# Ethics and Regulation of Research with Children

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## Balancing Over- & Under-Protection

- "Protective exclusion" of children from research
  - "off label" medication use with risks of decreased efficacy and increased toxicity
- Economic incentives (NIH, FDA) have increased number of children in clinical research
- "Protective inclusion" has focused new attention
  - adequacy of existing regulatory framework for protecting children in research
  - FDA adopting Subpart D protections in April 2001

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## U.S. System of Protection

- Independent scientific & ethical review
  - Additional safeguards for vulnerable persons
- Voluntary and informed consent
  - Parental permission and child assent
- Responsible and Competent Investigators

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## Thesis

The ethical basis for the U.S. regulatory approach is a "shared" understanding of the proper scope of parental authority and responsibility in balancing a child's protection from and exposure to risk.

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## Two basic moral questions

- What conditions should a research study fulfill so that parental permission to enroll a child in research is morally justified?
  - ☑Moral intuition: Research should reflect a parent's everyday decisions about risk and benefit in similar non-research settings.
- Why is it important whether an intervention or procedure offers the prospect of direct benefit?
  - ☑The moral authority of a parent to expose a child to risk is based on the judgment that the intervention or procedure may be in the child's "best interest."

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## IRB Review of Pediatric Research

- Risks are reasonable in relation to anticipated benefits, if any, to subjects and importance of knowledge that may reasonably be expected to result

  45CFR§46.111; 21CFR§56.111
- Additional Safeguards for Children
  - Restricts allowable risk exposure for research not offering the prospect of direct benefit
    - "minimal risk" (45CFR§46.404; 21CFR§50.51)
    - "minor increase over minimal risk" (§46.406; §50.53)
  - Restricts justification of risk exposure for research that offers prospect of direct benefit
    - "equipoise" (45CFR§46.405; 21CFR§50.52)

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## Categories of Research

- Interventions not offering prospect of direct benefit & restriction on allowable risk exposure
  - "minimal risk" (45CFR§46.404; 21CFR§50.51)
  - "minor increase over minimal risk" (§46.406; §50.53)
- Interventions offering prospect of direct benefit & restriction on justification of risk exposure
  - "equipoise" (45CFR§46.405; 21CFR§50.52)
- Interventions not approvable under the above
  - "reasonable opportunity" (45CFR§46.407; 21CFR§50.54)

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## Research (Clinical Investigations) with no greater than minimal risk

Research "in which no greater than minimal risk to children is presented, [may involve children as subjects] only if the IRB finds [and documents] that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians"

2/23/2003 45CFR§46.404; 21CFR§50.51

## Definition of Minimal Risk

"the probability and magnitude of [physical or psychological] harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily [normally] encountered in daily life or during the performance of routine physical or psychological examinations or tests [of healthy children]."

2/23/2003 45CFR§46.102i; 21CFR§50.3k; 21CFR§56.102i

## What is the purpose of the category of "minimal risk"?

- The concept of "minimal risk" restricts the scope of parental decision-making in research to that which parents may permit in similar non-research contexts.
- Parents make decisions everyday that may involve exposing a child to risk. If the research risks are similar to the risks of everyday life, parents may properly permit a child to be exposed to these risks even in the absence of the prospect of direct benefit.

2/23/2003 The National Commission (1977)

## Canada Tri-Council Policy

- Children should only be research subjects if…
  - the research does not expose them to more than minimal risks without the potential for direct benefits (Article 2.5c)
- Minimal risk is commonly defined as
  - if potential subjects can reasonably be expected to regard the probability and magnitude of possible harms implied by participation in the research to be no greater than those encountered by the subject in those aspects of his or her everyday life that relate to the research (Section C1)

2/23/2003 Tri-Council Policy Statement - Canada (August 1998)

## NHRPAC Children's Workgroup Report

"We interpret …minimal risk to be that level of risk associated with the daily activities of a normal, healthy, average child.… Conceptually, the minimal risk standard defines a permissible level of risk in research as that level of [socially allowable] risk which parents generally permit their children to be exposed to in non-research situations."

