Adaptive Designs in Clinical Trials: An Overview

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Outline
- Motivation: need for greater efficiency in drug development
- Definition, types of adaptation
- Potential benefits and challenges
- PhRMA Adaptive Designs Working Group
- Moving forward

Motivation
- Drug development "pipeline problem": promise of revolutionary advances in basic sciences has yet to be fulfilled into innovative therapies reaching patients
- Decrease in number of new drug and biologic approvals over last decade → development path increasingly difficult, inefficient, and costly – success rate in phase III currently estimated at 50%
- Root cause of problem: outdated development paradigm has not kept up with progress in basic sciences – need to improve applied sciences (Critical Path Initiative)
- Adaptive Designs is one of the tools available to improve and modernize clinical drug development

Definition
Adaptive Design
- uses accumulating data to decide on how to modify aspects of the study without undermining the validity and integrity of the trial
- providing correct statistical inference (such as adjusted p-values, unbiased estimates and adjusted confidence intervals, etc)
- assuring consistency between different stages of the study
- minimizing operational bias

Validity means
- providing convincing results to a broader scientific community
- preplanning, as much as possible, based on intended adaptations
- maintaining confidentiality of data

Integrity means
- providing convincing results to a broader scientific community
- preplanning, as much as possible, based on intended adaptations
- maintaining confidentiality of data

What to adapt?
- Re-calculation of sample size: assess design assumptions (e.g., variability in response) to avoid underpowered study – blinded or unblinded
- Adaptive dose-ranging: change dose/regimen allocation ratios based on accumulating information → increase information value per patient
- Treatment selection – seamless phase II/III: start with larger number of arms (e.g., doses) and make decision on which to continue at interim point
- Changes in population (e.g., based on genetic marker)
- Stopping rules for futility and efficacy

Adaptive by Design

Adaptive dose finding: illustration

Adaptive dose finding
Prior to study the true position of dose response curve is unknown
In the adaptive dose finding approach, a small number of patients on many initial doses are used to explore the unknown dose response. As the dose response strength in some patients is allocated to doses (including one dose) within the broad range of interest, number of patients assigned to 'uninformative' doses is decreased.
**Benefits and Opportunities**

- Adaptive Designs add value across entire development process.
- For the patient in the trial: Higher probability of being allocated to a treatment that works than in a traditional, non-adaptive design (more ethical).
- Improved development strategies: Answering the right development questions more efficiently and accurately (improving critical path).

**Learn**

- Improved understanding of dose response relationship leading to improved dose(s) selection for phase III.
- Combining PoC and dose ranging.

**Confirm**

- Dose selection (dropping doses): to improve selection of dose with better efficacy and safety profile for launch.
- Revisiting study design assumptions (e.g., sample size re-estimation).
- Population enrichment.
- Early stopping for futility/success.

**Challenges**

- Not always feasible/better: accrual rate/availability of endpoint for decision ratio low enough to allow adaptation to be effective – use of biomarkers can help.
- Considerable more up-front planning required – assess impact of pre-planned adaptations on operating characteristics (e.g., type I error rate, power, etc); trial simulation often used (also a benefit: better planning).
- Logistcs: drug manufacturing (e.g., larger number of doses than usual), drug supply management (adaptive dose allocation), IVRS – may be more costly.
- Potential need for sponsor involvement in interim decision (e.g., treatment selection, futility rule); need for acceptable operational model for DMC-sponsor interaction to ensure trial integrity preserved.

**PhRMA Adaptive Designs Working Group**

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**Vision**

- To establish a dialogue between statisticians, clinicians, regulators and other lines within the Pharmaceutical Industry, Health Authorities and Academia, with a goal to contribute to developing a consensus position on when and how to consider the use of adaptive designs in clinical drug development.

**Mission**

- To facilitate the implementation adaptive designs, but only where appropriate.
- To contribute to standardizing the terminology and classification in the rapidly evolving field of adaptive designs.
- To contribute to educational and information sharing efforts on adaptive designs.
- To interact with experts within Health Authorities (FDA, EMEA, PMDA, and others) and Academia to sharpen our thinking on defining the scope of adaptive designs.
- To support our colleagues in health authorities in their work towards the formulation of regulatory draft guidance documents on the topic of adaptive designs.

**Executive Summary of White Paper**


**Adaptive Designs in Clinical Drug Development—An Executive Summary of the PhRMA Working Group**

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Pharma ADWG Activities

- Communication
- Case studies
- ICH
- Best practices
- KOL

http://biopharmnet.adtm.com/PharmaADWHome

Outreach activities
- EFPIA/EMEA workshop (Dec '07) – Currently working with EFPIA on agenda for follow-up EFPIA/EMEA workshop
- FDA visit (April 02, 2008)
- Health Canada training (April 29/30, 2008)
- PMDA/JPMA "sharing western examples of adaptive designs" (tbc)

Moving forward

- FDA to release draft guidance on adaptive designs later this year: clarifications/recommendations to industry
- Need to increase sharing of experience (both good and bad) with the use of adaptive designs – case studies workstream of AD WG
- Try to develop a “three-bucket” classification for adaptations: broadly accepted (e.g., blinded sample size reassessment); unacceptable (e.g., unblinded, unplanned change in primary endpoint); and case-by-case discussions (e.g., seamless phase II/III)
- Although useful, adaptive designs alone will not solve drug development inefficiency: need combined effort in different fronts, with different methods/approaches