# Ethical Issues Concerning Testing of New Drugs in Children

(Incentives and Disincentives for Pediatric Drug Development)

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## Ethics: Incentive or Disincentive?

- In spite of general agreement that children should receive drugs with an appropriate balance of risks and potential benefits ("safe and effective"), the success of BPCA suggests that the only effective incentive for testing drugs in children is money.
- The difficulty with enforcing post-marketing study commitments rather than requiring pre-marketing pediatric studies (PREA), if ethically appropriate, further reinforces the observation that money is the only effective incentive.
- This fact does not imply that the only reason to test drugs in children is for the money.



## Ethics as a Disincentive/Barrier?

- Some (but not all) of the regulations (i.e., policy and procedures) governing pediatric research are grounded in ethical principles.
- The regulations implementing independent review and informed consent may obscure these principles and create confusion about the nature of barriers to pediatric research.
- There is broad international agreement on the core ethical principles that should guide pediatric research.



### **Research without Direct Benefit**

#### Restricted to "minimal risk"

- Canada (Tri-Council Policy, 2005); United Kingdom (MRC, 2004); Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (Council of Europe, 2005)
- Broadens minimal risk to include "minor" or "slight" increase, <u>only</u> if scientifically necessary
  - United States (Subpart D, 1983; FDA, 2001); CIOMS Guideline 9 (World Health Organization, 2002)
- "Low" foreseeable risk
  - India, 2000; Pan-American Health Organization, 2002; EMEA, 1997 (ICH GCP E6, 1996); Australia (2006)



## Variation in Defining Minimal Risk

#### United States (The Common Rule, 1991)

- "[risks] ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests"
- Canada (2005)
  - "no greater than those encountered by the subject in those aspects of his or her everyday life that relate to the research"

#### Council of Europe (2005) (minimal risk and minimal burden)

 "very slight and temporary negative impact on the [person's] health" and "discomfort [i.e., burden] will be...temporary and very slight"

#### United Kingdom (2004) – Most Restrictive? "Minimal"/"Low"

- "procedures such as questioning, observing, and measuring children [and] obtaining bodily fluids without invasive intervention; [no] more than a very slight and temporary negative impact on [child's] health"
- <u>Low</u>: "might cause no more than brief pain or tenderness, small bruises or scars, or very slight, temporary distress; e.g., a blood test"



## **Research with Prospect of Direct Benefit** United States (Subpart D; 21 CFR §50.52) risk justified by anticipated benefits to subjects - relation of anticipated benefit to risk at least as favorable as that provided by available alternative approaches (i.e., equipoise) Canada (2005): proportionate, equipoise Council of Europe (2005): proportional UK (2004): acceptable balance, equipoise



## Wide Agreement on Ethical Principles

- Children should not be enrolled in research unless necessary to answer an important scientific question about the health and welfare of children.
- Research involving children either must present a balance of risks and potential benefits comparable to the available alternatives, or be restricted to "minimal risk" absent direct benefit to the child.
- The variability in defining "minimal" or "low" risk is insignificant, and contributes little to the inevitable differences of judgment when applying broad ethical principles to specific research protocols.



### So What are the Ethical Barriers? ("I hope to provoke, with a little help from my friends")

- Clinicians are willing to prescribe drugs "off label" absent sufficient pediatric data.
- Sponsors (as expected) are acting out of financial "self interest."
- Academic institutions bemoan the loss of clinical research, yet struggle to reverse the trend.
- A lack of transparency at all levels of the clinical research enterprise have undermined public trust.



### Is Prescribing "Off Label" Drugs Unethical?

- The enthusiasm generated by introducing a new drug often results in wide "off label" pediatric use.
  - The mythology of "individualized care" absent data on appropriate pediatric use delays needed research.
  - The feasibility of research then requires a waning of this enthusiasm which may undermine recruitment.
  - The availability of the drug "off label" outside of the clinical trial undermines the research, and results in a study population who may need the research for the provision of otherwise unavailable medical care.
- For new drugs, safer to receive "off label" drug in research. Also may be true for "off patent" drugs.



## Industry Pursuit of "Self-Interest"?

Sponsors pursue pediatric clinical trials late in drug's "life cycle" once true market value (exclusivity payoff) of a drug is known. Desire for "cost effectiveness" may bring... - Emphasis on enrollment, not quality Too many study objectives and procedures Inadequate PK/PD (wrong dose or interval) Protects IP (stock price? legal exposure?) by restricting access to clinical trial results.



## Academics "as usual"?

There is a lack of reward for participation in a clinical trial (i.e., single PI grant "culture" prevails) There is a lack of institutional support for clinical research infrastructure (e.g., study coordinators) There is discordance between academic and industry contracts (e.g., data use, publication, IP) There is lack of academic interest in "old drugs" There is resistance in moving from an academic model to an industry model in the design and conduct of clinical research (e.g., CRO, IRB)



## Lack of Transparency; Loss of Trust?

- Lack of justification for requested studies in FDA Written Requests may create "downstream" problems (i.e., "the FDA made me do it!")
- NIH RFP process for "off patent" drugs may lead to wasted effort (i.e., "guess what I'm thinking")
- IRBs prefer to deliberate "behind closed doors"
- Well-publicized failures (and delays) by industry to investigate or publish adverse results of clinical trials undermines public trust in clinical research.



## **Concluding Remarks**

- The ethical principles for research involving children are widely accepted and do not present a barrier to the responsible conduct of appropriately designed pediatric studies.
- The barriers that exist may arise from our reluctance to set aside "business as usual" (given the inertia of existing practices) to focus on the goal of finding efficient and effective ways to develop adequately studied drugs for the treatment of children.

