Some Current US FDA Thinking on Adaptive Design Clinical Trials

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Presented at "EMEA/EFPIA Workshop on Adaptive Designs in Confirmatory Clinical Trials"
London, England, December 14, 2007

Acknowledgments

Robert T. O'Neill
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H.M. James Hung
Robert Temple

Members of the statistical review teams and clinical review teams within Center for Drug Evaluation and Research that work with Office of Biostatistics on the reactive adaptation or adaptive design IND/NDA submissions

Outline

- Adaptive Design for Exploratory Trials
- Eligibilities for Adaptive Design as a Confirmatory Trial
- Adequate and Well-Controlled Trials
- Statistical Issues
- Validity, Integrity, Interpretability
- Summary: Current FDA Thinking

Learning using adaptive designs in exploratory trials has different context than that in confirmatory trials in therapeutic drug development. The potential advantage of Adaptive Design is its flexibility nature. In exploratory trials, adaptation tries to deal better with learning and formalize the learning. Such exploration should not be confused with prospectively planned adaptive design trial for confirmatory evidence

Wang, Hung, O'Neill – Stagewise Planning for Clinical Trials from Ph II to Ph III (JSM proceedings 2007)

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Learn while Explore

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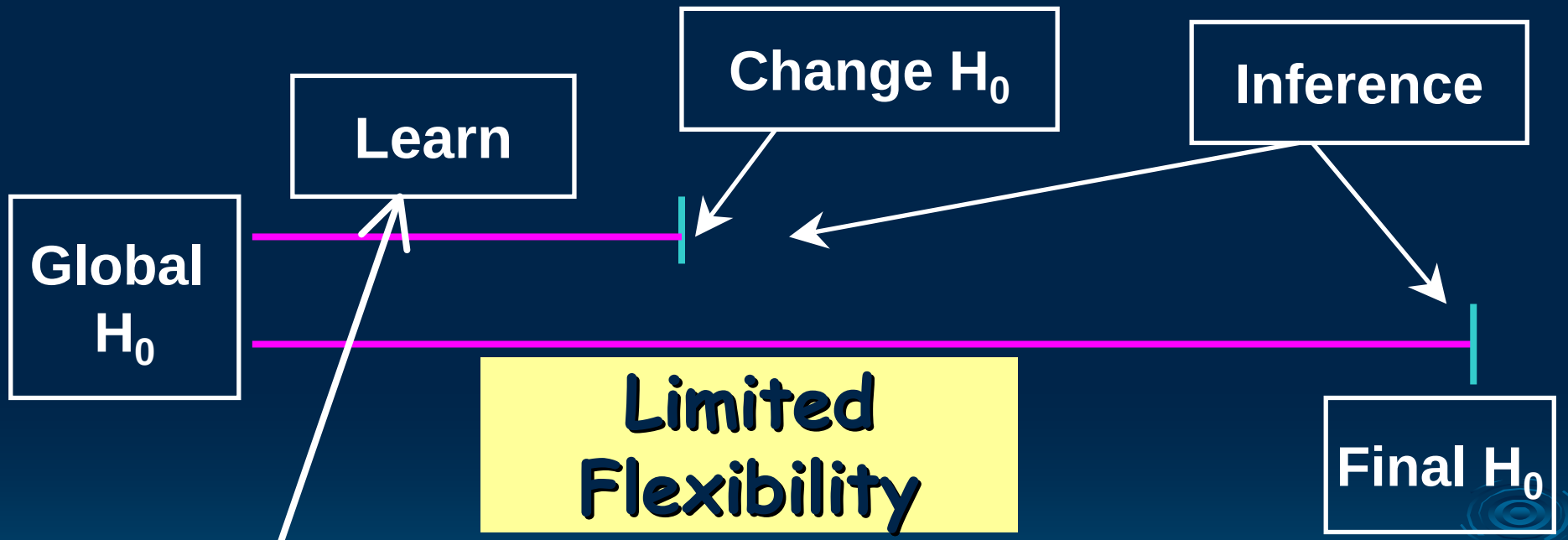
Dealing with Learning

