Futility Design Incorporating Concurrent Controls: A Variation on the Phase II Trial Design

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SCT 2013

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Single Arm Futility Design

- Objective: discard ineffective therapies
- Pre-specified futility threshold, based on historical control data and a clinically relevant treatment effect
- H_A: $\pi_{tx} < (\pi^* + \delta)$
- Drawbacks of Historical Control Data
  - Temporal changes in patient management
  - Protocol variations across trials

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Objective

- Conclusions from single arm futility design subject to the relevance of the historical control data.
- Traditional, 2-arm, Phase II designs often criticized as underpowered Phase IIIs.

- Objective: to describe the application of an appropriately powered concurrently controlled futility design

Concurrently Controlled Futility

- Statistical Hypotheses
  - H_0: $\pi_{tx} \geq (\pi_{ctrl}+\delta)$ ←→ H_0: $(\pi_{tx}-\pi_{ctrl}) \geq \delta$
    H_A: $(\pi_{tx}-\pi_{ctrl}) < \delta$
    futility

- Sample size can be determined using standard methodology, taking into account the δ specified in the hypotheses.

Intracerebral Hemorrhage

- 70,000 patients diagnosed annually in the US
- Societal burden
  - Mortality at one month: ~40%
  - >70% of survivors left with serious and permanent disability
- Financial burden: estimated >$7B annually
- No treatment beyond supportive general medical care

Hi-Def in ICH: Overview

- High Dose Deferoxamine in ICH
- Randomized double blinded phase II clinical trial
  - Active treatment: DFO at 62 mg/kg/day
  - Control: Saline placebo
- π is the proportion of subjects with good outcome (mRS 0-2)
- H_A: $\pi_{DFO} - \pi_{Ctrl} < 0.12$
- Analyzed via one-sided upper 90% confidence bound on the risk difference

HI-DEF
High Dose Deferoxamine in Intracerebral Hemorrhage

Futility Design

Single Arm

- Assumptions
  - $\pi^* = 28\%$ (historical control)
  - δ: absolute 12% (futility threshold)
  - H_A: $\pi_{DFO} < 0.40$
  - $\alpha = 0.10$, one-sided
  - Power 80% at $\pi_{DFO} = 0.28$
- Sample size:
  71 subjects

Concurrently Controlled

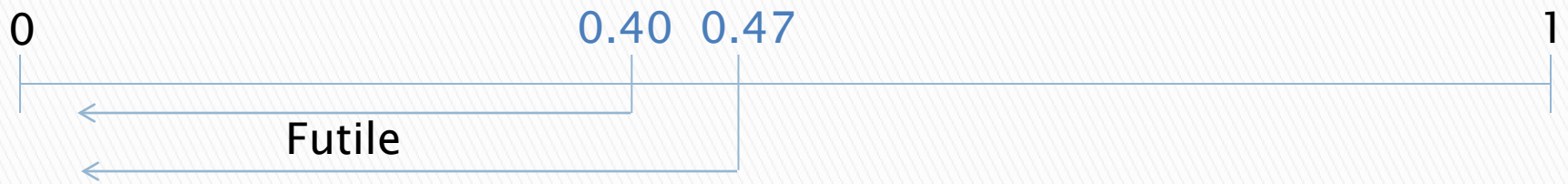
- Assumptions
  - $\pi_{Ctrl} = 28\%$ (based on historical control)
  - δ: absolute 12% (futility threshold)
  - H_A: $(\pi_{DFO} - \pi_{Ctrl}) < 0.12$
  - $\alpha = 0.10$, one-sided
  - Power 80% at $\pi_{DFO} = 0.28$
- Sample size:
  254 subjects

What if our Assumptions are Wrong?

Single Arm

- Assumed
  - $\pi^* = 28\%$
  - δ: absolute 12%
  - $H_A: \pi_{tx} < 0.40$
- Actual
  - $\pi^* = 35\%$
  - δ: absolute 12%
  - $H_A: \pi_{tx} < 0.47$

Result: We may be testing an irrelevant hypothesis, and we have no way of knowing (or adjusting).

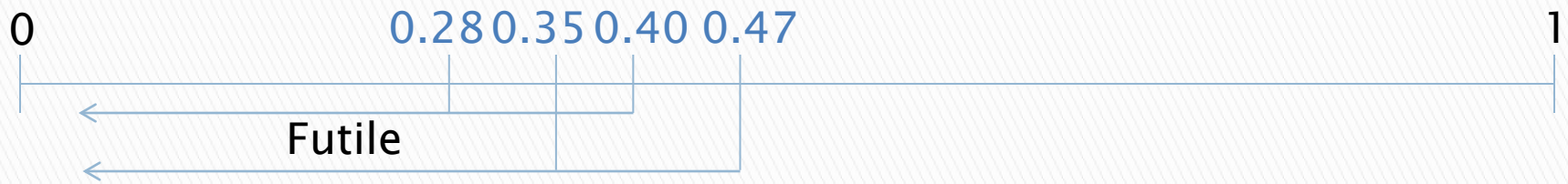


What if our Assumptions are Wrong?

Result: The hypothesis is still relevant, the analysis is based on the estimated control rate (and not the assumed), but the power may be adversely impacted.

Concurrently Controlled

- Assumed
  - $\pi_{Ctrl} = 28\%$
  - δ: absolute 12%
  - H_A: $(\pi_{DFO} - \pi_{Ctrl}) < 0.12$
- Actual
  - $\pi_{Ctrl} = 35\%$
  - δ: absolute 12%
  - H_A: $(\pi_{DFO} - \pi_{Ctrl}) < 0.12$



Concurrently Controlled Futility

- Disadvantage
  - Increased sample size over single arm design
  - Potential compromise on power with incorrect assumption
- Advantages
  - Direct comparison of treatment arms
    - Compensates for incorrect historical control data
    - Provides current estimate of both the control rate and the treatment effect
    - Allows for exploratory analyses on 2° endpoints
  - Logistics of randomization and blinding

Acknowledgements

- NIH/NINDS
  U01 NS074425 (PI Selim): Hi-Def in ICH
  SDMC: Data Coordination Unit (PI: Yeatts)
- Coauthors:
  - Magdy Selim, MD, PhD: Hi-Def Study Chair

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HI-DEF
High Dose Deferoxamine in Intracerebral Hemorrhage