

# Risky Business: Exposing Children to Potential Harm Without Compensating Clinical Benefit

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Breakout C3, November 15, 2016

# Disclosure

- The views expressed in this presentation do not necessarily represent the policies of the Food and Drug Administration, the Department of Health and Human Services or the Department of the Navy.
- The speakers have no relevant personal, professional or financial relationship(s) with respect to this educational activity.

# Learning Objectives

- Research interventions and procedures that present more than minimal risk, but offer no prospect of direct benefit to children provoke controversy about their acceptability. This session will review critically the development of this category by The National Commission, and the ethical concerns it raises.
- During this session, faculty and attendees will:
  - Review the reasons for the development of this category of pediatric research by The National Commission.
  - Identify the ethical concerns raised by this category of pediatric research and how they might be addressed.
  - Apply this category of pediatric research to the analysis of the ethical acceptability of selected case examples.

# Topics

- Development of the regulatory framework found in 21 CFR 50/45 CFR 46 subpart D
  - Focus: §50.53/§46.406 (minor increase over minimal risk)
- Some Ethical Reflections on §50.53/§46.406
  - Normal children; scientific necessity; single standard
- Case Studies
  - Single dose PK studies; randomized withdrawal studies
  - Use of procedural sedation
  - “Invasive” placebos
  - Liver biopsy

# Origin of 21 CFR 50/45 CFR 46, subpart D

- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (referred to as the National Commission) issued the Report and Recommendations on Research Involving Children in January 1978.
- The ethical framework proposed by The National Commission was adopted as “subpart D” by HHS in 1983 (45 CFR 46) and FDA in 2001 (21 CFR 50).
- A review of their deliberations provides important background as we discuss and debate the ethics of exposing children to potential harm without compensating clinical benefit.

43 Fed. Reg. 2083 (1978)

# Research Involving Children

## The National Commission (1978)

- Research is necessary to safeguard and improve the health and well-being of children.
  - “Much research on childhood disorders or conditions necessarily involves children as subjects. The benefits of this research may accrue to the subjects directly or to children as a class. The Commission considers, therefore, that the participation of children in research related to their conditions should receive the encouragement and support of the federal government.”
- Children are vulnerable and require additional safeguards.
  - “The Commission recognizes, however, that the vulnerability of children, which arises out of their dependence and immaturity, raises questions about the ethical acceptability of involving them in research. Such ethical problems can be offset, the Commission believes, by establishing conditions that research must satisfy to be appropriate for the involvement of children.”

43 Fed. Reg. 2085 (1978)

# The Belmont Report



- As The National Commission was working on the report on research involving children, it was also discussing the ethical principles that should apply to all research.
- The three ethical principles that were identified, and became the foundation of The Belmont Report were:
  - Respect for Persons
  - Beneficence (and the corollary of non-maleficence)
  - Justice
- These ethical principles were woven into the rationale for The National Commission's recommendations on research involving children.

44 Fed. Reg. 23192 (1979)

# Three Principles

- Respect for Persons
  - “incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection.”
- Beneficence
  - “Two general rules have been formulated as complementary expressions of beneficent actions in this sense: (1) do not harm and (2) maximize possible benefits and minimize possible harms.”
- Justice
  - Equitable selection – for example, “it can be considered a matter a social justice that there is an order of preference in the selection of classes of subjects (e.g., adults before children).”

The Belmont Report - 44 Fed. Reg. 23192 (1979)



# General Conditions for All Research



- The research is scientifically sound and significant;
- Where appropriate, studies have been conducted first on animals an adult humans, then on older children, prior to involving infants;
- Risks are minimized by using the safest procedures consistent with sound research design and by using procedures performed for diagnostic and treatment purposes whenever feasible;
- Adequate provisions are made to protect the privacy of children and their parents;
- Subjects will be selected in an equitable manner.

Recommendation 2: 43 Fed. Reg. 2085 (1978)

# Early Agreement

- Two types of pediatric research were agreed upon early in The National Commission's deliberations.
  - Research that does not involve greater than minimal risk.
  - Research where an intervention presents greater than minimal risk, but where the risk is justified by the anticipated direct benefit to the enrolled children and the relation of the anticipated benefit to such risk is at least as favorable as that presented by available alternative approaches.