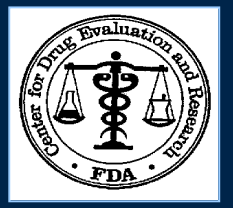
Combine Learn that Formalizes Learn in Confirmatory trial
Exploratory Trials - Hypothesis generation



Patient subpopulation? Objective?
Minimum design modification
Dose range? Endpoint? Effect size?
and eligibility for AD as confirmatory trial

Multiplicity

Eligibility for Adaptive Design As Confirmatory Trials



- Is it a new drug without prior/external controlled trial knowledge? NO
- Are there reasonable empiric safety database that alleviate concerns or can be managed ?
  Indication dependent ?
- Is it a new drug under some drug class that has approved products in the market? Yes
- When can stagewise adaptive trial be considered a confirmatory trial ?

Adequate and Well-Controlled Trials

- Not exploratory adaptive designed trial
- Not only experimentwise type I error rate control
- Should possess the following characteristics
  - clear statement of the objectives, proposed and actual methods of analysis in protocol, SAP, and reports
  - design that permits a valid comparative evidence of T-effect
  - methods of adequate assurance of patient selection
  - patient assignments that minimize bias, group comparability
  - minimize bias on all parties: pts, investigator, data analyst
  - endpoints well-defined that address clinical primary hypo.
  - analysis results – interpretability of the effects of drug

Statistical Issues (1)

- If combining stages
  - Multiplicity of hypotheses – (partially) ignored ?
  - Multiplicity of repeated analyses – no efficacy decision ?
  - Design and analysis features adapted across stages – but only the final hypothesis counts ???
  - If all above are appropriately prospectively addressed √
- If separating stages
  - Conduct seamless: two consecutive studies with no break
  - Planning account for learning data (exploratory AD) without mixing confirmatory data (confirmatory AD) for inference
  - Independence b/w stages and well-controlled trial in later stage
- But, in the absence of eligibility for AD - not clear of confirmatory objective for effective/safe drug

Statistical Issues (2)

- Bias associated with adaptations
  - Due to adaptive monitoring and adaptive decision
  - Due to trial conduct/implementation (unblinded parties)
  - Treatment effect estimate before/after adaptation
  - Impact on type I error

Bias: The systematic tendency of any factors associated with the design, conduct, analysis and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value – Operational & Statistical

- Simulation studies
  - Planning that lays out mid-stream multiple change options
  - Characterize statistical properties on adaptive scenarios
- Statistical efficiency in development program
  - Strategic weighting within confirmatory trial
  - Avoid cherry picking for adaptation
- Control of false positive, minimize false negative

To Maintain Validity/Integrity of Trial Results

Principle – Independence and objectivity

- **Sponsor-Only Model (Sponsor only) – uneasy about**
  Interim Monitoring Committee (~DMC)
  Clinical Trial Team (usual team)
  Unblinded Statisticians (~ unblinded ISAC)
- **ISAC-Only Model (ISAC ←→ Sponsor)**
  e.g., CRO, ISAC has its own blinded vs. unblinded team
- **DMC-Only Model (DMC ←→ Sponsor)**
  Sponsor may provide unblinded statistician for DMC IA report
  DMC makes recommendation for adaptation
- **Combination Model (ISAC → DMC/Spon; DMC → Sponsor)**
  DMC and ISAC: unblinded or blinded; Sponsor: blinded

→ Relevance to multi-regional trials (size, practice, genomic)
→ Legal consequence of confidentiality agreement
→ Need more experiences

Current FDA Thinking

- In adaptive confirmatory trial, alpha error control is one part needed for interpretability, should have limited adaptivity if not fixed, satisfy criteria as A&WC trials
- Meeting with Sponsor to request SOP/Logistics and Charters on firewalls, adaptive monitoring, adaptive recommendation, and adaptive decision
- Pre-specified strategy on results consistency due to prospectively specified interim adaptation on design and/or analysis
- FDA requests documentation of actual monitoring process, extent of compliance, potential impact on study results
- Timing of finalized Protocol and finalized SAP, Actual Adaptation Summary – for interpretability assessment