

# Research Involving Children

## (Focusing on FDA Regulations)

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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

## 1) The Basic Ethical Principles of Pediatric Research

- ✓ Two Key Concepts – Direct Benefit and Component Analysis
- ✓ The “low risk” and “higher risk” pathways for pediatric product development

## 2) The Application of Component Analysis

### ✓ Case: The ESSENCE Protocol

“A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy (DMD)”

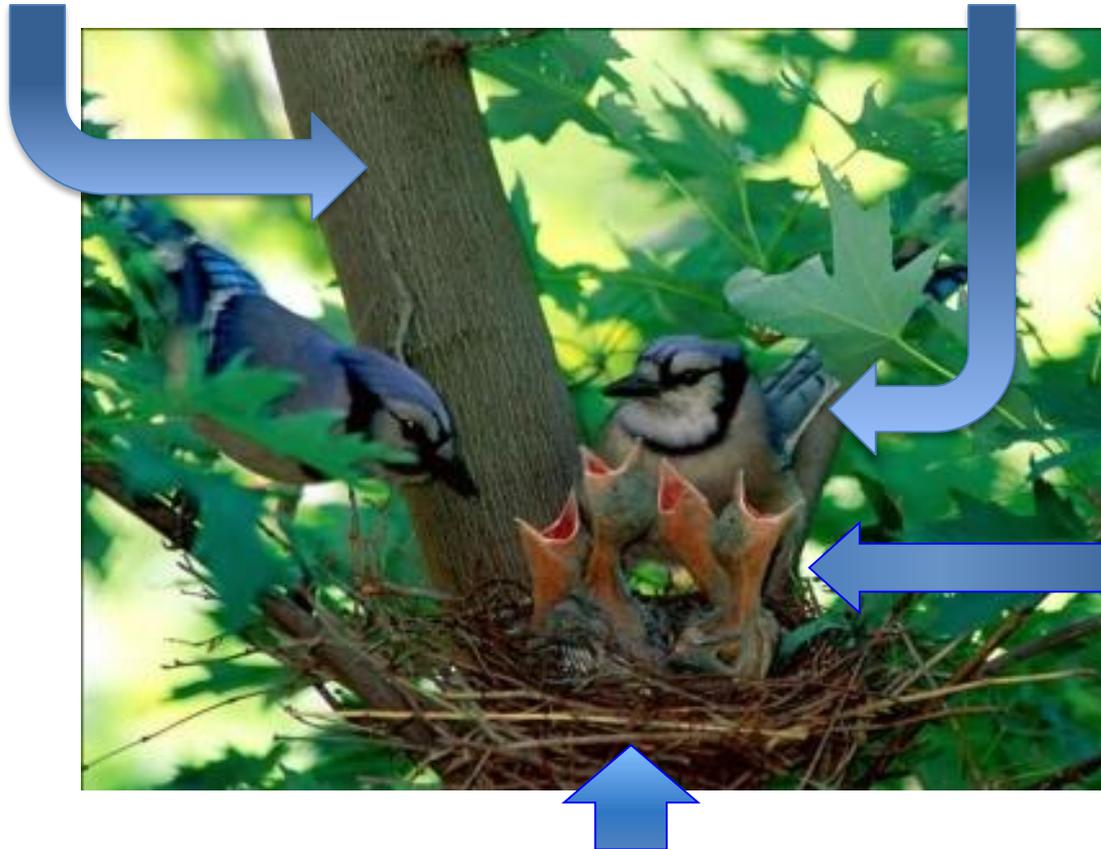
# Basic Ethical Framework in Pediatrics

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.

