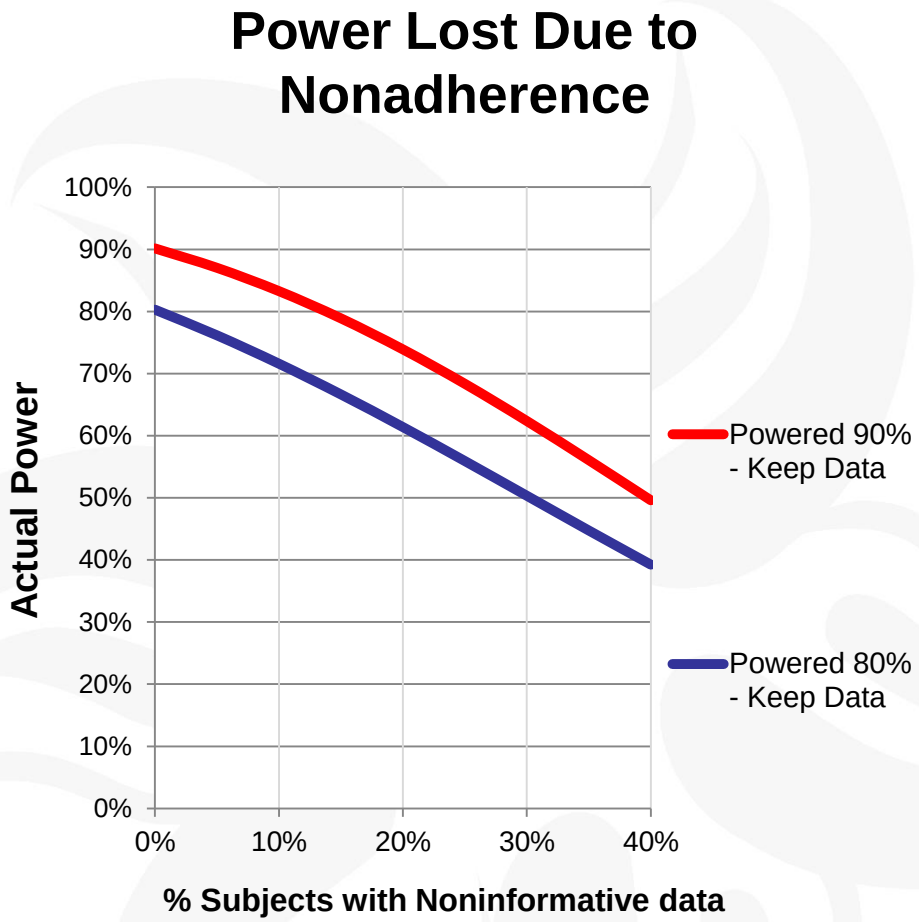
How does nonadherence affect the information used for hypothesis testing?

- Informative data – data may provide information relevant to hypothesis
  - (e.g., medication nonadherence due to drug-related adverse events, partial medication adherence)
- Noninformative data – data provide no meaningful information relevant to the hypothesis being tested.
  - (e.g., total nonadherence, subject does not have the diagnosis)
  - *Whether data are noninformative depends on the hypothesis.*

Impact of Noninformative Data on Study Power: A Simulation

- Assume subjects with noninformative data contribute no signal ($\Delta = 0$), but have same SD as other subjects
- Observed effect size (ES) is reduced proportionally with noninformative data
- E.g., if 20% noninformative data, then
  - True ES = 0.5 → Observed ES = 0.4
  - Study power of 80% is reduced to 61%



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Impact of Noninformative Data: Recovering Power by Increasing Sample Size

