conduct and support pediatric research.[3,4]

The imperative to improve pediatric medicine through research must be balanced with the need to protect the individual children who participate in research.[5-7] Of particular concern are pediatric research studies that generate vital scientific knowledge but do not offer participants a compensating prospect of direct benefit.[8-14] For example, the initial toxicity studies of the Dryvax smallpox vaccine (Wyeth Laboratories Inc, Madison, NJ), necessary preludes to future efficacy studies, posed risks to participants but did not offer a prospect of direct benefit.[15]

United States federal regulations allow institutional review boards (IRBs) to approve pediatric research that does not offer participants a "prospect of direct" benefit only when the risks are minimal or a "minor" increase over minimal. The federal regulations define minimal risks based on the risks "ordinarily encountered in daily life or during routine physical or psychological examinations or tests." In the absence of empirical data, IRB members may assume they are familiar with the risks of daily life and with the risks of routine examinations and tests and rely on their own intuitive judgment to make these assessments. Yet intuitive judgment of risk is subject to systematic errors, highlighting the need for empirical data to guide IRB review and approval of pediatric research. Current data reveal that car trips pose the highest risk of mortality ordinarily encountered by healthy children. On average, these risks are approximately 0.06 per million for children aged 14 years and younger, and approximately 0.4 per million for children aged 15 through 19 years. Riskier, but still ordinary, car trips pose an approximately 0.6 per million chance of death for children aged 14 years and younger and an approximately 4 per million chance of death for children aged 15 through 19 years. Participation in sports represents the upper end of the range of morbidity risks for healthy children. For every million instances of playing basketball, approximately 1900 individuals will sustain injuries, including 180 broken bones and 58 permanent disabilities. These findings suggest IRBs are implementing the federal minimal risk standard too cautiously in many cases. These data also raise the question of whether the federal minimal risk standard may sometimes fail to provide sufficient protection for children, prompting the need to consider alternative standards.

JAMA. 2005;294:826-832 www.jama.com

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3. Decision-making

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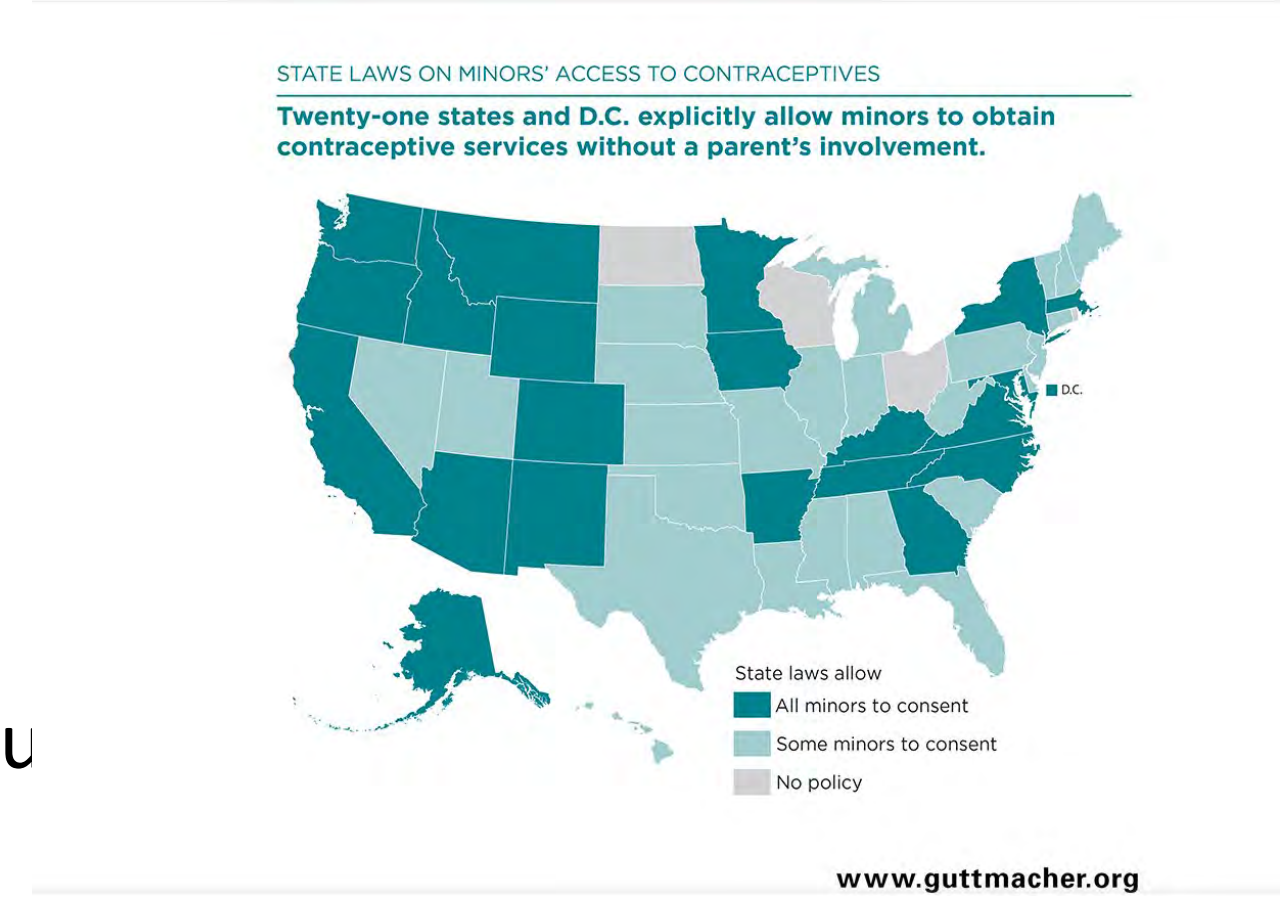
Parental consent & child assent

- Children should be enrolled in research only with the permission of their legal guardian, typically their parents.