# “Nested” Protections

1: Scientific Necessity

4: Parental Permission



4: Child Assent

2,3: Appropriate Balance of Risk and Benefit

# Ethical Principle of Scientific Necessity



- Children should not be enrolled in a clinical trial unless necessary to answer an important scientific and/or public health question about the health and welfare of children
  - Practical application (using extrapolation): determine the type (and timing) of clinical studies required to establish "safe and effective" pediatric use of drugs or devices
- Derives from requirements for equitable selection<sup>†</sup>
  - Subjects capable of informed consent (i.e., adults) should generally be enrolled prior to children

<sup>†</sup> Minimize Risks and Equitable Selection [US 21 CFR 56.111(a)(1) and (b)]

# General Justification of Research Risk (Both Adult and Pediatric)



- Criterion for IRB approval of research.
  - Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.
    - 21 CFR 56.111(a)(2); 45 CFR 46.111(a)(2)
- This general criterion is modified by the additional protections for children enrolled in clinical investigations and/or research in that there is a limit to the risk that knowledge can justify.

# Additional Safeguards for Children



## 21 CFR 50 Subpart D

### (Appropriate Balance of Risk and Benefit)

- Research involving children either
  - 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
  - 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

# 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)<sup>†</sup>
- Requirements for permission by parents or guardians and for assent by children (§50.55; §46.408)

# Two Key Concepts

- Prospect of Direct (Clinical) 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.
  - A “direct benefit” of an experimental intervention or procedure should improve the health or well-being of the individual child.
  - Thus, assessing the prospect of direct (clinical/therapeutic) benefit is an essential aspect of the ethical acceptability of the research protocol.
- Component Analysis
  - A protocol usually contains 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 50.53.

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# Linking Science and Ethics

- To start a pediatric clinical trial, the ethical challenge is to establish sufficient evidence using either preclinical animal models or adult human clinical trials<sup>†</sup> to conclude:
  - “Low Risk” Pathway: Absent sufficient prospect of direct benefit, administration of investigational product to children presents an acceptably “low” risk (minimal, minor increase over minimal), or...
    - 21 CFR 50.51/50.53 (cf. ICH E-6 §4.8.14)
  - “Higher Risk” Pathway: Administration of investigational product to children presents a sufficient prospect of direct benefit to justify “higher” risks.
    - 21 CFR 50.52

<sup>†</sup> Data also may come from post-marketing pediatric (i.e., "off label") and/or adult data



# “Low” Risk in FDA Regulations

- “Minimal risk” is defined as those risks “ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” [21 CFR 50.3(k)]
  - This definition should be indexed to the experience of “healthy children” (as originally proposed by The National Commission in 1978).
  - Generally, administration of an experimental drug/biological product is not considered “minimal” risk.
- Interventions/procedures that do not offer a prospect of direct benefit must be no more than a “minor increase over minimal risk;” and enrollment limited to children with a “disorder or condition” (absent a federal exception). [21 CFR 50.53]
  - There is no definition of a “minor increase over minimal risk.” The National Commission described is as “slightly more” than minimal risk, and not presenting any “substantial risk.” (Caveat: “Relative” Definition)



# 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 the research setting (whether in “daily life” or during “routine examinations”) does not make that same risk morally acceptable in the research context.

# “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†

- 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”).

† IOM, Ethical Conduct of Clinical Research Involving Children (2004)



# Key Points: “Low Risk” Pathway

- Need to be able to generate an accurate risk estimate for administration of the investigational product given adult testing experience AND this risk estimate needs to indicate that risks are sufficiently “low” to proceed under this pathway.
- If risks are not “low” OR insufficient information is available to generate an accurate risk assessment, product will be considered under the “higher risk” pathway.
- Some single-dose PK studies may be considered “low” risk.
- Longer-term dosing of investigational drugs or biological products generally not considered “low” risk.

# “Higher Risk” Pediatric Studies



- For “higher risk” interventions, administration of FDA-regulated products in a clinical investigation 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.
  - Additional Safeguards for Children (21 CFR 50.52)
- Thus, we need “proof of concept” data from human adults and/or animal disease models establishing a sufficient prospect of direct benefit to justify exposing children to the known (and unknown) risks of the intervention.
- This requirement does not imply that adult studies must be completed before beginning pediatric studies. Rather, once sufficient adult and/or animal data exist to make this judgment, pediatric development should proceed without further delay.