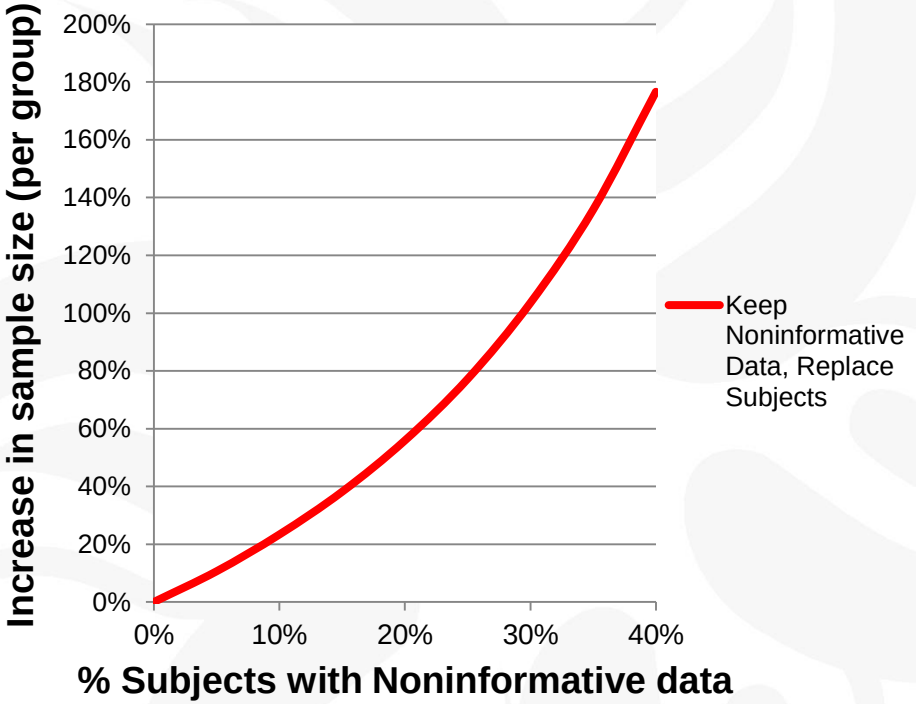
Attempting to "Power Through" the Problem

- Increasing *N* can overcome a reduction in Δ

$$t \cong \frac{\Delta \cdot \sqrt{N/2}}{SD}$$

- …but, increasing *N* has limited benefits
  - Incremental change in $\sqrt{N}$ decreases with larger *N*
  - Maintaining Δ and controlling SD becomes harder
    - PBO effects and variance from larger study size, # of sites, countries, etc.

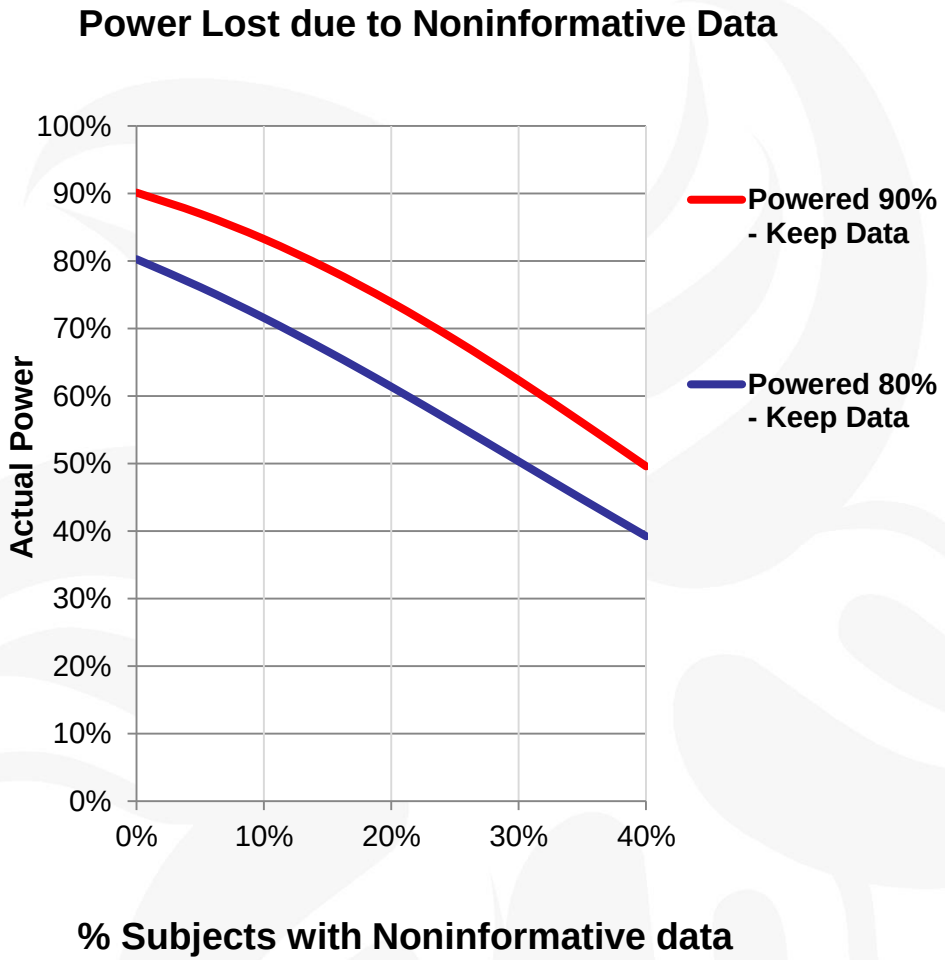
Additional *N* Needed to Recover Original Power



