



# Enhancing the Persuasiveness of Clinical Trials

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# Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.

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Fundamentally, we have a math problem driven by small absolute effect sizes and low event rates.

Enroll many subjects and follow them for a long time.

Composite outcomes differ in clinical impact.

Large NNTs (numbers needed to treat) mean that most treated patients will derive no additional benefit (and most payments are for ??)

# The Preferred Road to Therapeutic Coverage

- ✓ Provide adequate evidence that
- ✓ A treatment strategy using the new therapeutic technology compared to alternatives
- ✓ Leads to improved clinically meaningful health outcomes
- ✓ In Medicare beneficiaries

# The Preferred Road to Diagnostic Coverage

- ✓ Provide adequate evidence that
- ✓ The incremental information obtained by new diagnostic technology compared to alternatives
- ✓ Changes physician recommendations
- ✓ Resulting in changes in therapy
- ✓ That improve clinically meaningful health outcomes
- ✓ In Medicare beneficiaries

# Common Concerns

- Inadequate randomization, blinding, controls
- Unrealistic comparators
- Intermediates/Surrogates don't map rigorously to clinical utility outcomes
- Composite outcomes with asymmetry
- Lack of generalizability to typical targeted Medicare beneficiary
- Conflicts of interest
- Bad results get buried

# The Challenges of Non-Inferiority

*Why would CMS prefer superiority trial designs to inform coverage?*

- Derivation of the delta
- Clinical creep – inferiority to placebo
- Assay sensitivity – bias toward N-I
- Blinding – bias toward N-I

“Mrs. Jones, I am 80 percent confident that this new treatment is no more than 15 percent worse than what we would have done last year.”

# Category B IDEs

# Why?

- CMS review of IDE protocols gives sponsors early feedback on questions that will eventually arise for coverage.
- Reduce local variability in protocol review and coverage decisions
- Enhance administrative efficiency

# Summary

- December 10, 2013 Federal Register (78 Fed. Reg. 74429)
- Effective Jan 1, 2015
- Coverage of the device, related and routine costs
- Standards – similar to CED standards – *MACs may choose to apply them in 2014*
- Centralized CMS review
- If you don't want Medicare coverage you can choose to not apply

1. The principal purpose of the study must be to test whether the device **improves health outcomes of appropriately selected patients.**
2. The **rationale** for the study must be well supported by available scientific and medical information, or intended to clarify or establish the health outcomes of interventions already in common clinical use.
3. The study results must not be anticipated to **unjustifiably duplicate** existing knowledge

4. The study must be **sponsored** by an organization or individual capable of successfully completing the study.
5. The study design must be **methodologically appropriate**, and the anticipated number of enrolled subjects must be adequate to confidently answer the research question(s) that are being asked by the study
6. The study must be in compliance with all applicable federal regulations concerning the **protection of human subjects** found in 21 C.F.R. parts 50, 56, 812 and 45 C.F.R. part 46.

7. Where appropriate, the study must not be designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Studies of all medical technologies measuring **therapeutic outcomes** as one of their objectives may be exempt from this criterion — but only if the disease or condition being studied is life threatening and the patient has no other viable treatment options.
  
8. The study must be registered with the National Institute of Health's National Library of Medicine's **ClinicalTrials.gov**.

9. The study protocol must describe the method and timing of **release of results** on all pre-specified outcomes, including release of negative outcomes and the release should be hastened if the study is terminated early.
  
10. The study protocol must describe how Medicare beneficiaries may be affected by the device under the investigation, and how the study results are or are not expected to be **generalizable to the Medicare beneficiary population**. Generalizability to populations eligible for Medicare due to age, disability, or other eligibility status must be explicitly described.