# Justification of Risks



- Are data regarding the drug's potential (clinical) benefit to the patient (subject) sufficiently compelling to justify the potential (known, suspected, and unknown) risks?
- Is the balance of these risks and potential benefits at least as favorable as the (evidence-based) alternative treatments (if any)?
- This assessment is similar to the judgment a clinician might make regarding whether to use a therapy in clinical practice.

# “First-in-Children” under 21 CFR 50.52



- Can one infer a sufficient prospect of direct benefit from animal studies alone to justify a “first-in-children” clinical trial under 21 CFR 50.52?
  - The data necessary to establish a sufficient prospect of direct benefit (PDB) to justify the risks of product administration varies with the severity of the disease and the adequacy of alternate treatments.
- Proposal: Sliding Threshold
  - Structure (generally insufficient for PDB)
  - Function (based on mechanism of action)
    - Molecular target (receptor); Biomarker (RNA/protein); Physiologic pathway (metabolic product)
    - Transgenic Technology (human target + mouse)
  - Clinical Disease Model
    - Surrogate endpoints
    - Clinical endpoint (e.g., survival) (FDA “Animal Rule”)

# Maximum Recommended Starting Dose (MRSD) for “first-in-human” clinical trials



- MRSD is frequently based on the “no observed adverse effect level” (NOAEL) in the tested animal species, with conversion of the NOAEL to a human equivalent dose with application of an additional safety factor.
- Risk/potential benefit for NOAEL “safe starting dose” may not be equivalent to MRSD dose associated with greatest efficacy in animal studies.
- A NOAEL dose may not offer a sufficient Prospect of Direct Benefit to justify a “first-in-children” clinical trial, although the MRSD may present greater risks.

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# Referral of ESSENCE for Review

## Under 21 CFR 50.54

- ESSENCE is a double-blind, multi-center, placebo-controlled, 96-week study to evaluate the efficacy and safety of SRP-4045 and SRP-4053 in Duchenne Muscular Dystrophy (DMD) patients with genotypically confirmed deletion mutations that are amenable to skipping exons 45 or 53.
- Boys with DMD, an X-linked chromosome disorder, have a gene defect that results in decreased production of dystrophin, a muscle sarcolemma protein. Without dystrophin, the muscle membrane is destabilized resulting in the muscle weakness, motor delay and associated symptoms characteristic of the disease.
- SRP-4045 and SRP-4053 are phosphorodiamidate morpholino oligomers (PMO) or synthetic versions of naturally occurring nucleic acids designed to bind to targeted pre-mRNA sequences, causing the areas of exon deletion in the gene to be skipped and allowing further production of a potentially functional modified dystrophin by restoring the reading frame.

# ESSENCE Protocol



Week 48 Interim Efficacy Analysis

- Randomization
- Muscle Biopsy: Baseline (All Patients)
- Muscle Biopsy: Week 48 (All Patients)
- Interim Efficacy Analysis (Week 48 data)



# Timeline of Referral for Review Under 21 CFR 50.54

- In 2015, the ESSENCE protocol allowed use of a venous access port at the discretion of the investigator at all study sites (US and Europe).
- FDA reviewed the ESSENCE protocol and noted that implantation of a venous access port for patients in the placebo arm of the study was not approvable under 21 CFR 50.51, 50.52 or 50.53. The sponsor amended the ESSENCE protocol to preclude the use of a port at sites in the US.
- In March 2017, the UCLA IRB received a “complaint” from a parent asking why indwelling infusion ports were not allowed in the study.
- The IRB reviewed the ESSENCE protocol and determined that the protocol met criteria under 21 CFR 50.54.
- An amended ESSENCE protocol to allow the use of alternative venous access methods, including midline catheters (MC), central lines and ports at all study sites was referred to the FDA for review under 21 CFR 50.54.

