The ethics of research with children
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Disclaimer
The opinions expressed are the author’s own. They do not reflect any position or policy of any U.S. governmental entity, including the National Institutes of Health.
Case study
Researchers wanted to learn how and why the brains of children with attention deficit hyperactivity disorder (ADHD) do not develop normally.
Planned to use a device that uses magnetic fields to stimulate nerve cells in the brain.
Device had not been tested in children before.
Case study
The device also made a loud noise (110 decibels even if the kids wore earplugs and headphones).
In ordinary life, people are exposed to louder noises when:
Mowing the lawn
Going to a loud rock concert
Listening to loud music on an iPod
Photos: People blowing horns
Case study
The researchers asked for an ethics consult and wanted to know:

Is it ethical to expose kids with ADHD to this risk of harm?

Is it ethical to expose healthy kids to this risk of harm?
Need for pediatric research
Tremendous need to find the right treatments and dosages for children, given that children are not small adults.

It has been estimated that 75% of drugs prescribed to children have not been tested in children, even for basic safety and efficacy.
Problem
If you were a parent with a sick child, you would want good evidence for the medical care your child receives.

But, you probably do not want your child to be exposed to risk in research for the benefit of other children.
How do we address this problem?
First, protect children from harm:
Regulations and guidelines provide acceptable risk/benefit ratios for research & limits on acceptable risk.

Second, respect people’s ability to make choices that fit with their values and interests:
Focus on parental consent/permission and child assent.
Overview

When to enroll children in research
Child assent/parental consent
Risks/benefits
Recent controversy over “best interests” & the Federal regulations
1. When to enroll children in research
When to enroll children in research

First question: Who is a child?

From both legal and cultural perspectives, who is considered a child varies from place to place.

Children are typically defined by the fact that they have not reached the legal age to give their own consent.
Definition of a child

The age at which children become adults ranges from 14-21 in different countries. E.g., In the U.S., legal age for consent is 18; in Singapore, it is 21. Some laws have exceptions for “mature minors” or emancipated minors.

Photo of the kid from the movie “Home Alone”
Adults first as a general rule, with exceptions

CIOMS: Adults first in all cases.

Declaration of Helsinki: Adults first unless there is a prospect of direct benefit.

Open question: Should research go through Phase III in adults before it can be conducted in children?
Adults first?
May prevent children from receiving benefits of research in some cases.
Some diseases or conditions only affect children.
Could still do pharmacokinetic studies of drugs in adults, depending on the risk levels.
And delay in pediatric testing may affect licensure or availability of the tested intervention.
2. Parental consent & child assent
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Children should be enrolled in research only with the consent of their legal guardian, typically their parents.

Most guidelines allow waiver of the requirement for parental consent in some cases.
Parental consent
In U.S., regulations require that both parents give consent in riskier, non-beneficial research.

What should you do for divorced parents?
Depends on local law; rights can be divided in different ways. Custody agreement will specify.
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 he is capable, even though the child cannot understand enough to give valid consent.
Why do we require assent?  
To the extent children are able to assent, assent can:  
Allow children some measure of control  
Help them prepare for what will happen and what is required of them  
E.g., overnight hospital stay  
Respect their growing autonomy  
Children do not magically become autonomous at 18
Respectful assent process
Inform
Engage (questions and concerns)
Assent
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

IRB study asking about assent.

Approximately half of IRB chairs in study sample required investigators to use a particular method.

Of these, 80% used an age cut-off (majority used age 7).

The remainder of IRBs left it up to the investigators.

Can children give 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.
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

We 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 a child wanting to control what happens to him, or to express his/her developing autonomy.

Distress is when a child is experiencing psychological harm from research participation, like when a child is deathly afraid of injections.
Dissent

Importantly, can override dissent or distress if:

A child can obtain benefit from the research that she cannot obtain otherwise, and

The harms of proceeding are outweighed by that benefit.
3. Risks and benefits
International regulatory frameworks
Most regulations, including the Council of Europe, Uganda, CIOMS, British MRC, Canada Tri-Council, U.S. Federal Regulations, Australia and South African MRC, permit pediatric research:

That offers a prospect of benefit, or
That poses “minimal” risks.