# Incorporation into subpart D



- General conditions incorporated into criteria for IRB approval of research found in 21 CFR 56.111(a)/45 CFR 46.111(a).
- The category of research that presents no more than minimal risk became 21 CFR 50.51/45 CFR 46.404.
  - Caveat: Definition of minimal risk in 21 CFR 56.102(i)/45 CFR 46.102(i) omits the phrase “of healthy children.”
- The category of research in which more than minimal risk is presented by an intervention that presents the prospect of direct benefit became 21 CFR 50.52/45 CFR 46.405.
  - Note (component analysis): Use of the term “intervention” is exceedingly important, as a single research protocol may contain interventions that do or do not offer any prospect of direct benefit to the enrolled children.

# Ethical Justification



- The National Commission concluded the ethical justification of these two types of research was “straightforward.” Two Commissioners dissented from another recommendation; however, there was unanimity on these two categories.
- The National Commission’s report includes two statements outlining the rationale for these two recommendations, each signed by an overlapping group of Commissioners.
- These two types of research are an application of the ethical principles of beneficence (and non-maleficence), along with the view that exposure to minimal risk activities falls within the appropriate scope of parental responsibility.

43 Fed. Reg. 2109, 2111 (1978)

# Developing an “Escape Hatch”

- The National Commission was concerned that limiting research to these two categories would exclude important research that may present greater than minimal risk without any compensating direct benefit to the enrolled children.
- Early themes in the discussion (March 1977) included:
  - “Grave public health concern”
  - “Full public disclosure and debate” (“National Advisory Board”?)
  - “Adequate protective measures could be developed” (i.e., benefit)
  - Examples discussed included polio and “swine flu” (1976 outbreak).
- The focus of subsequent discussion was to define criteria for use of the “escape hatch” and to clarify the process.

Meeting Transcript, March 7, 1977.

# Key Components



- “Public review and comment”
  - The National Commission did not want to allow approval of research under an “escape hatch” to be an administrative procedure absent oversight by “society” (e.g., Congressional review).
- “Sound ethical principles”
  - The National Commission viewed research approved under this category as applying (not suspending) the ethical principles of respect for persons, beneficence and justice to a “new and unanticipated state of affairs.”
- “Serious health problem”
  - The National Commission did not limit the research to a “national emergency” but did restrict it to research of “major significance”

Meeting Transcript, May 6, 1977.



# Incorporation into subpart D

- Recommendation for “National Advisory Board” (NAB) was incorporated into 21 CFR 50.54/45 CFR 46.407.
- The criteria for approval of a clinical investigation include:
  - presents a reasonable opportunity to further the understanding, prevention, or alleviation of a *serious problem* affecting the health or welfare of children; and,
  - consultation with a *panel of experts* in pertinent disciplines; and,
  - opportunity for *public review and comment*; and,
  - will be conducted in accordance with *sound ethical principles*; and
  - adequate provisions are made for soliciting the *assent* of children and the *permission* of their parents or guardians.
- However, a NAB was not established until 2003.



# Ethical Justification/Process

“Faced with such a hypothetical situation, the Commission found itself confronted by a common dilemma: regardless of whatever course is chosen, some benefit may be foregone and some harm may be done. Rather than attempt to resolve the dilemma in the abstract, the Commission has chosen to recommend that the ethical argument should be made, not over a hypothetical case, but over an actual situation, in which the real issues and the likely costs of any solution can be more clearly discerned.”

(continued)

43 Fed. Reg. 2112 (1978)



# Ethical Justification/Process

“The ethical principles at stake are the moral obligation to protect the community or to come to the aid of certain sufferers within it and the moral prohibition against using unconsenting persons, at considerable risk to their well-being, for the promotion of the common good. These principles are of such moment and their observance so basic to a just and humane society that any debate about their application should be held at the most public level of discourse.”

43 Fed. Reg. 2112 (1978)

# Limiting Referrals to a NAB

- The National Commission developed a fourth category of research out of concern that frequent referral to a National Advisory Board would prove burdensome.
- The recommendation for this category of research proved controversial, and provoked two dissenting statements in the final report.
- Concerned that this category could be abused based on an assessment that the research is important, The National Commission added the restriction that the risks of the interventions that do not offer any prospect of direct benefit must be no more than “a minor increase over minimal risk.”

Meeting Transcript, May 6, 1977.

