Accelerating Clinical Development
With Adaptive Study Designs

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Outline

- Background
- Adaptive Study Designs
  - Definitions
  - Types
  - Logistics
- Adaptive Dose Ranging Studies (ADRS)
  - Goals of ADRS Working Group
  - Simulation study to evaluate methods
  - Recommendations
• Pharmaceutical industry pipeline problem: decreasing number of drug approvals and increasing cost, despite advances in basic science

• US FDA white papers
  – *Challenge and Opportunity on Critical Path to New Medicinal Products* (2004)

• Pharmaceutical industry (PhRMA) response: Pharmaceutical Innovation Steering Committee (PISC) Working Groups
Critical Path Opportunities and PISC WGs

- Streamlining clinical trials
  - Adaptive Dose Ranging Studies WG
  - Adaptive Designs WG
  - Improving Efficiency of Late-Stage Clinical Research (ECR WG)
- Better evaluation tools: Biomarkers WG
- Harnessing bioinformatics: Data Mining Tool Validation WG
- Addressing public health needs: Predictive Models for Safety and Efficacy WG
What is an Adaptive Clinical Study?

- Definition: A multi-stage study in which data from the ongoing study is used to modify the conduct of the study without undermining the *validity* and *integrity* of the trial.

- Adaptive BY design: Adaptation is a *prospective* design feature, not a remedy for inadequate planning.
  - Through upfront planning is required.
  - Rules for adaption are prespecified.

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*a*Adaptive Designs: Terminology and Classification (Dragalin, 2006)
Types of Adaption and Prespecified Rules

- Group sequential designs (Stopping Rule)
- Sample-size reassessment (Sampling Rule)
- Response adaptive designs (Allocation Rule)
- Flexible designs (e.g. Seamless Phase 2/3 designs)
  - Allocation Rule
  - Sampling Rule
  - Stopping Rule
  - Decision Rule

\(^a\)Adaptive Designs: Terminology and Classification (Dragalin, 2006)
Logistics of Implementing Adaptive Designs

- Planning and education
- Recruitment rate
- Data monitoring
- Randomization
- Drug supply
• Poor understanding of dose response (DR) for both efficacy and safety is pervasive in drug development

• Sub-optimal dose selection identified by both FDA and industry as one of root causes of late phase attrition and post-marketing problems with approved drugs

• Current dose finding designs and methods focus on selection of registrational study dose out of fixed, generally small number of dose levels, via pairwise hypothesis testing ⇒ inefficient

• Optimize patient treatment within a study, by minimizing patients exposed to ineffective treatments
Goals: ADRS WG

- Investigate and develop designs and methods for efficiently learning about safety and efficacy dose-response → benefit/risk profile
- More accurate and faster decision making on dose selection and improved labeling
- Evaluate statistical operational characteristics of alternative designs and methods to make recommendations on their use in practice
- Increase awareness about this class of designs, promoting their use, when advantageous
- Document and publish findings of the working group
Dose Finding Methods – Fixed Doses

- **ANOVA**: Conventional method based on pairwise comparisons and multiplicity adjustment (Dunnett); common approach used in dose finding studies – Amit Roy and Frank Shen

- **MCP-Mod**: combination of multiple comparison procedure (MCP) to identify presence of DR, and modeling to estimate target dose(s) and DR profile (Bretz, Pinheiro and Branson, 2005) – José Pinheiro and Frank Bretz

- **MTT**: novel method based on Multiple Trend Tests (Liu, 2006) – Qing Liu

- **BMA**: Bayesian Model Averaging (Hoeting, Madigan, Raftery and Volinsky, 1999) – Beat Neuenschwander and Amy Racine

- **LOCFIT**: Nonparametric local regression fitting – Björn Bornkamp and Frank Bretz
Dose Finding Methods – Adaptive dose allocation

- **GADA**: Adaptive dose allocation based on Bayesian normal dynamic linear model (Krams, Lees and Berry, 2005); allocation of patients to dose adaptively changed according to model-based optimization criteria (e.g., variance of target dose estimate) – Tom Parke and Michael Krams

