Stagewise Planning for Clinical Trials Learning vs. Confirming

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Outline

- "Learn-and-Confirm" vs. "Learn-vs-Confirm"
- Stagewise planned learning
  - (i) Combine Learning with Confirming (ASD): this includes Frequentist and Bayesian Adaptive Design, Can it be a freebee?
  - (ii) Separate Confirming from Learning
- What does ASD offer ? Early vs. Late phase
- Concluding Remarks

* Views presented are not necessarily those of U.S. FDA

Learning vs. Confirming is a unique feature to adaptive design in clinical drug development. The potential advantage of Adaptive Design is its flexibility nature. However, where adaptation tries to deal with better learning and formalize the learning, that should not be confused with necessity of prospectively planned adaptive design adding to confirmatory evidence

Rationale for

Adaptive design where data from Phase II and III are to be combined for inference

Learn/Confirm

Adaptive Seamless (Two-Stage) Design

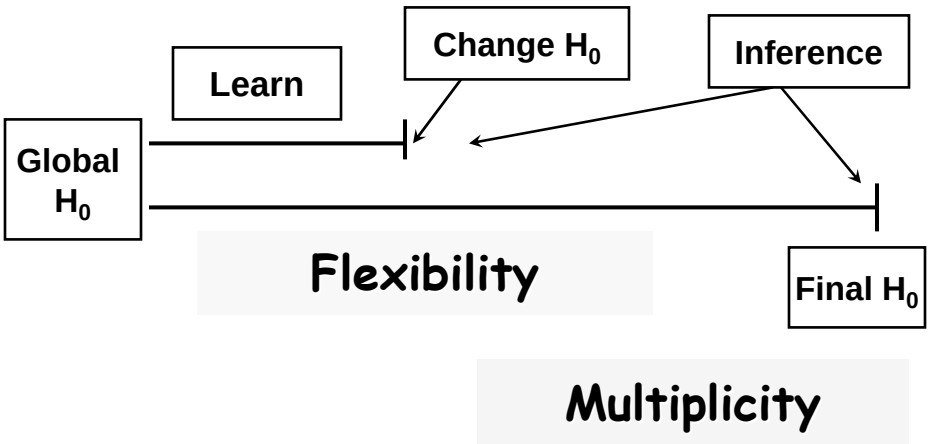
Known as ASD

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Dealing with Learning (i)

(i) Combine Learning with Confirming



In the simplest case:

When learning does not involve extending the total sample size

Use Treatment Selection to Illustrate

When learning data is used to select a treatment arm

placebo, T_1, T_2, …., T_J

μ_0, μ_1, μ_2, …, μ_J

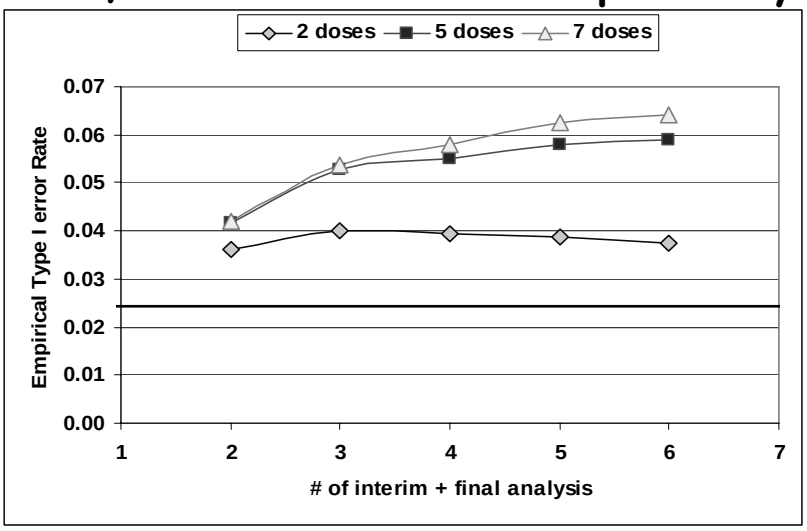
H_0: $\Delta_1 = \Delta_2 = \ldots = \Delta_J = 0$