# Incorporation into subpart D

- The recommendation to allow for local IRB discretion for interventions that do not hold out a prospect of direct benefit yet presents no more than a minor increase over minimal risk was incorporated into 21 CFR 50.53/45 CFR 46.406.
- Additional criteria necessary for approval include:
  - presents experiences to subjects that are *reasonably commensurate* with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
  - likely to yield generalizable knowledge about the subjects' disorder or condition that is of *vital importance for the understanding or amelioration of the subjects' disorder or condition*; and
  - Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

# Difficult Ethical Problem

“A difficult ethical problem remains, for example, about research that presents more than minimal risk without immediate prospect of direct benefit to the children involved. Some have argued that such research is inadmissible, while others have pointed out that this limit would rule out much research promising great benefit to children in the future. Here again, as with all hard cases, the different claims covered by the principle of beneficence may come into conflict and force difficult choices.”

The Belmont Report - 44 Fed. Reg. 23194 (1979)

# Ethical Justification

“Most of the Commissioners agreed that a minor increase in risk would be permissible in order to attain *substantial future benefits* to children other than the subject. “Minor increase” refers to a risk which... poses *no significant threat* to the child's health or well-being. Moreover, the Commission requires that the research activities presenting such risks be similar to the experiences familiar to the children who would be the subjects of the research, *Such activities, then, would be considered normal for these children.*”

(continued)

43 Fed. Reg. 2112 (1978)

# Ethical Justification

“Given this conservative limit, the Commission concluded that promise of substantial benefit does justify research which goes beyond, but only slightly beyond, the minimal risk. The Commission considers that... permission to allow such research lies *within the scope of parental responsibility*.”

43 Fed. Reg. 2112 (1978)

# Additional Safeguards

## 21 CFR 50/45 CFR 46, Subpart D

- Not involving greater than minimal risk (§50.51; §46.404)
- Greater than minimal risk but presenting the prospect of direct benefit to individual subjects (§50.52; §46.405)
- Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about subjects' disorder or condition (§50.53; §46.406)
- Not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (§50.54; §46.407)
- Requirements for permission by parents or guardians and for assent by children (§50.55; §46.408)

# Topics

- Development of the regulatory framework found in 21 CFR 50/45 CFR 46 subpart D
  - Focus: §50.53/§46.406 (minor increase over minimal risk)
- Some Ethical Reflections on §50.53/§46.406
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# Dissenting Statement (Turtle)



“The substantial majority of the Commission (9-2) has committed clear error in approving recommendation (5) [§50.53/§46.406], potentially subjecting sick children to greater risks than other children without regard to foreseeable benefit.”

1. “Sick children cannot be deemed to be a morally relevant separate class for purposes of relaxing protective measures and mechanisms.”
2. “Sick children, if capable of being placed into a morally relevant separate class, would require even greater protection than that afforded to children in general.”
3. “There is no legal, ethical or social basis for subjecting sick children to more than minimal risks merely because a foreseeable benefit might accrue to an identifiable class of children in the future.”

43 Fed. Reg. 2113 (1978)

# Response by Dr. Ryan (Chair)



Slide 1 of 2

- Conservative Definition of Minimal Risk
  - “The Commission has adopted a conservative definition of "minimal risk," i.e., the risk of harm that is normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children.”
- Only “minor” or “slight” Additional Risk
  - “Virtually the entire Commission is in agreement that a "minor" or "slight" additional risk over that normally encountered may ethically be presented in very limited circumstances by research not intended to benefit directly the children who are subjects.”

43 Fed. Reg. 2114 (1978)

# Response by Dr. Ryan (Chair)



Slide 2 of 2

- Ethical Principle of Scientific Necessity
  - “The limited circumstances under which such research may be approved under Recommendation (5) clearly indicate that the research must be related to the disorder or condition affecting those subjects who are involved. Such research cannot by its very nature be conducted on normal subjects.”
  - “The Commission's intention in Recommendation (5), and the likely effect of this recommendation, are clearly not to encourage any unnecessary involvement of sick children in research, but rather to permit the conduct of research intended to develop important knowledge of disease states from which certain children suffer and for which research they are the only appropriate subjects.”

43 Fed. Reg. 2114 (1978)

# Dissenting Statement (Turtle)



## Involvement of Normal Children?

- “Nowhere is such a direction countered by any requirement that research projects not involve sick children if normal children would likewise be scientifically appropriate subjects.”
- “The Commission notes that "the scope of parental authority routinely covers a child's participation in many activities in which risk is more than minimal, and yet benefit is questionable. ...This same rationale holds true for normal children as well as sick children.”
- “Both sets of Commission deliberations conclude that "foreseeable benefits in the future to an identifiable class of children may justify a minor increment of risk to research subjects." That statement can be used to justify large quantities of applied research utilizing sick as opposed to normal children. The statement itself is without legal, ethical or social justification. If such justification did exist, it could be applied equally as well to normal children.”