Photo: Globe in right hand corner
U.S. Federal Regulations

IRBs can approve research if:
No direct benefit & minimal risk (45 C.F.R. 404),
Prospect of direct benefit that outweights the risk (45 C.F.R. 405), or
No direct benefit, minor increase over minimal risk, & likely to produce generalizable knowledge for the subject’s condition or disorder (45 C.F.R. 406).
Approved by a special panel (45 C.F.R. 407).
Minimal risk

Commonly defined as the risks of daily life, or the risks of routine examinations or tests.
Risks and benefits
How should we interpret the minimal risk standard?

The different ways of interpreting minimal risk fall under 3 main standards:

- Risks of routine exams or tests
- Risks of daily life (subjective)
- Risks of daily life (objective)
Risks of routine exams or tests

Interpretation: A procedure is minimal risk if it is the type of procedure that is a part of a child’s daily life.

However, this standard is both under- and over-inclusive.

E.g., massage therapy, chemotherapy.
Risk of daily life standard (subjective)

Interpretation: Minimal risk is measured by the risks an individual child faces in daily life, and may vary for different children.

However, this could compound or exacerbate existing unfairness, particularly in research conducted in violent or impoverished places in the world.

E.g., a child in Baltimore who runs the risk of being shot on his way to school.
Risks of daily life standard (objective)

Risks of daily life should be based on the average daily risks that children face.

Problems:

Perhaps some risks of daily life of the average child should not justify research risks.

E.g., risks of car accidents.
Does not account for local values.

This standard has the advantage of tying research risks to widely-accepted risks.
More than minimal risk
Unlike most other countries, the U.S. permits non-beneficial research that poses a “minor increase over” minimal risk.

Both parents have to give consent,
The subjects must have a condition or disorder, and
The research must be designed to develop important knowledge about the condition or disorder.
Is it acceptable to expose children with a condition to greater risk?
Maybe sick children could benefit in the future

Very speculative
This category of research is defined as non-beneficial
Putting research results into practice takes time (est. 17 years), may no longer be relevant
Is it acceptable to expose children with a condition to greater risk?
What if sick children have more comfort and familiarity with medical procedures?

Risks of anxiety might be lower for them

But actual risks of physical harm from the procedure are the same
Is it acceptable to expose children with a condition to greater risk?
Are sick children more likely to want to help others with the same disease?

Empirical question
Categories of altruistic people should not be targeted for more research
IRBs decide the research is acceptable; children and their parents decide what motivates them
Is it acceptable to expose children with a condition to greater risk?
My critique of the regulations: it would be unfair to expose sick children to greater risk of harm because they are already burdened.

May make more sense to permit the same level of risk for sick and healthy children, but factor in the subjective likelihood of risks of distress/anxiety.
Assessing risks

How are these standards interpreted and applied in practice?
- Survey of U.S. IRB Chairpersons (%; N=188)

*Procedures performed in healthy 11 year olds*

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<td>Allergy Skin Testing</td>
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<tr>
<td>Lumbar Puncture</td>
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Survey of U.S. IRB Chairpersons (%; N=188)

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The need for a systematic approach

Review committees should not assess the risks of pediatric research using just their own personal judgments.

Instead, we need a more systematic approach to assessing risks.
4. Recent controversy over “best interests” and the Federal regulations
Recent legal critique of pediatric research

Debate in literature over whether permitting pediatric research violates the “best interests” standard.

If a parent can only give permission for things that are in her child’s best interests, how can she consent to the child’s participation in research with risk but no benefit? Yet, the Federal regulations allow non-beneficial research in children.
Critique of pediatric research
One law professor has argued that research is too risky, and IRBs are too permissive, so pediatric research has to change.

Some non-beneficial research should not be done.
Local child welfare agencies should evaluate research based on the best interest standard.

Best interests standard
Do parents only allow their children to do what is in their children’s best interests?

No. Examples range from:

Taking a child along in the car when the parent needs a haircut, to

Allowing one child to donate bone marrow to another child.
Should parents only allow children to do things that are in their best interests? Being a parent is very hard and important work. Reasonable to allow some flexibility and discretion in child-rearing. Family interests should also count. Federal regulations reflect these realities better than the best interests standard does.
Summary
Research with children requires balancing protection with the need for data to treat children as a group. We should try to involve children in research decisions in developmentally-appropriate ways. Most guidelines allow children to participate in research that benefits them, and non-beneficial research that poses minimal risks.
Summary
Defining acceptable risk is controversial, and we need to find a more systematic approach.

Legal standards for research may need to be better harmonized than they currently are, but should not be radically overhauled.
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