- **D-opt**: adaptive dose allocation based on D-optimality criterion used with sigmoid-$E_{\text{max}}$ model; model parameters re-estimated at interim analysis and corresponding D-optimal allocation determined for next interval – Alex Dmitrienko and Chyi-Hung Hsu
Simulation study: Design and assumptions

- Objective: proof-of-concept + dose finding for neuropathic pain
- Primary endpoint: change from baseline in pain score on visual-analog scale (VAS)
- Key questions:
  - is there evidence of a dose response
    * Significance level (one-sided): 0.05
    * Clinically relevant change in VAS: 1.3
  - which dose(s) should be tested in large confirmatory trials
  - how well is the dose response (DR) curve estimated
- Study design scenarios:
  - Sample sizes: 150 and 250 patients
  - Number of doses: 5, 7, and 9 doses\(^a\)

\(^a\) 5 doses (0, 2, 4, 6, 8), 7 doses (0, 2, \ldots, 6, 8), and 9 doses (0, 1, \ldots, 8)
Dose response profiles

Expected change from baseline in VAS at Week 6

-1.5 -1.0 -0.5 0.0

Dose

Umbrella  Emax  Sigmoid Emax

Flat  Linear  Logistic
Measuring performance

- Probability of identifying dose response: $Pr(DR)$
- Probability of identifying clinical relevance and selecting a dose for confirmatory phase: $Pr(dose)$
- Dose selection: Distribution of selected doses (rounded to nearest integer, if continuous estimate possible)
Selected Simulation Results
Type I Error is controlled at 5% by all methods
Pr(DR) generally ↑ as # doses ↓ (for fixed sample size)
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**Pr(dose | flat DR)**

- **LOCFIT**
- **BMA**
- **MTT**
- **MCPMod**
- **GADA**
- **Dopt**
- **ANOVA**

False positive for clinically relevant effect is generally greater for ANOVA
Most methods performed poorly, GADA generally best
Distribution of selected doses is wide for all methods.
Sample predicted curves – Logistic DR, 9 doses (N = 150)

Overall shape of DR was described fairly well by all methods
Conclusions

- Detecting DR is considerably easier than estimating it, or identifying a target dose to advance into a confirmatory trial.

- Sample sizes for DR studies that are based on power to detect a DR are generally inadequate for DR estimation and dose selection.

- Adaptive dose finding methods lead to gains in power to detect DR, precision of DR estimation, and selecting correct target dose – greatest potential in the latter two.

- In practice, need to balance gains associated with adaptive dose ranging designs approach against burden of greater methodological and operational complexity.
**Recommendations**

- Adaptive, model-based designs should be routinely considered for dose ranging studies.
- Proof-of-concept (PoC) and dose selection should be combined into a single seamless trial, when feasible.
- Trial simulations should be used to determine the operating characteristics of designs/methods under consideration, and for sample sizes estimation.
- Sample size calculations for Phase II studies should take into account desired precision of estimated target dose.
- Consider using more than one dose in Phase III, when sample size of Phase II was inadequate.
Recommendations (contd.)

- Early stopping rules, for both efficacy and futility, should be used when feasible
- Software for designing, implementing, and analyzing data from adaptive dose-ranging studies needs to be developed
- In practice, need to balance gains associated with adaptive dose ranging designs approach against greater methodological and operational complexity

NOTE: A white paper describing this work is available from http://biopharmnet.editme.com/PhrmaAdrsHome, and has been published in the November 2007 issue of the Journal of Biopharmaceutical Statistics, along with commentary by Carl-Frederik Burman (Astra-Zeneca), Andy Grieve (King’s College, Univ. of London), Robert Hemmings (MHRA, UK), Sergei Leonov (GSK), and Sue-Jane Wang (US FDA)
Future Work

- Assess probability of success in Phase 3
- Determine sample sizes needed for adequate assessment of dose-response
- Investigate novel adaptive designs and analysis methods
- Evaluate utility of exposure-response modeling to target dose identification
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Affiliations noted are as of initiation of ADRS WG
Leaders of ADRS WG
References