# Alternative Venous Access Methods

- Problems with venous access may occur in patients with DMD due to contractures, positioning issues, fragile veins due to steroid use and scarring.
- In Sarepta’s DMD clinical trial experience with multiple products, 42% (N=30) had a totally implantable central venous access devices (port, TICVAD), placed for infusions during the study, with approximately 23% (N=7) placed due to loss of peripheral IV access, and 73% (N=22) due to patient preference. In one study, in patients that received a TICVAD, 83% of patients had a TICVAD placed in the first 48 weeks.
- Techniques to aid in peripheral intravenous (PIV) insertion such as infrared visualization have varying rates of success in non-DMD patient populations.
- Of the available central venous access devices, including peripherally inserted venous catheters (PICC), central venous catheters (CVCs), tunneled CVCs, and TICVAD, TICVADs are less likely to become infected and have the longest dwell time.
- Disadvantage of a TICVAD; general anesthesia is required.

# Component Analysis

- Applications of Component Analysis to...
  1. different interventions or procedures (“classic” component analysis)
  2. different subject populations (intervention and control)
  3. different interventions in same subject population (intervention and control)

# Component Analysis

- “To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively.”
  - The National Commission 1978

# “Classic” component analysis



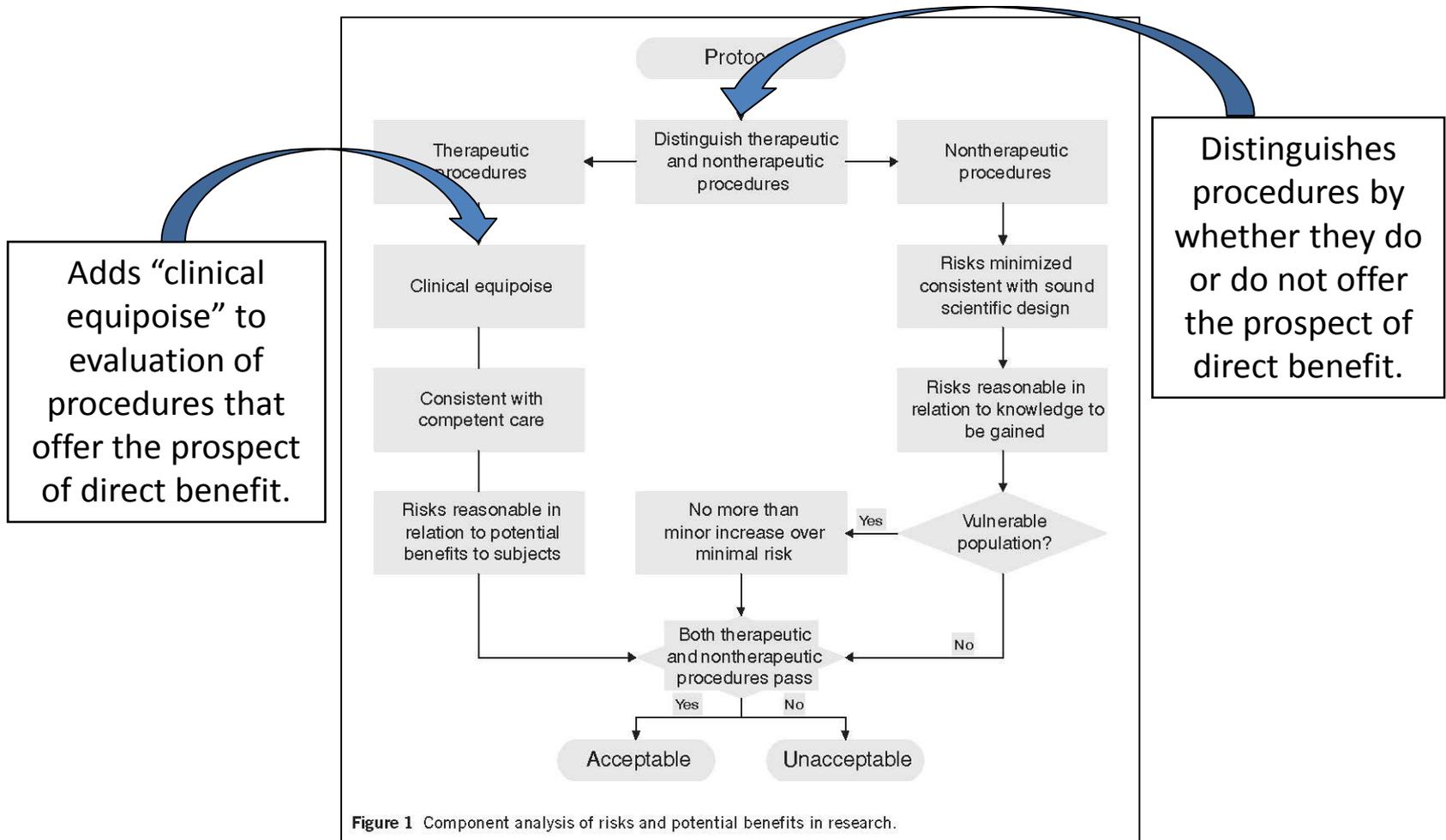
- A clinical investigation may include more than one intervention or procedure.
- Each intervention/procedure must be evaluated separately to determine whether it does/does not hold out the prospect of direct benefit to the enrolled child.
  - This “classic” approach is consistent with recommendations of the National Commission (1978) and the resulting regulations.
- Interventions or procedures that hold out the prospect of direct benefit should<sup>†</sup> be considered under 21 CFR 50.52.
- Interventions or procedures that do not hold out the prospect of direct benefit should<sup>†</sup> be considered under 21 CFR 50.51 or 50.53 (but not 50.52).