What are the benefits of eliminating noninformative data?

What if we simply exclude data from "bad" subjects?

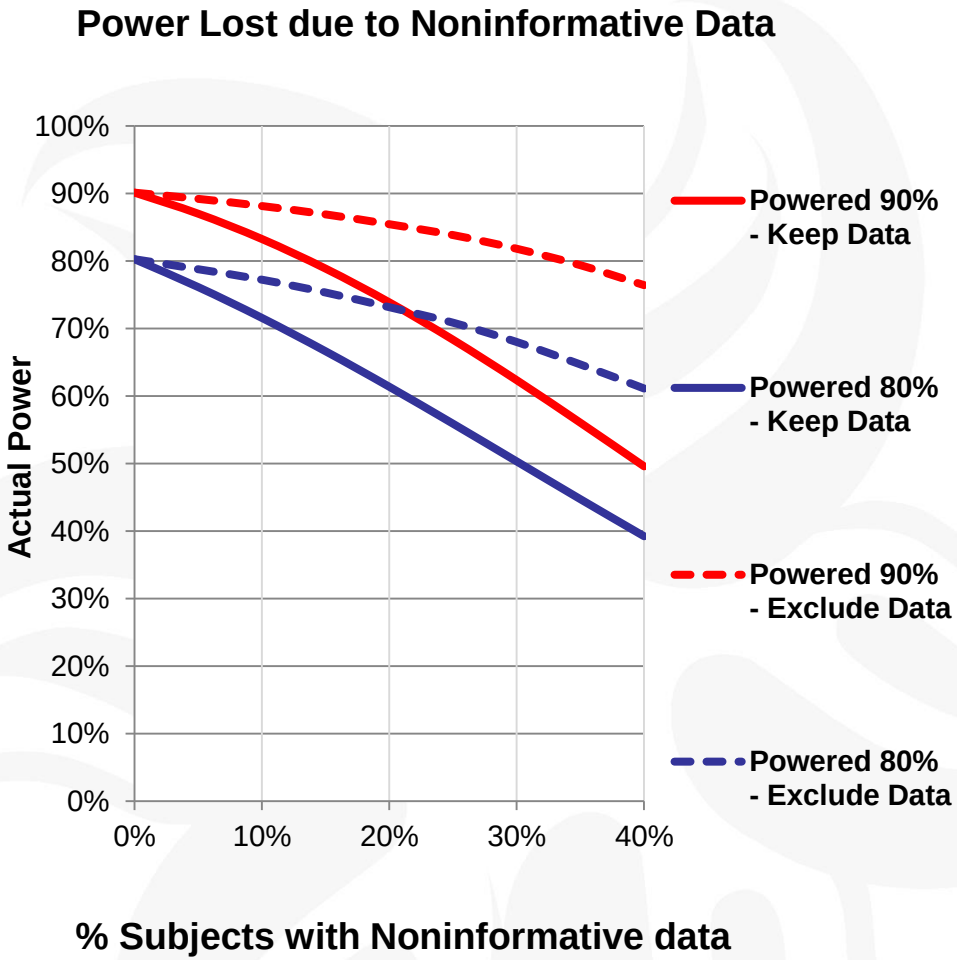
– Lose the benefit of a larger N, but remaining subjects exhibit the "true" Δ



What are the benefits of eliminating noninformative data?

What if we simply exclude data from "bad" subjects?