43 Fed. Reg. 2113-14 (1978)

# Implementing §50.54/§46.407

- Protocols (since public review process established in 2003)
  - Effects of a Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder: A Functional MRI Study (2004)
  - Precursor Preferences in Surfactant Synthesis of Newborns (2005)
  - Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty (2005)
  - A Phase III Randomized Trial of Granulocyte Colony Stimulating Factor Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source in Matched Sibling Donor Transplantation (2008)
- Common Theme
  - Administration of an intervention that presented a minor increase over minimal risk to children lacking a disorder or condition (i.e., normal, healthy children).

# Some Ethical Reflections



## The Ethical Principle of Scientific Necessity in Pediatric Research

- “The rationale for the inclusion of children with a disorder or condition is scientific necessity rather than in-kind benefits.... “Shared vulnerability” and the goal of “to-kind benefits” are not assumed by the federal regulations that provide additional protections to children enrolled in research.”

Roth-Cline M and Nelson R. Am J Bioethics 2014;14:14-15.

## In Defense of a Single Standard of Research Risk for All Children

- “Whether a child ought to be exposed in research to a minor increase over minimal risk, assuming scientific necessity, should not depend on whether he or she has a condition or disorder. Rather, the “scrupulous parent” standard should be interpreted to incorporate both minimal risk and a minor increase over minimal risk within a single ethically justified standard.”

Nelson RM and Ross LF. J Pediatr 2005;147:565-6.

Caveat: IRBs may lack expertise to assess scientific necessity.

# Defining Acceptable Risks

(Note: Parent/Child Perspectives Important)

- The definition of risk as “the probability and magnitude of harm” gives the misimpression that risk assessment can be purely quantitative.
- The disvalue of a harm (or risk) cannot be quantified to where a uniform or comparative standard can be established.
- Defining “minimal risk” by using as a “reference” either “daily life” or “routine examinations” reduces a moral evaluation to a comparison of “factual” risks.
- The fact that a risk occurs outside of research setting (whether in “daily life” or during “routine examinations”) does not make that same risk morally acceptable in the research context.

Rossi J and Nelson RM J Med Ethics 2012; 38:423-7.

# Topics

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# OTC<sup>†</sup> Cough & Cold Products (1 of 2)

- Single-dose PK studies of OTC cough and cold products are necessary to establish the correct dose to be used in subsequent efficacy studies.
- Based on available data, a single dose of an OTC cough and cold product may not offer a prospect of direct benefit to the enrolled child, but can be considered a “minor increase over minimal” risk (but not “minimal” risk).
- Therefore, enrolled children must have a disorder or condition.

† OTC = "over the counter" (i.e., non-prescription)

# “Disorder or Condition”

- FDA regulations do not define either “disorder” or “condition”
- A Proposed Definition
  - “A specific (or set of specific)... characteristic(s) that an established body of scientific evidence or clinical knowledge has shown to negatively affect children’s health and well-being or to increase their risk of developing a health problem in the future.”

Institute of Medicine (US): Recommendation 4.3<sup>†</sup>

- Key Concept: being “at risk” for disorder or disease.
- Using the word “healthy” can be misleading.
  - A child can be healthy and “at risk” (i.e., have a “condition”); a child with a condition may not have the condition related to the research (and thus be “healthy”).

<sup>†</sup> IOM, Ethical Conduct of Clinical Research Involving Children (2004)