<sup>†</sup> Can be considered under 21 CFR 50.54 (thus "should" and not "must").

# How is this “classic” component analysis different from what has been discussed in the literature?

- “Component Analysis<sub>w</sub>” (with equipoise)
  - as proposed by Charles Weijer and Paul B. Miller (Nature Medicine, June 2004)
- “Net Risks” Test
  - as proposed by David Wendler and Frank G. Miller (Journal of Medical Ethics, August 2007)
  - refers to “component analysis<sub>w</sub>” as “dual track”

# “Component Analysis<sub>w</sub>”



Weijer, C. and P. B. Miller (2004). Nat Med 10(6): 570-573.



# Clinical Equipoise

- Combines two separate concepts
  - Adequate “uncertainty” to justify the clinical trial.
  - Known effective treatment should be provided to subjects (based on a fiduciary “duty of care”).
- Dispute about “component analysis<sub>w</sub>” (i.e., “dual track”) is primarily about whether a fiduciary “duty of care” should be the ethical basis for clinical research.
- Criteria in 21 CFR 50.52 bear resemblance to clinical equipoise, but do not entail that known effective treatment can never be withheld.

# Assessment of the Debate

- Both the “dual track” (i.e., “component analysis<sub>w</sub>” ) and “net risks” approach agree on the importance of assessing interventions/procedures individually as to whether they do or do not hold out a prospect of direct benefit.
- Neither approach offers advantages (and both have disadvantages) compared to a “classic” component analysis using categories in 21 CFR 50 subpart D.

# Why is component analysis important?

- Failure to carefully distinguish the different components of a clinical investigation may result in the risks of an intervention or procedure that does not hold out the prospect of direct benefit exceeding the IRB approvable ceiling of a minor increase over minimal risk (absent IRB referral and FDA and/or HHS determination under 21 CFR 50.54/45 CFR 46.407).

# Assessment of Muscle Biopsies

- The ESSENCE protocol includes baseline and repeat (after 48 weeks) muscle biopsies to assess dystrophin levels.
- The muscle biopsies offer no direct clinical benefit and are not clinically indicated for disease management.
- If the muscle biopsies are nonbeneficial, the biopsy and required anesthesia/sedation must 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, the protocol would need to be referred by an IRB for federal panel review under 21 CFR 50.54.
- Muscle biopsies have been included in DMD protocols for many years, and have never been referred by an IRB.

