

Adaptive Design Trial Issues: Goals and Needs

Adaptive Design Clinical Trials Conference

FDA-PhRMA


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Marc K. Walton, M.D., Ph.D.

OPPL / FDA

*The views expressed are those of the author, and do not represent an
official FDA position*

Ultimate Goal of Drug Development Programs

- Approved, Marketed, Available Therapy
 - Favorable Risk-Benefit Assessment
 - Safety
 - Effectiveness
 - Adequate Directions for Use
 - Optimal is preferable
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Difficulties in Therapeutic Development

- Identifying candidate therapeutics
- Selecting which are Safe & Effective products
 - Only feasible through clinical testing
- Understanding how to use product
 - Only feasible through clinical testing
- Clinical testing lengthy and costly
 - Accurate, precise information especially so
 - Leads to incompletely optimized therapies
 - ✦ Better clinical use information desirable

Difficulties in Therapeutic Development

- Many of these issues not in scope of workshop
- Perspective of overall situation
 - Keep expectations balanced
- Improved clinical trial design not likely to enable vast majority of drugs entering Phase 1 becoming successful products
- Goal of better information
 - May yield some improvement in success rate
 - ✦ Better optimization of use
 - May also only lead to recognition of true potential sooner (e.g., inadequate benefit)
- *Faster, Cheaper, Better*

Premise of Workshop

- Additional clinical trial techniques can improve efficiency of clinical development process
- Adaptive design techniques may offer one approach to advancing that goal
- Advances achieved in understanding statistical issues
 - Over past decade or so
 - Help to ensure the statistical interpretability of results
- Further understanding of performance remaining
- Necessary, but not sufficient step for appropriate application

Further areas of evaluation

- Advances illustrate what techniques can provide in idealized settings
- Lesser discussion of underlying necessary assumptions
 - Necessary important pre-existing knowledge
 - ★ i.e., product knowledge that does not need to be produced by clinical study
- Lesser discussion of trade-offs to gain the advantages of the technique
- Important, but incompletely explored and discussed

Interim Data Analysis & Design Revision

- Revise study design on interim results
 - Dose, regimen, population, endpoint, etc.
- Interim results less precise
 - Need to fully understand risk of erroneous selection
 - Disease factors affecting this risk
 - Drug characteristics affecting this risk
- Prospective selection of elements to redesign around
 - What are the circumstances where only a limited number of aspects are unknowns
 - What are the consequences of employing method where more aspects are unknown but ignored

Continuously Conducted Study

- “Seamless” study design
 - No Gap between studies or
 - Interim-based revision of a single study
- Eliminate WhiteSpace
 - Term from print publishing
 - ✦ White space deemed essential to increase comprehension of information

Seamless Study Method

- Time between studies has multiple components
 - Analysis of observed data
 - Interpretation of analyzed results
 - Planning next study
 - Resource allocation
 - Selection of, agreements with, investigators
 - IRB submission and approval
 - Other
- Data analysis and interpretation allow exploration of richness of clinical data
- Comprehension of information important in drug development as well as publishing

Realistic Expectations

- Faster, Cheaper, Better
- Limits to satisfying all goals simultaneously is related to real-world constraints
- Unlikely that Adaptive design will eliminate these constraints



Competing Constraints





Potential Conference Discussion Results

- Need for detailed understanding of incorporated assumptions
- Assumptions that need further sensitivity evaluation
 - Consequences of inaccurate assumptions
- Consideration of specific clinical areas and circumstances where:
 - May be appropriate to use these techniques
 - Not appropriate to use
 - Careful thought to identify these in concrete terms may lead to identifying generalizable features
- Particularly in breakout session discussions