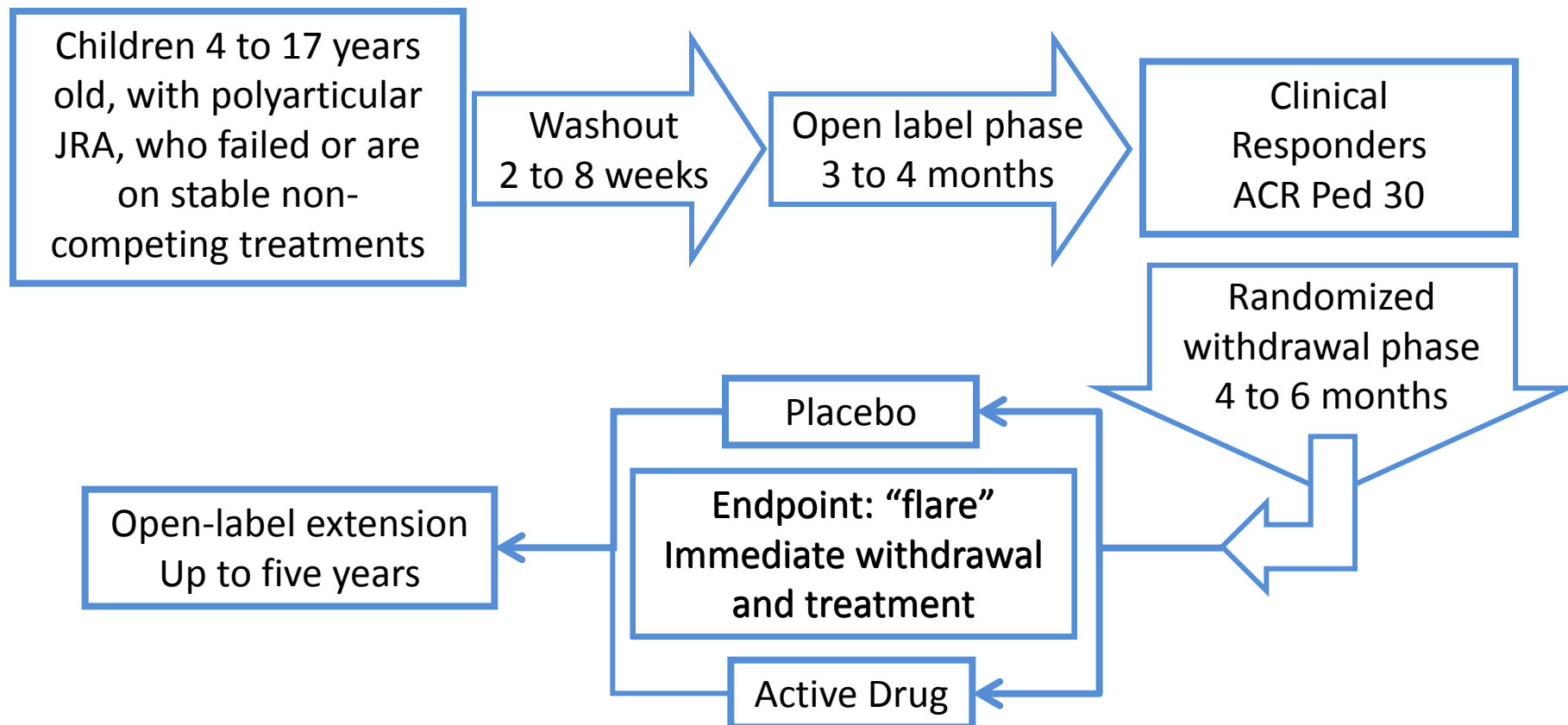
# OTC<sup>†</sup> Cough & Cold Products (2 of 2)

## *Who may be enrolled?*

- Children who are symptomatic from a cold have a condition (disease).
- Asymptomatic children may be “at risk” for a cold based on empirical data that clearly defines an “at risk” population (using US data).
  - *Frequency Criterion*: >6 infections per year for children aged 2 to <6 yrs and >4 infections per year for children aged 6 to <12 yrs.; AND,
  - *Crowding Criterion*: ≥4 persons living in the home or ≥3 persons sleeping in one bedroom; AND,
  - *Exposure Criterion*: another ill family member in home or child in the family who is attending preschool or school with ≥6 children in group.

† OTC = "over the counter" (i.e., non-prescription)

# Enrichment Design with Randomized Withdrawal<sup>†</sup>



<sup>†</sup> Used for etanercept, adalimumab, abatacept and tocilizumab

# Enrichment Design with Randomized Withdrawal

- Use of placebo injections
  - Limited in scope (i.e., only children with clinical response in open label phase) and duration (i.e., immediate withdrawal upon disease flare to open label treatment; re-induction of clinical response).
  - Thus “minor increase over minimal risk” (21 CFR 50.53/45 CFR 46.406)
- Valid test of the ‘null hypothesis’
  - If “flare” rate of placebo > drug, then some (not all) treatment effect seen in open label study phase due to efficacy of the drug.
- Open label phase overestimates drug response rate as it includes placebo response (i.e., clinical response rate).
- No randomized placebo controlled safety data.