# Component Analysis

- Applications of Component Analysis to...
  1. different interventions or procedures (“classic” component analysis)
  2. different subject populations (intervention and control)
  3. different interventions in same subject population (intervention and control)

# Component Analysis: Different Subject Populations



- Selected federal panel reviews (public process began 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
  - Intervention presents a minor increase over minimal risk to a control group of children lacking a disorder or condition (i.e., normal, healthy children).

<http://wayback.archive-it.org/4657/20150930181816/http://www.hhs.gov/ohrp/archive/children/>

# Component Analysis

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# NIH Human Growth Hormone (hGH) Protocol Review Committee (1992)



## Pre-Randomization vs. Post-Randomization Analysis of Benefit

- “Should the prospect of benefit be calculated before randomization or after the subjects have been separated into the treatment and placebo arms? On the (yet unproven) assumption that treatment with hGH is beneficial, and that the benefit exceeds the risks, the former approach would allow approval because each subject in this protocol has a 50 percent chance, i.e. some prospect, of benefitting. The latter approach asks whether there are prospects of benefit to the subjects in the treatment arm alone and, additionally, whether there are prospects of benefits to those in the placebo arm alone. The committee did not resolve the question of which approach is mandated by the regulations. *The former was favored by a majority but both approaches were considered in the deliberations and, in this case, yielded the same conclusions.*” (Report, page 10-11; emphasis added)

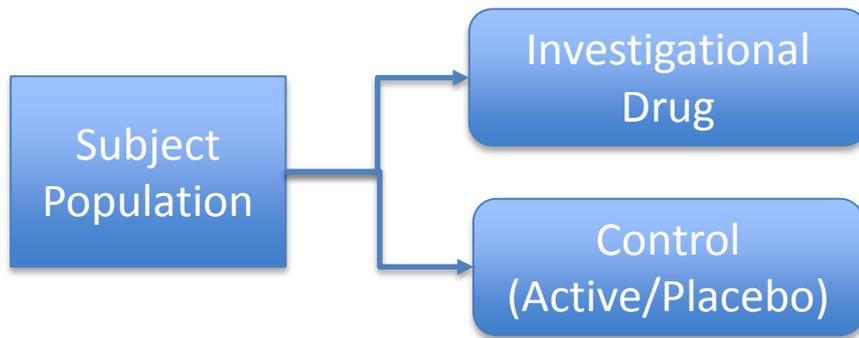
# Critical Analysis

- The NIH Protocol Review Committee...
  - did not clearly perform a “classic” component analysis.
  - ignored the second criterion under 45 CFR 46.405 (i.e., comparable to available alternatives) as there were none, which may be one of the few circumstances in which pre- vs. post-randomization analysis of benefit gives the same result.
  - determined that the risks to the placebo group (injections 3/wk. for  $\leq 7$  yrs.) was no more than a minor increase over minimal risk. If the risk was believed to be higher, the results of the two analytical approaches may have been different.
  - concluded the protocol satisfied 45 CFR 46.406 (one dissent).

# Withholding Known Effective Treatment

- How would the availability of an alternative treatment impact on this analysis?
- If a placebo is needed to assess the efficacy of an intervention, withholding known effective treatment must not result in “additional risks of serious or irreversible harm” (Declaration of Helsinki, §33) or “serious harm, such as death or irreversible morbidity” (ICH E-10).
- These risks to the placebo/control group can only be assessed properly if one does a post-randomization analysis of benefit.

# RCT – Active/Placebo Control



Known effective treatment is withheld from subjects receiving investigational drug, but this is justified if the risks/ potential benefits are believed to be comparable (i.e., “ equipoise ”).

With an active controlled RCT, known effective treatment is provided to the control group (regardless of whether a superiority design or a non-inferiority design is used, if a non-inferiority margin can be estimated).

With a placebo controlled RCT, known effective treatment is withheld from the control group. A pre-randomization analysis of benefit would justify this fact given that all of the subjects participated in a “lottery” to receive the investigational drug even if withholding known effective treatment would result in serious harm, such as death or irreversible morbidity.

