



# Enhancing Regulatory Oversight for Challenging Clinical Trials: Observations from FDA

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# Disclaimer and Disclosures

- The views expressed in this presentation are my own, and do not represent the policies of the Food and Drug Administration or the Department of Health and Human Services.
- I have no financial relationships to disclose or any conflicts of interest to resolve.

# Understanding Risk

- The broad issue raised by discussions of the SUPPORT study is how we should understand the risks of enrolling in a clinical trial from three different perspectives:
  1. Receiving a different treatment in a study than what might be preferred by a patient's treating clinician
  2. Which risks are "reasonably foreseeable"
  3. Whether clinical trials randomizing participants to two "standard of care" interventions are "minimal risk"

# Unifying Theme

**“In God we trust; all others  
(must) bring data.”**

Attributed to W. Edwards Deming (1900 – 1993)

# Epistemological Status of Clinicians' "Concerns" or Beliefs

- RCT: Treatment A versus Treatment B
  - If a clinician “prefers” treatment A due to “concerns” about the benefit and/or risks of treatment B for an individual patient, are there sufficient data to support those beliefs?
- If yes, the subject inclusion and/or exclusion criteria for the clinical trial should be modified to restore uncertainty (i.e., “ equipoise”) regarding whether treatment A or B is better.

# Epistemological Status of Clinicians' "Concerns" or Beliefs

- If there are insufficient data to support these "concerns," the informed consent document should read (under Alternatives, not Risks):
  - "There is no evidence to suggest that treatment A is better or worse than treatment B for your condition. Your doctor may have a preference. You should talk to your doctor about the different treatments before making a decision."

# “Equipoise” (i.e., uncertainty)

- Interpretations of available data may result in variable degrees of uncertainty (not an either/or)
  - Difference: “individual” versus “community” uncertainty
- Recommending treatments absent data may reflect “value” differences in potential harms (e.g., death vs. blindness)
- Adequate uncertainty existed to justify SUPPORT
  - “When the SUPPORT study was initiated, there was no clear recent evidence indicating that different oxygenation levels within the then-current standard of care (85%-95%) would produce differences in neurological damage or survival.” (emphasis added)

OHRP Letter (dated June 4, 2013)

# Risks of Randomization?

- In a properly designed clinical trial, there is no general reason to prefer to be treated according to individual clinician preference rather than to be treated based on a protocol-based assignment strategy (e.g. randomization.)
- However, individual patients may have a preference for one treatment over another treatment based on a personal value judgment about the acceptability of different harms.
- Randomization *per se* does not create risks, but the risks to individual patients may differ if they are assigned to a different treatment than the one their clinician would have prescribed if they were treated outside of the study.



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# “Reasonably Foreseeable Risks”

- What does “reasonably foreseeable” mean?
    - A risk of foreseeable harm means that a reasonable person would be able to predict or expect the harmful result of their action (thus be liable for injury to another party). The duty to act reasonably to avoid foreseeable risks of physical injury extends to any person.
- US Legal Definitions (<http://definitions.uslegal.com/f/foreseeable/>)
- What does “risk” mean?
    - Risk (in the research context) is defined as the probability and magnitude of harm or discomfort that may result from an intervention or procedure.

See 21 CFR 56.102(i)

# The Risks of Oxygen?

- Prior to the results of the SUPPORT study, were the risks of blindness, neurological damage and death from keeping  $S_aO_2$  between 85 to 89% versus 91 to 95% “reasonably foreseeable”?
- Data on outcomes related to the use of either “low” or “high” levels of oxygen prior to the introduction of pulse oximetry in the mid-1980s are useless.
- How can a “risk” be “reasonably foreseeable” if one is unable to assign a probability to the harm?

# Hypotheses and Risks

- Hypotheses about the probability of certain harms that may occur from the study interventions do not establish those harms as “reasonably foreseeable” risks.
- Nevertheless, the primary purpose or aim (i.e., main hypotheses) of a clinical trial should be clearly described in the informed consent document.
- This description should be in the introduction, not in the section on risks (which should be limited to risks that are “reasonably foreseeable”). To be consistent, any possibility of clinical benefit based on the results of the clinical study should not be described under the “benefits” section.

# Risk Disclosure

- The known risks of Treatment A and Treatment B should be disclosed even if both are provided as part of “standard of care” in order to accommodate patients’ personal value judgments about the acceptability of different harms.
- Clinicians’ “concerns” that Treatment A or Treatment B may be better or worse, absent supporting data, are not “reasonably foreseeable risks” that must be disclosed.
- Any reference to these “concerns” should be included in the introduction (i.e., study purpose), because the clinical trial often is designed to generate the data necessary to resolve these “concerns.”

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# RCT as Minimal Risk?

According to Morris and Nelson (2007), “a randomized, controlled trial poses no more than minimal risk only when all of the following five criteria are met:

1. genuine clinical equipoise exists;
2. all of the treatment options included in the research study fall within the current standard of care; (emphasis added)
3. there is no currently available treatment with a more favorable risk-benefit profile than the treatments included in the research study;
4. the nontherapeutic components of the research are safely under the minimal risk threshold; and
5. the research protocol provides sufficient latitude for treating physicians to individualize care when appropriate.”

# Two Caveats (upon further reflection)

- The argument that the incremental risk of an RCT between two alternative “standard(s) of care” is no more than minimal risk presumes sufficient data to evaluate the risks and potential benefits of each intervention.
  - In other words, an existing “standard of care” based on physician preference alone is an insufficient justification.
- The purpose of designating an RCT as “minimal risk” is to be able to waive the requirement for informed consent.
  - A “minimal risk” waiver of informed consent is not allowed for FDA-regulated clinical trials (which Morris and Nelson do not discuss).
  - Rather than debate whether an RCT is or is not minimal risk, we should focus directly on the question of informed consent.



# “On label” RCT as Minimal Risk?

- Generally, administering an FDA-regulated investigational product presents more than minimal risk.
- A comparative RCT studying marketed drugs for a labeled (and thus evidence-based) indication may present no more than minimal risk over the use of those same drugs in clinical practice.
  - But there is a great deal of “off-label” pediatric prescribing, which may or may not be “evidence-based” (i.e., supported by one or more adequate and well-controlled study).

# “Off label” RCT as Minimal Risk?

- A comparative RCT studying marketed drugs for an “off label” indication that is not evidence-based may be different
- The “off-label” use of a marketed drug in a pediatric clinical trial may not be allowed to proceed if FDA judges the use to present “an unreasonable and significant risk of illness or injury” (21 CFR 312.42b), even if such off-label use would be allowable in “standard” clinical practice.
- Sufficient data must be available to evaluate the risks and potential benefits of the intervention to determine whether the incremental “research” risk of being randomized to that intervention may be considered no more than minimal risk.

# Concluding Remarks

- Clinical “concerns” are not “reasonably foreseeable risks.”
- “Reasonably foreseeable risks” of study interventions that are “standard of care” should be disclosed.
- Whether a study hypothesis is true or false is not a “risk,” but should be included in the aims or purpose of the study.
- Similarly, speculative benefits based on the yet unknown results of the study should not be included in the benefits.
- Whether the study interventions are considered “standard of care” is neither necessary nor sufficient to establish a comparative RCT as “minimal risk.”



# Thank you.