# Topics

- Development of the regulatory framework found in 21 CFR 50/45 CFR 46 subpart D
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# Caveat: Risks of Neurotoxicity

- Risks to neurocognitive development must be considered when performing "research only" procedures requiring sedation. However, we do not intend to discuss this issue today.
- Assume duration of cumulative exposure to general anesthetics and/or sedatives is *below the threshold* (e.g., less than three hours) or that the children are *beyond the age of vulnerability* (e.g., over three years) at which these neurotoxic changes in the developing brain may be observed in non-clinical animal models.
- Children who are less than three years of age are included in the following examples to illustrate that many FDA-regulated studies may enroll children who are within an age range in which the possibility of anesthetic-associated neurotoxicity is a concern.

## Example 1: MPS Type IIIA (Sanfilippo syndrome type IIIA)

- Randomized, open-label, concurrently controlled safety and efficacy study of children with Mucopolysaccharidosis (MPS) type IIIA
- Children are  $\geq 12$  months and  $\leq 48$  months of age at baseline
- Intrathecal (IT) administration of drug every 2 weeks, every 4 weeks, or a no drug control
- Outcome measures require cerebral spinal fluid (CSF) assessment and periodic magnetic resonance imaging (MRI)
- MRIs usually require procedural sedation in this age group, and sedation may be used for lumbar punctures (LPs) to obtain CSF



# LPs in Patients Receiving Active Drug

- Assume administration of the drug is approvable under 21 CFR 50.52 (prospect of direct benefit)
- Risk of LPs and any procedural sedation necessary to administer the investigational drug is judged against the potential benefits of the drug
- This is true because LPs are necessary to administer the drug intrathecally (i.e., into the spinal fluid)

# CSF Measurements

## Patients Receiving Active Drug

- Additional CSF measurements merely require a small additional volume of CSF that may be withdrawn when children are already undergoing LPs for the purpose of receiving an investigational drug
- If CSF measurements for outcome assessments are obtained at the same time as drug is administered, then there is little additional risk to children

## Patients Not Receiving Active Drug

- The risks of the LP cannot be weighed against the benefit of a drug if no drug is given during the LP.
- CSF assessment is not standard of care, and would not otherwise guide treatment in this population of children.
- Thus, LPs for CSF assessments (along with any procedural sedation) do not offer a prospect of direct benefit to children who do not receive an active drug during the LP.

# MRI Scans

- All enrolled patients would undergo periodic MRI scans for research endpoints
- Periodic MRI scans are not standard of care and would not guide treatment in this patient population
- Thus, MRI scans would not offer a prospect of direct benefit, and cannot be evaluated under 21 CFR 50.52
- Nontherapeutic procedures (not offering a direct benefit) may be evaluated under 21 CFR 50.53 or a “minor increase over minimal risk”

# Overall Assessment

- To be approvable under 21 CFR 50.53, the risks of the nontherapeutic procedures *and the procedural sedation necessary to perform them* must not exceed a minor increase over minimal risk
- If some forms of procedural sedation are determined to pose more than a minor increase over minimal risk, federal panel review would be required under 21 CFR 50.54 if these forms of sedation are used for nontherapeutic procedures

## Example 2: Spinal Muscular Atrophy

- Phase 3 multicenter, double-blind, randomized, sham-procedure controlled study
- Ages 2 to 12, with SMA onset at > 6 months of age
- IT drug or sham procedure (i.e., needle prick in the skin of the lower back where LP is usually performed)
- Procedural sedation may be used to facilitate LPs/sham injections

# Assessment of Lumbar Punctures



## Patients Receiving Active Drug

- Assume administration of the drug is approvable under 21 CFR 50.52 (prospect of direct benefit)
- Risk of LPs and any procedural sedation necessary to administer the drug is then judged against the potential benefits of the investigational product

## Patients Not Receiving Active Drug (Sham LP)

- No prospect of direct benefit from the sham procedure (regardless of any placebo effect)
- Sham LPs and any procedural sedation necessary to maintain blinding may not be assessed under 21 CFR 50.52
- To be approvable under 21 CFR 50.53, the risks of the sham procedures and any procedural sedation necessary to maintain blinding must not exceed a minor increase over minimal risk

# Example 3: Limb-Girdle Muscular Dystrophy Type 2D

- Dose escalation study of gene transfer product
- Ages 7 years and older with LGMD2D
- Gene delivery by arterial injection
- The study requires muscle biopsies performed at baseline and at day 180 for the purpose of establishing the effects of gene transfer
- Anesthesia/sedation is required for muscle biopsies