# Post-Randomization Analysis of Benefit

- This approach does not pre-judge the results of the clinical trial (i.e., does not assume that the investigational drug is more effective than placebo); rather, it only assumes that the placebo is “inert” (which is the purpose of the placebo).
- If a subject is randomized to placebo, the risks are not incurred by failing to get the investigational drug (unknown) but rather by failing to get an alternative treatment known to be effective.
- One cannot selectively decide based on the protocol whether to apply a pre- or post-randomization analysis of benefit.
- The analysis of risks to the placebo group must be assessed separately (i.e., post-randomization) to be in consistent with existing FDA and international ethical guidance.

# Applying Component Analysis to ESSENCE

- Participants who receive active treatment with SRP-4045 and SRP-4053 directly benefit from participation in the study.
- Risks of a central catheter needed to administer the active treatment are judged against the potential benefits of the drug.
  - Risks of non-therapeutic procedural sedation, if required, must also be considered.
- Use of a central catheter in patients receiving active treatment and associated non-therapeutic procedural sedation, if required, is approvable under 21 CFR 50.52/45 CFR 46.405 as providing a prospect of direct benefit.

# Applying Component Analysis to ESSENCE

- Participants who receive placebo with SRP-4045 and SRP-4053 do not directly benefit from participation in the study.
- Risks of central catheter cannot be judged against the potential benefits of the drug if no drug is administered, and thus cannot be evaluated under 21 CFR 50.52.
  - Risks of procedural sedation, if required, must also be considered.
- Use of a mid-line catheter meets the requirements under 21 CFR 50.53 as a minor increase over minimal risk.
  - Use of non-therapeutic procedural sedation is not required.

# Applying Component Analysis to ESSENCE: 21 CFR 50.53

- Use of a PICC, CVC or TICVAD in patients receiving placebo and the use of associated non-therapeutic procedural sedation is not considered approvable under 21 CFR 50.53 as a minor increase over minimal risk and consequently a federal panel review under 21 CFR 50.54 is required.
  - Risk exceeds a minor increase over minimal risk
  - Procedures are not “reasonably commensurate” with expected medical situations
  - Procedural sedation/anesthesia is required



# Non-Therapeutic Procedural Sedation

- The Pediatric Ethics Subcommittee (PES) of the Pediatric Advisory Committee (PAC) met in March 2015 to discuss the use of procedural sedation/anesthesia for non-therapeutic research interventions
- The PES/PAC was unable to reach consensus on whether one or more approaches to procedural sedation/anesthesia should be considered a minor increase over minimal risk (YES: 7; NO 9).
- The committee did agree upon recommendations that should be included in a protocol to minimize the risks of procedural sedation/anesthesia.†

†<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM510177.pdf>.

# Questions for the Expert Panel

- (1) Are there any circumstances under which the use of an indwelling central venous access device in the ESSENCE clinical trial ought to be allowed? (Vote: yes 14, no 0)
- (2) If yes, please discuss the following issues:
  - a) Whether the choice and timing of placement of a central venous access device should be left to the discretion of the study site investigator, in consultation with the child's parent;
  - b) Whether the protocol should include criteria for when an individual study participant has difficulties with peripheral intravenous access such that use of a central venous access device may be appropriate;
  - c) How the burden of undergoing multiple failed attempts at establishing peripheral intravenous access should be taken into account (e.g., anticipatory anxiety, post-traumatic stress).

<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM558411.pdf>

# FDA Determination

- The protocol could proceed under 21 CFR 50.54 with the following stipulations:
  - A TICVAD was the preferred alternative venous access method; other methods should only be used with a documented contraindication to TICVAD.
  - A TICVAD may be placed at the discretion of the parent/child in consultation with the investigator.
  - The expertise of the consulting surgeon inserting the TICVAD should be documented.
  - Parental Permission and Child Assent forms should include information on risk and benefits of TICVAD.

<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM560819.pdf>

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