- Who can consent is set by local law

Exceptions to parental consent requirements

- Most guidelines allow waiving parental consent sometimes (e.g., not a protection)
- State/local laws allow minors to consent for themselves based on statu maturity, or condition



Shah, SK., et al. "Advancing Independent Adolescent Consent for Participation in HIV Prevention Research." *Journal of Medical Ethics* 2018.

Parental consent/permission

- In U.S., regulations require that both parents give consent in riskier, non-beneficial research.

- Note permission is distinct from consent

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

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- 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).

Should children give assent or consent?

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- As children grow, they develop capacities to reason and understand, so children might become legally able to consent during the course of a study.

- CIOMS: If children become capable of giving independent informed consent during the research, researchers should obtain their consent to continuing participation at that time.

Should children give assent or consent?

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- As mentioned earlier, states/countries allow minors to legally consent to treatment based on:
  - age,
  - status,
  - maturity, or
  - their conditions

- E.g., laws based on concern about adolescents failing to receive needed treatment because would reveal sexual risk behaviors—note public health (rather than autonomy) justification

Can children give assent or consent?

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Several studies of adolescent participation in HIV research

Simplified assent form: 56% of adolescents answered all questions correctly

Comparing adolescents to adults, one study found no significant difference in comprehension of research between adults and adolescents aged 14+

Adolescents understood placebo & clinical trials, but did less well with risks, randomization, and false positive HIV tests

Lee S, et al. JME 2013; Alexander AB, et al. Vaccine 2015; Dyer J, et al. J Assoc Nurses AIDS Care 2022

Li H et al. *Journal of the International AIDS Society* 2023, **26**:e26057
http://onlinelibrary.wiley.com/doi/10.1002/jia2.26057/full | https://doi.org/10.1002/jia2.26057

RESEARCH ARTICLE

"[T]he laws need to change to reflect current society": Insights from stakeholders involved in development, review or implementation of policies about adolescent consent for HIV testing, care and research in Kenya

Huangqianyu Li[1], Seema K. Shah[2,3,§], Elise Healy[4], Kawango Agot[5], Jillian Neary[6], Kate Wilson[4], Jacinta Badia[5], Winnie O. Atieno[5], Hellen Moraa[7], Hendrika Meischke[1], James Kibugi[5], Irene Inwani[8], Nok Chhun[4], Ferdinand C. Mukumbang[4], Grace John-Stewart[4,6,9,10], Pamela Kohler[4,11] and Kristin Beima-Sofie[4]

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Study of policy stakeholders on adolescent consent

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- Semi-structured interviews
- Purposive sampling of 15 Policy Stakeholders
- Conducted thematic analysis

ELSI Stakeholders (n=15)	
Lawyers	5
Institutional Review Board members	3
School administrators	4
Policymakers	6

RESULTS: Themes

Age is a poor proxy for decision-making capacity—factors like maturity, context, risk/benefit matter more

Policies should evolve with changing societal views about adolescent autonomy

Adults should empower and involve adolescents in decision-making towards ownership over their own health

Theme 1: Age as a poor proxy for capacity to decide

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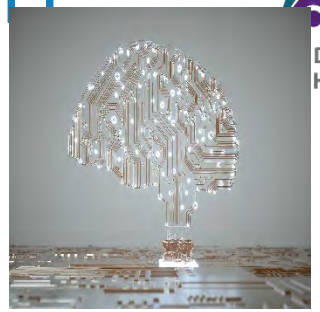
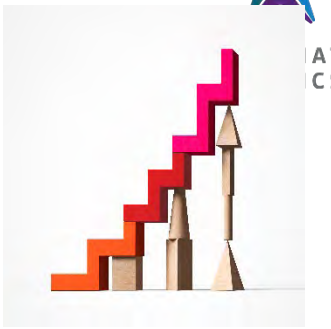
"[P]eople don't mature the same way…"

Theme 2: Policies should evolve with societal views



"Who is it helping? Is the policy in place for us to feel right and religious and moral or isn't the policy in place to protect and to work for our adolescents? So for me I just feel the policies need to completely change; even the laws need to change to reflect current society."

Theme 3: Empowerment Towards Ownership



"[Y]ou guide them but ultimately they make decisions."

Implications

- Laws without strict age cut-offs and greater flexibility (e.g., mature minor laws) may help address diverse decision-making capacities

- Need for continued research on how to support caregivers and adolescents in making decisions

  - Train caregivers/other adults in how to guide adolescent decision-making?

  - Support adolescents with interventions to address developmental limitations (e.g., foster ability to resist peer pressure, focus on long-term risks)?

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 is a factor
- Should respect sustained dissent by a child who understands what he/she is doing.
- 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

Wendler DS. Assent in paediatric research: theoretical and practical considerations. J Med Ethics. 2006 Apr; 32(4): 229–234.

Summary

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- 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

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- Consideration should be given to enrolling children in certain types of research earlier
- To ensure earlier inclusion is ethical, important to ensure solid justification, respectful permission & assent process
- Need clearer guidance on when children should decide on their own and how caregivers can support them in research decisions

Thank you!