# Assessment of Muscle Biopsies (1 of 2)

## Prospect of Direct Benefit?

- Whether muscle biopsies could be considered beneficial in this patient population is doubtful
- Not clinically indicated for disease management
- Unclear whether biopsies in the research setting would be necessary for safety considerations (e.g. therapeutic drug monitoring)
- If muscle biopsies are nontherapeutic, the biopsy and associated anesthesia/sedation cannot be evaluated under 21 CFR 50.52



# Assessment of Muscle Biopsies (2 of 2)

- As before, all children in the study have a disorder or condition (LGMD2D)
- The muscle biopsy and procedural sedation could be evaluated as to whether they present no more than a “minor increase over minimal risk” (21 CFR 50.53)
- If the biopsy and sedation were not approvable under this category, protocol would need to be referred by an IRB for federal panel review under 21 CFR 50.54

# Pediatric Ethics Subcommittee of Pediatric Advisory Committee (PAC)



## Question 1 (non-voting):

- Please discuss the factors which should be taken into account when designing a protocol to provide procedural sedation for nontherapeutic procedures in pediatric clinical investigations.
- In light of these (and any other) factors, please comment on how the risks of procedural sedation may be minimized. In addition, please comment on how these factors may influence your assessment of whether one or more approaches to procedural sedation may be considered a minor increase over minimal risk.

March 23, 2015

# PAC Pediatric Ethics Subcommittee



The Subcommittee generally agreed that

- (1) procedures should be performed at a high volume center with a dedicated pediatric sedation service;
- (2) there should be rigorous scientific justification for the need for the nontherapeutic procedures;
- (3) the approach to procedural sedation and risk minimization procedures should be described in the protocol;
- (4) children with chronic conditions that may place them at higher risk from procedural sedation should be carefully evaluated and potentially excluded from the protocol;

continued

March 23, 2015

# PAC Pediatric Ethics Subcommittee



The Subcommittee generally agreed that

- (5) nontherapeutic procedure should be terminated if complications of sedation arise or level of sedation inadequate; inappropriate to escalate procedural sedation beyond what would be considered a minor increase over minimal risk;
- (6) if particular procedure in particular patient population normally accompanied by sedation when performed for clinical reasons, sedation should not be withheld in the nontherapeutic research setting to avoid risks and enhance procedure's approvability; and
- (7) clear communication with potential subjects (and parents) about nontherapeutic nature of procedures and procedural sedation

March 23, 2015

# PAC Pediatric Ethics Subcommittee



## Question Two (voting):

- Assuming the risks have been minimized, are there one or more approaches to procedural sedation that would present no more than a minor increase over minimal risk? (Yes/No)
- Following the vote you will have the opportunity to comment individually on the factors you considered in making your assessment.

March 23, 2015

# PAC Pediatric Ethics Subcommittee



## Committee Vote and Discussion: YES: 7 NO: 9

- The Subcommittee was not able to agree on whether one or more approaches to procedural sedation would present no more than a minor increase over minimal risk.
  - Members voting yes cited the importance of limiting nontherapeutic procedural sedation to high-volume centers with highly experienced providers, and to children for whom procedural sedation would not pose elevated risks (e.g. based on ASA risk classification).
  - Members voting no commented that procedural sedation posed greater risks than those allowed under a minor increase over minimal risk category or were concerned about the likelihood that nontherapeutic procedures requiring sedation would be allowed in situations that posed greater risk to children.

March 23, 2015

# AAP Guidelines: Update 2016



- “The work of the Pediatric Sedation Research Consortium has improved the sedation knowledge base, demonstrating the marked safety of sedation by highly motivated and skilled practitioners from a variety of specialties practicing the above modalities and skills that focus on a culture of sedation safety.”
- “However, these groundbreaking studies also show a low but persistent rate of potential sedation-induced life-threatening events, such as apnea, airway obstruction, laryngospasm, pulmonary aspiration, desaturation, and others, even when the sedation is provided under the direction of a motivated team of specialists.”