2/23/2003 Report to NHRPAC from Children's Workgroup, 05-01-2002

## Three aspects of "minimal risk"

- Combines both descriptive and normative judgments ("socially allowable")
- Involves "equivalence of risk" rather than only tests and/or procedures actually used
- Index to "normal, healthy, average child"

2/23/2003 Report to NHRPAC from Children's Workgroup, 05-01-2002

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## Minor increase over minimal risk

- Research presenting more than minimal risk; no prospect of direct benefit, only if…
  - ✓ a minor increase over minimal risk
  - ✓ experiences reasonably commensurate with actual or expected situation
  - ✓ yield generalizable knowledge of vital importance for understanding or amelioration of disorder or condition
- Adequate provisions for child assent & parental permission

2/23/2003 45CFR§46.406; 21CFR§50.53; CIOMS Guideline 9

## Indexing Minimal Risk

- The US National Commission indexed…
  - minimal risk to "daily lives… of healthy children."
  - "minor increase" over minimal risk to the "normal" experience of children with a disorder or condition
    - poses no significant threat to child's health or well-being
    - presents experiences familiar to the child
- CIOMS Guideline 9: "risk attached to routine medical or psychological examination of such persons."
- By removing index, current US regulations undercut the moral justification of §46.404 and §46.406

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## Relation of Risk and Condition

- "Minimal risk" research (§46.404; §50.51)
  - Not restricted to research on child's condition
  - No stipulation of scientific importance
- "Minor increase" research (§46.406; §50.53)
  - Must be relevant to child's disorder or condition
  - "Vital importance" to child's condition
- If minimal risk indexed to experience of child with condition, that child may be exposed to greater risk in research unrelated to condition

2/23/2003 Also CIOMS Guideline 9

## NHRPAC Children's Workgroup Report

"…a minor increase over minimal [risk] should [pose no significant threat to the child's health or well-being,] be just a bit more than [minimal]… and also commensurate with the risks of interventions or procedures having been experienced or expected to be experienced in the lives of children with a specific disorder or condition. …Commensurability is important to allow the child and parents to have a basis upon which to make thoughtful judgments about assent and permission."

2/23/2003 Report to NHRPAC from Children's Workgroup, 05-01-2002

## NHRPAC Children's Workgroup Report

The concept of disorder or condition…

- "…a specific characteristic…, a physical or social condition…, or the risk of…developing a disease… based on diagnostic testing or physical examination."
- "prematurity, infancy, adolescence, poverty, living in a compromised…environment, institutionalization, or having a genetic predisposition…are… disorders or conditions of children that can, under the appropriate circumstances, warrant permissible research."

2/23/2003 Report to NHRPAC from Children's Workgroup, 05-01-2002

## ICH E6 (non-therapeutic trials)

- Objectives not met with consenting subjects
- Foreseeable risks are low (§50.51 or §50.53?)
- Negative impact on well-being minimized & low
- Trial not prohibited by law
- IRB/IEC written approval
- Absent justified exception, subjects should have relevant disease or condition (§50.53?)
- Subjects closely monitored and withdrawn if unduly distressed

2/23/2003 ICH E6 (§4.8.14)

## Limitations on Risk

(subjects not capable of informed consent)

"…the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them."

2/23/2003 CIOMS Guideline 9 (2002)

## Commentary on CIOMS Guideline 9

When risks exceed those, the IRB/REC must find:

1) research designed to be responsive to disease or conditions affecting the prospective subjects;

2) risk of interventions only slightly greater than those of routine medical or psychological examination of such persons for condition or clinical circumstances under investigation;

3) objective of research sufficiently important to justify exposure of the subjects to the increased risk; and

4) interventions reasonably commensurate with clinical interventions subjects have or may be expected to experience in relation to condition under investigation.



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## When may a parent permit a child to undergo an unproven procedure that offers prospect of direct benefit?

- A child should not be disadvantaged by a research study. A parent's decision to enroll a child in research should be similar to a decision to permit exposure to risks and benefits of any non-research alternative.
- The general requirement is equipoise
  - Risks must be justified by anticipated benefits (for each arm of the study)
  - Risk/benefit relationship should be as favorable as available (research and non-research) alternatives

## Equipoise

"Clinical [research] equipoise means a genuine uncertainty on the part of the expert medical community about the comparative therapeutic merits of each arm of a clinical trial.The tenet of clinical equipoise provides a clear moral foundation to the requirement that the health care of subjects not be disadvantaged by research participation."

2/23/2003 Tri-Council Policy Statement (August, 1998)

## Why is the prospect of benefit modified by the term "direct"?

- The prospect of benefit…
  - should apply to the particular child (whether or not the knowledge gained benefits other children and/or society)
  - ideally should not depend on other events outside of the study (i.e., participation in study should be causally sufficient)

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## Greater than minimal risk; prospect of direct benefit to subject

Only if the IRB finds [and documents] that:

- Risk justified by benefit
- Relation of benefit to risk at least as favorable as available alternatives
- Adequate provisions for assent and permission

May require research designs that minimize risk, such as randomized withdrawal

2/23/2003 45CFR§46.405; 21CFR§50.52

## Why use the terms "intervention or procedure", and not research?

- Risks associated with an intervention or procedure that does not offer the prospect of direct benefit cannot be justified by benefits offered by other interventions or procedures included in the research study.
- Thus, the analysis of research risks should be procedure-specific. Each component of the research study should be analyzed separately.