Allow early discontinuation of potentially ineffective or toxic dose(s) $\Rightarrow$ H_0 may be changed

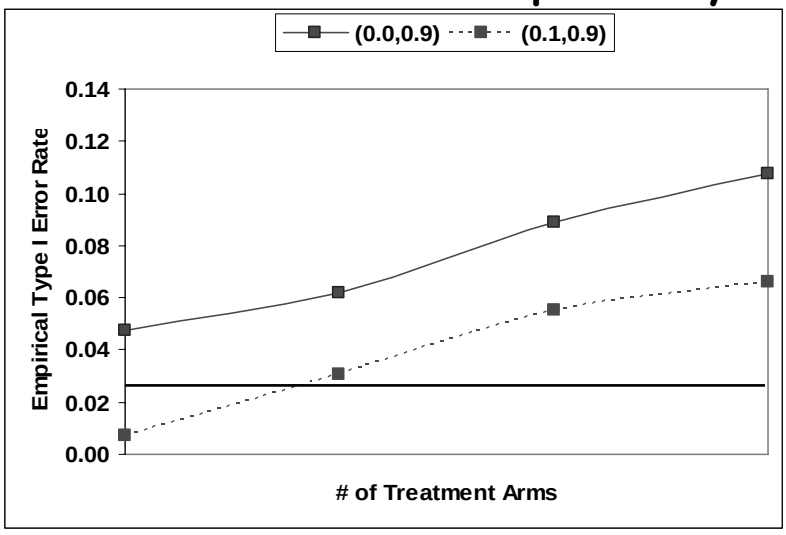
In ASD, interested in ONE most promising dose or small # of promising doses

$\Delta_j = \mu_j - \mu_0$ (j=1,2, …, J)

Select among TRT dose groups by imposing Tmax – Tj ≥ D for all j but max, D=1, based on outcome endpoint only



Keep Promising Doses (CP ≥ cpH) and Drop futile doses (CP < cpL) at τ = 0.5 based on outcome endpoint only



Selection (Arms) Process Mid-Stream

- Frequentist

  Select among dose regimens only (non-comparative)
  Select dose regimens based on CP (considered clinical endpoint or surrogate endpoint)

By simulating the selection process using the above criteria, except for stringent selection criteria or very different surrogate effect sizes, majority of the scenarios considered in simulation studies showed α-inflation

– in principle, this should be applicable to Bayesian where selection criteria are based on predictive power or posterior prob.

Learning involves flexibility to extend total sample size or modification of other design parameters

When ignore multiplicity in GSD and in ASD ➔ $\alpha \uparrow$

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A Valid Two-Stage Adaptive Design

- Conventional Clinical Objective

$$H_{0a}: \Delta = 0 \qquad H_{1a}: \Delta > 0$$

- Acknowledge Potential Qualitative Heterogeneity

$$H_{0g+}: \Delta_{g+} = 0 \qquad H_{1g+}: \Delta_{g+} > 0$$

- Extended Objective (composite alternative hypothesis)

$$H_0 = H_{0a} \cap H_{0g+} = \{\Delta = 0 \text{ and } \Delta_{g+} = 0\}$$

$$H_1: \Delta > 0 \quad or \quad \Delta_{g+} > 0$$

* Wang, Hung (2005, JSM Biopharmaceutical Proceedings)
* Simon, Wang (2006, The Pharmacogenomics Journal)
* Wang, O'Neill, Hung (2007, Pharmaceutical Statistics)