Cote CJ et al. Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures: Update 2016. Pediatrics 2016

# Topics

- Development of the regulatory framework found in 21 CFR 50/45 CFR 46 subpart D
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# Placebo (Sham) Controls in Pediatrics



- Sham procedures (and placebos) do not offer any prospect of direct benefit to the enrolled child.
- Two types of risk
  - Risk of placebo itself may be “minimal” unless placebo is invasive (e.g. sham injections)
  - Risk of harm from not receiving “proven” or “effective” treatment.
- Both types of risk must be no greater than a “minor increase over minimal risk” (21 CFR 50.53/45 CFR 46.406)
  - This approach consistent with ICH E-10 and 2013 Declaration of Helsinki.

# “Invasive” Placebos

- What is an acceptable placebo risk? One subcutaneous injection? An intramuscular injection? Peripheral Intravenous Catheters? For how long? Percutaneous inserted central catheters (PICC)? Sham surgery?
- How many “low” risk interventions (e.g. sham injections) are still “low” risk?
  - 1 year double-dummy study of oral versus weekly injectable drugs for multiple sclerosis?
  - 2 year placebo-controlled trial using daily injections of human growth hormone?

# Example: RSV Treatment with Interferon-alpha 2a

- RCT of interferon for children with RSV
- 3 injections of either interferon or placebo
- (Assume interferon offers PDB)
- Placebo (sham) injections offer no medical benefit (even if other medical care is provided in the protocol) so the sham injections must be minimal risk or a minor increase over minimal risk

# Topics

- Development of the regulatory framework found in 21 CFR 50/45 CFR 46 subpart D
  - Focus: §50.53/§46.406 (minor increase over minimal risk)
- Some Ethical Reflections on §50.53/§46.406
  - Normal children; scientific necessity; single standard
- Case Studies
  - Single dose PK studies; randomized withdrawal studies
  - Use of procedural sedation
  - “Invasive” placebos
  - Liver biopsy

# Cysteamine Bitartrate for Treatment of NAFLD in Children (CyNCh)



- Multi-center, placebo-controlled, double blind, clinical trial of children ages 8 to 17 years with biopsy-confirmed moderate to severe nonalcoholic fatty liver disease (NAFLD).
  - Inclusion: Liver biopsy within 90 days of screening visit and not more than 120 days before randomization.
- Primary Outcome Measure:
  - Improvement in NAFLD - assessment of histologic improvement between baseline liver biopsy and follow-up biopsy after 52 weeks of treatment with cysteamine bitartrate
- Study conducted between June 2012 and September 2015

Schwimmer JB, et al. Gastroenterology (2016), doi: 10.1053/j.gastro.2016.08.027.

NCT01529268; IND 114,924

# Cysteamine Bitartrate (CBDR) for Treatment of NAFLD in Children (CyNCh)



- Enrolled 169 children, with repeat liver biopsies in 146 children
  - No validated non-invasive measure for the severity of NAFLD
  - First clinical trial for any pediatric liver disease to use changes in liver histology as primary outcome
- Liver biopsy complications “uncommon, generally mild in severity and self-limited”
  - No cases of clinically apparent bleeding or infection.
  - Pain reported in 5/146 (3%) children following repeat liver biopsy; in 4/5 children, pain resolved within 24 hours; remaining child hospitalized after liver biopsy for pain that resolved with supportive care.
  - “liver biopsy is an acceptable and important outcome measure for clinical trials of pediatric NAFLD as it was safe, well tolerated, and feasible.”

Schwimmer JB, et al. Gastroenterology (2016), doi: 10.1053/j.gastro.2016.08.027.

# Sonography-Guided Percutaneous Liver Biopsies in Children

- Retrospective analysis of 597 liver biopsies in 470 patients (270 male; 200 female; mean age of 10.5 years, range 1 month-21 years), performed either under sedation (n=311, 52.1%) or general anesthesia (n=286, 47.9%).
- Diagnostic yield obtained in 596 biopsies (99.8%) from an average of 2.4 cores in patients with diffuse disease (n=541, 90.6%) and 6.5 cores in patients with focal disease (n=55, 9.2%).
- Ten patients (1.7%) experienced a major complication, including pneumothorax (n=1, 0.2%), abdominal wall pseudoaneurysm (n=1, 0.2%), and symptomatic bleeding (n=8, 1.3%). Five of these children required transfusion, two were only admitted for observation, and one required surgical evacuation. There were no procedure-related deaths.
- Minor complications (n=49, 8.2%) included a symptomatic subcapsular hematoma (n=35) and stable small hemoperitoneum (n=9).

Govender, P et al. (2013). AJR Am J Roentgenol 201(3): 645-65

# Thank you.