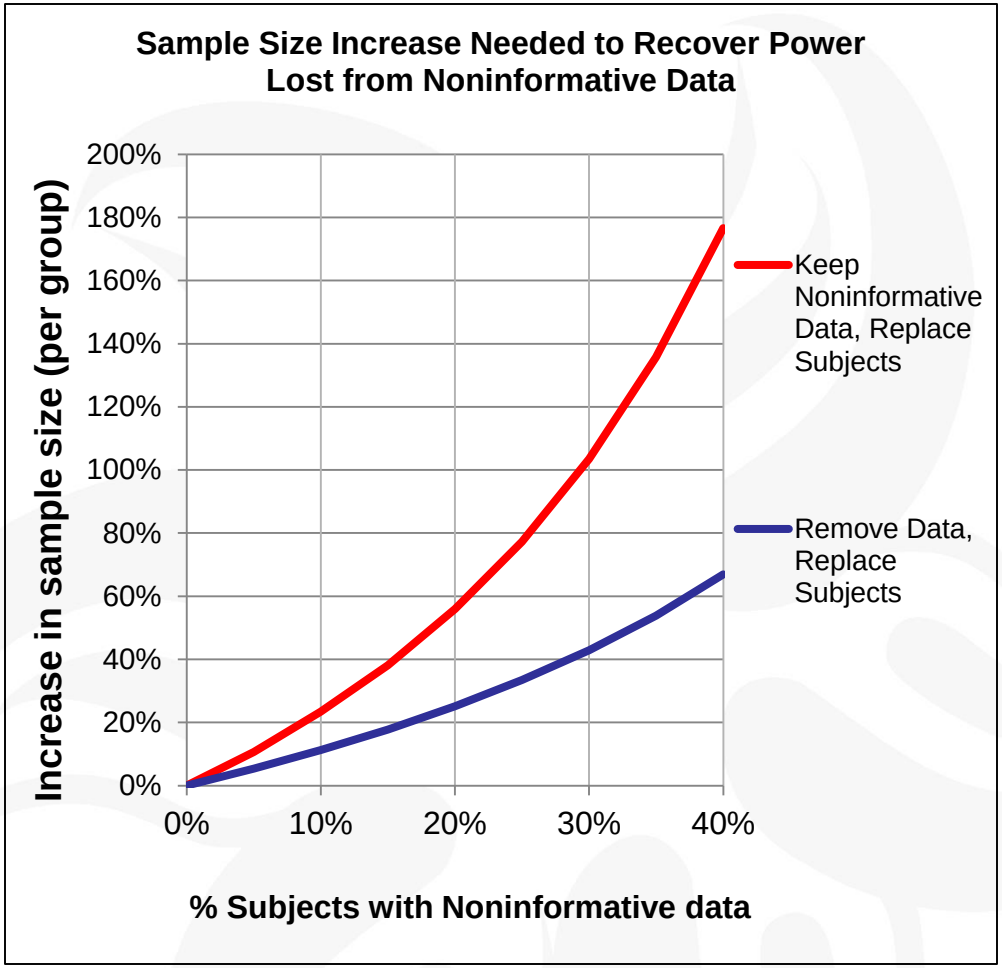
- Lose the benefit of a larger N, but remaining subjects exhibit the "true" Δ
- Power is improved, *even without replacing the missing data*
  - I.e., removing bad data doesn't "cost" anything



What are the benefits of eliminating noninformative data?

What if we remove "bad" subjects and replace them to recover original power?

– Strategy is more efficient than "powering through" with bad data



Summary from Simulations

- Noninformative data from nonadherent subjects significantly reduces statistical power
  - Impact is worse than that from *missing* data

- Excluding nonadherent subjects or censoring their data is a more efficient strategy for recovering statistical power than “powering through” the problem

What Are the Potential Options for Eliminating a Subject's Noninformative Data?

- Exclude subject (prior to randomization)
  - e.g., based on large Screening → BL change; large change during PBO lead-in; evidence (or predictors) of poor medication compliance
- Discontinue subject (after randomization)
  - Prior to inclusion in the Intent-to-Treat population (e.g., before first post-baseline efficacy measure)
- Censor subject's data (from primary statistical analysis)
  - Criteria based on findings/behavior *prior to randomization*
    - Same strategies as above, but subject allowed to participate in trial
  - Criteria based on findings/behavior *post-randomization*
    - Potential problems with bias between treatment groups

Discussion (10 min)

Next up:

Phil Skolnick, Ph.D., D.Sc (hon.),

Director, Division of Therapeutics & Medical Consequences, NIDA, NIH, Bethesda, MD