

# Ethical Challenges in Clinical Trial Design Lessons Learned from DMD

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# Disclaimer

- The views expressed in this presentation do not necessarily represent the policies of the Food and Drug Administration or the Department of Health and Human Services.
- Robert Nelson has no financial conflicts of interest to disclose.

# Topics Covered

- 1) Basic Ethical Framework in Pediatrics
  - Key Concepts: Prospect of Direct Benefit; Component Analysis
- 2) Use of Muscle Biopsies as a Biomarker
  - Need for Procedural Sedation and/or General Anesthesia
- 3) Choice of Control Group
  - Placebo (Sham) Controls in Pediatrics
  - Early Randomization
  - “Gaming” or “Improving” the System?

# Basic Ethical Framework in Pediatrics

1. Children should only be enrolled in research if the scientific and/or public health objective(s) cannot be met through enrolling subjects who can consent personally (i.e., adults).
2. Absent a prospect of direct therapeutic benefit, the research risks to which children are exposed must be “low.”
3. Children should not be placed at a disadvantage by being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care.
4. Vulnerable populations unable to consent (including children) should have a suitable proxy to consent for them.

# Additional Safeguards for Children



## 21 CFR 50 Subpart D

### (Appropriate Balance of Risk and Benefit)

- Research interventions involving children either
  - “Low Risk Pathway” - must be restricted to “minimal” risk or a “minor increase over minimal” risk absent a potential for direct benefit to the enrolled child, or
    - 21 CFR 50.51/53;45 CFR 46.404/406
  - “Higher Risk Pathway” - must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.
    - 21 CFR 50.52;45 CFR 46.405

# Two Key Concepts

- Prospect of Direct Benefit
  - The risks to which a child may be exposed depend on whether the intervention does or does not offer that child a prospect of direct benefit.
  - Thus, defining and assessing the possibility of direct (clinical or therapeutic) benefit is an essential aspect of the ethical acceptability of the (interventions included in a) research protocol.
- Component Analysis
  - A protocol may (and usually does) contain multiple interventions or procedures, some that offer a prospect of direct (clinical) benefit and others that do not.
  - These interventions and procedures must be analyzed and justified separately (i.e., as “components” of the protocol).
  - Thus, a protocol may include components that must be evaluated under 21 CFR 50.52 and others that must be evaluated under 21 CFR 50.51/53.

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# Use of Muscle Biopsies as a Biomarker in Muscular Dystrophies

- At a minimum, muscle biopsies are performed at baseline and study completion to measure effect of an experimental product
- Other than to establish the initial diagnosis, muscle biopsies are not clinically indicated for disease management and do not offer a prospect of direct clinical benefit to the enrolled child
- In addition, anesthesia/sedation is required for muscle biopsies
- Thus, the muscle biopsy and anesthesia/sedation must present no more than a “minor increase over minimal risk” (21 CFR 50.53)
- Otherwise, the protocol could 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.

## 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)

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



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



# Source of Ongoing Controversy

- Some IRBs approve the muscle biopsy/procedural sedation under 21 CFR 50.52 (ignoring that biopsies may be performed in children randomized to a placebo and/or an untreated control), believing the procedure exceeds a minor increase over minimal risk, rather than refer for federal review under 21 CFR 50.54.
  - This approach is not in compliance with FDA regulations
- Dystrophin levels are not yet proven (i.e., validated) as a surrogate marker of meaningful clinical benefit, but may serve as the basis for an accelerated approval (“reasonably likely”).
- The controversy should provide us with a sense of urgency to develop alternative biomarkers that are less invasive and do not require a surgical procedure under general anesthesia.



# Good Science is a Moral Obligation

- “The poor quality of many of the biopsies and the failure of the sponsor to implement a high-quality procedure for assay validation led to a situation in which only a fraction of the data could be used to make the regulatory decision. Given the serious nature of the disease and the invasiveness of the procedures, any studies must be conducted according to the highest standards, so that each child and parent who volunteers can be confident that they have contributed as much as possible to the generalizable knowledge needed to provide effective treatment based on high-quality evidence.”

Memorandum, Robert M. Califf, M.D., FDA Commissioner (September 16, 2016): Scientific Dispute Regarding Accelerated Approval of Sarepta Therapeutics' Eteplirsen (NDA 206488) — Commissioner's Decision (page 10).

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# Choice of Control Group



- Placebo Control (i.e., masking treatment assignment)
  - Concurrent “no treatment” control (i.e., not masked)
  - May be used in “add on” trial of a new treatment compared to existing standard of care (or known effective treatment)
- Another Alternative (avoids use of placebo)
  - Dose-response design (but need separation between doses)
- Active Treatment Control
  - Non-inferiority design (based on previous placebo-controlled trials so that a non-inferiority margin can be estimated)
  - Superiority design (as is done with a placebo control)
- External Controls
  - Retrospective (or prospective) “natural history” control

# Placebo (Sham) Controls in Pediatrics



- Placebos (and sham procedures) do not offer any prospect of direct benefit to the enrolled children
- Placebos present two types of risk
  - Placebo risk itself may be “minimal” unless invasive (e.g. injections)
  - Risks from withholding “proven” or “known effective” treatment
- Both types of risk must be no greater than a “minor increase over minimal risk” (21 CFR 50.53)
  - This approach consistent with ICH E-10 and 2013 Declaration of Helsinki.
- Placement of an indwelling port or central catheter (PICC) exceeds this level of risk, and thus is not approvable for children receiving placebo infusions absent referral for federal panel review under 21 CFR 50.54

# Randomization

- A randomized controlled trial (regardless of the choice of control group) should be performed as early as possible in the development program to avoid potentially misleading and uninterpretable findings from open-label clinical trials.
- Absent the use of biomarkers and/or clinical endpoints resistant to manipulation, treatment assignment must be masked.
  - The results of the six-minute walk test can be manipulated through coaching/training and/or altered motivation.
- Dose-response design avoids use of placebo (and problem of long-term intravenous access absent prospect of direct benefit); however, difference in doses must be sufficient to show clear separation in dystrophin levels/meaningful clinical endpoints (while still providing a prospect of direct benefit at both doses).

# “Gaming” or “Improving” System?

- Clinical trials may be “enriched” with children thought to have the best chance of a more robust response to an experimental intervention to improve the efficiency of the clinical trial.
- Children who are less severely affected may be excluded, with some parents “coaching” their child to “slow down” and thus meet the inclusion criterion based on the 6MWT.
  - If coaching is stopped in a “masked” RCT, the placebo group will improve. If coaching is not stopped, the active intervention group will not improve. Either way, the integrity of the RCT is undermined.
- Children who are more severely affected may be excluded, given their inability to perform required outcome measure (6MWT).
  - However, there are clinically meaningful benefits of treatment if a child who is unable to walk can maintain upper extremity function.

# “Improving” the System?

- Share existing clinical data (including natural history) to develop a disease progression model that will support future product development (see <https://c-path.org/programs/d-rsc/>)
- Develop meaningful clinical endpoints that do not require walking, and are more resistant to “coaching”
- Develop reliable non-invasive biomarkers that do not require surgery and general anesthesia
- Develop more sensitive “time to event” endpoints, allowing for earlier enrollment and cross-over to active treatment
- Expand inclusion criteria for clinical trial enrollment to include less (and more) affected children, perhaps with stratified analysis
- Develop expanded access programs for children not eligible for clinical trials, collecting standardized efficacy and safety data.

# Thank you.