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## Not otherwise approvable

- IRB: Reasonable opportunity to understand, prevent, or alleviate serious problem affecting health or welfare of children; and
- The Secretary/Commissioner, after expert consultation and public review and comment, has determined:
  - ✓ reasonable opportunity to understand, prevent, or alleviate serious problem affecting health or welfare of children
  - ✓ conducted in accord with sound ethical principles
  - ✓ adequate provisions for assent and permission

2/23/2003 45CFR§46.407; 21CFR§50.54

## System of Protection

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## Respect for Children

- Parental Permission (yet within limits)
  - A parent should protect the health and safety of his or her child (i.e., beneficence)
- Child Assent (not as a right, but a benefit)
  - A parent should nurture the moral growth and developing autonomy of his or her child

National Commission (1977)

2/23/2003 National Commission, Report on Research Involving Children (1977)

## Adequate Provisions for Assent

- Information
  - "the reasonable volunteer" (child)
- Comprehension ("respect for persons")
  - opportunity to choose to extent capable
  - seeking permission to protect from harm
- Voluntariness
  - conditions free of coercion and undue influence

2/23/2003 The Belmont Report (1979)

## Voluntariness

- Coercion
  - intentional overt threat of harm (unintentional? covert?)
- Undue influence (e.g., money)
  - excessive, unwarranted, inappropriate or improper reward or other overture
  - acceptable inducements may become undue influences if subject is especially vulnerable
- Examples
  - impact of persons with authority or influence
  - controlling influence of a close relative (e.g., parents)
  - threatening to withdraw health services

2/23/2003 The Belmont Report (1979)

## What is assent? Can it be waived?

- An affirmative agreement to participate in research
  - Mere failure to object should not be construed as assent
- Assent may be waived if…
  - a child is not capable (age, maturity, and psychological state)
  - prospect of direct benefit not available outside of research
  - research involves no more than minimal risk
- If honoring assent shows respect, it should only be waived (absent direct benefit) if child cannot appreciate being used for another's purpose

2/23/2003 45CFR§46.408; 21CFR§50.55

## What is the purpose of parental permission, and can it be waived?

- Purpose: assessment of appropriate risk exposure
- Permission may be waived if…
  - research involves no more than minimal risk, or
  - if permission is not a reasonable requirement to protect a child and an appropriate mechanism for protecting the child is substituted
- Does this second category apply to FDA-regulated pharmacological research? No.

2/23/2003 45CFR§46.408c; 21CFR§50.55

## Assent and Permission

- Respect links parental permission (protection) and child assent (acknowledgement)
- Require assent if capable; honor dissent
- Commensurability (for assent, not risk)
  - ✓knowledgeable decision based on familiarity
  - ✓participation closer to child's ordinary experience
- Research without benefit should preferentially involve children who can (and do) assent

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## ICH E-6 (and children)

- "Special attention" (3.1.1)
  - No specification of the nature of this special attention.
- Parental permission (i.e., LAR) (4.8.5)
  - "fully inform… the subject's" LAR
- Child assent (4.8.12)
  - "…to the extent compatible with the subject's understanding"

2/23/2003 Step Four, May 1996

## Research involving children

- The investigator must ensure that:
  - Research cannot be carried out with adults
  - Obtain knowledge relevant to children's health needs
  - Parent or LAR of each child has given permission
  - Child's assent obtained to extent of capabilities
  - Child's refusal to participate or continue always respected, unless…
    - child needs treatment not available outside research
    - investigational intervention shows promise of therapeutic benefit, and
    - there is no acceptable alternative therapy

2/23/2003 CIOMS Guideline 14 (2002)

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## The Responsible Investigator

- Appropriate pediatric expertise
- Committed to the well-being of the child
  - "In medical research on human subjects, …the well-being of the human subject should take precedence over the interests of science and society." Declaration of Helsinki, paragraph 5.
- Conflicts of Interest
  - No significant financial conflict of interest
  - Institutional environment that mitigates non-financial conflict of interest

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## Sufficient Pediatric Expertise

- Sponsor
  - Appropriate protocol design to minimize risk
- Institutional Review/Ethics Board
  - Knowledge of pediatric ethical, clinical, psychosocial issues
  - Consider risks from child's perspective
  - Familiar with research designs that minimize risk
- Investigator
  - Trained and experienced in studying children, including evaluation and management of AEs

2/23/2003 E-11 Clinical Investigation of Medicinal Products in the Pediatric Population

## General Conclusion

- The special protections for children in research answer the question: What are the conditions under which it is morally justified for a parent to enroll his or her child in a research study?
- If no direct benefit?
  - Risk no greater than child's "ordinary" life
- If direct benefit?
  - Risk comparable to child's available alternatives
- Otherwise, public discussion

2/23/2003