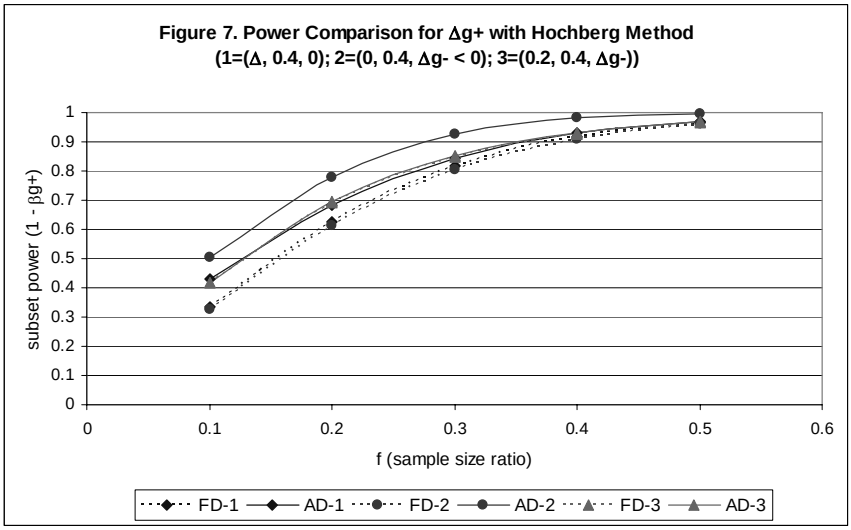
An example: Clinical Utility of GCB

- Scenario 1: **Predictive of T**
  $(\Delta, \Delta g+, \Delta g-) = (\Delta, 0.4, 0)$
- Scenario 2: Predictive of T
  $(\Delta, \Delta g+, \Delta g-) = (0, 0.4, -0.4)$
- Scenario 3: Prognostic-Predictive of T
  $(\Delta, \Delta g+, \Delta g-) = (0.2, 0.4, 0.1)$, e.g., f =1/3

Patient's Genomic Composite Biomarker (GCB) status, g+ or g–, is determined from a diagnostic assay

Wang, O'Neill, Hung (2007, Pharmaceutical Statistics)

Hochberg: Fixed vs. Adaptive



Dealing with Learning (i)

When early stage accumulating data is repeatedly used to learn one or more design parameters & also used with later data to confirm treatment effect:

Q: Can one argue that although the data is repeatedly used from what was learned & from within the same trial, but, because no formal statistical testing (also Bayesian's argument) is performed, so, there is no need to spend α or spend "symbolically" minuscule-α for repeated learning and essentially test at 1-sided 2.5% at the study end ?

Dealing with Learning (ii)

(ii) Separate Confirm from Learn: Independent

Learning | Confirming

Learn vs. Confirm: Use of point estimate of effect size from ph II to plan ph III can be valuable in prediction of useful doses, but, may be too optimistic with usual α-level and 1-β level → possibly regression toward mean

*Wang, Hung, O'Neill, Pharmaceutical Statistics 5(2): 85-97, 06)

What does ASD offer – Early Phase

- Hypothesis-generation acknowledging little data w/ or w/o prior data – Plenty of Flexibility
- Multiplicity w/i exploration: global & final H_0
- Improvement over pure exploration – strong α-control help reduce too many false +ves

What does ASD offer – Late Phase

- Limited flexibility in planning,seamless in conduct
- Require more careful (scenario) planning in early stage to increase the chance of success
- Multiplicity in confirmation: global & final H_0
- When more prior (safety/efficacy) data external to ASD trial - may aid in better (scenario) planning, though less stage-1 data

Concluding Remarks

Assessment of experimentwise α-error rate

- **Pre-specified flexibility: planned H_0 by stages**
- **Limited adaptation (Frequentist or Bayesian) in late phase**

Independent monitoring for Adaptive Process

- **Ongoing controversy, stakes are high, ensure no information leak is challenging, firewalls needed**
- **More research needed**
- **More experiences needed**

Collaborators*

H.M. James Hung

Robert T. O'Neill

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***Wang, Hung, O'Neill, JSM Proceedings, 2007**