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PhRMA Adaptive Dose Ranging Studies Working Group (ADRS WG)

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  - Björn Bornkamp
  - Frank Bretz
  - Christy Chuang-Stein
  - Vlad Dragalin
  - Parvin Fardipour
  - Bill Gillespie
  - Chyi-Hung Hsu
  - Frank Miller
  - Krishna Padmanabhan
  - Tom Parke
  - Inna Perevozskaya
  - Amit Roy
  - Ashish Sanil
  - Jonathan Smith

**My colleagues at Cytel**

Pralay Senchaudhuri and Suresh Ankolekar
Outline

1. Summary of study of adaptive dose finding designs by ADRS WG
2. Comparison of one of the best designs in the study with an adaptive dose finding design that explicitly models safety
   • For a typical scenario from the ADRS WG study
   • For a more challenging scenario that requires closer spacing of doses
4. Concluding Remarks
Introduction

- Selecting doses to take from Phase 2 to Phase 3 is one of the most important decisions during drug development.

- It is widely believed that high attrition rates in Phase 3 are largely due to inadequate dose selection.

- The Adaptive Dose Ranging Studies Working Group (ADRS WG) was formed by the PhRMA Innovation Steering Committee to evaluate and address the problem.
ADRS Simulation Study

Comparison of seven response adaptive methods and ANOVA on detection of DR, dose selection, estimation of DR profile. Only adaptive aspect considered was adaptive dose allocation based on **efficacy endpoint**

- **Doses:**
  - 9 doses: \{0,1,2,3,4,5,6,7,8\}
  - 5 doses: \{0,2,4,6,8\}

- **Endpoint:** change from baseline in VAS score vs. placebo

- **Clinically meaningful difference:** \(-1.3\)

- **Variance:** 4.5

- **Sample Size:** 250

- **Number of adaptations:** 0,1,2,4,9

- **Dose Response Curves (including flat DR):** 7
Main Conclusions

- Detecting Dose Response (DR) is much easier than estimating it.
- Adaptive dose ranging methods can lead to substantial gains over traditional approaches, especially for estimating DR and dose selection.
- No method is uniformly best: relative performance depends on scenario, assumptions.
- Sample sizes for Dose Finding (DF) studies are typically not large enough for accurate dose selection and estimation of DR.
General Adaptive Dose Allocation (GADA)

Probability of selecting a dose with response within 10% of target

(Bornkamp, et. al., 2007)
Safety was implicitly incorporated in the designs by setting target of -1.3 above minimum of -1.65 for all DR curves with clinically relevant effects.
Illustrative Example

- I will use the Sigmoidal Emax DR used in the ADRS WG studies to discuss modeling of safety along with modeling of efficacy.

- Target dose for this DR is 5, so I will assume that doses 7 and 8 carry significant risk of serious adverse events (SAE).

- I will use the Bayesian Generalized Adaptive Dose Allocation (GADA) method for discussion as it was among the best designs and is well known from the ASTIN trial. It is also one of the most popular Bayesian designs for dose finding.
GADA Design

- Sample size = 240 consisting of 10 cohorts of equal size (9 looks for adaptive randomization).
- Each cohort has 6 subjects on placebo and 18 subjects adaptively assigned to doses of the study drug.
- First cohort of 24 subjects randomized approximately equally to active doses.
- For subsequent cohorts the 18 subjects on study drug are assigned doses using information from the responses of subjects in previous cohorts. The dose allocation aims to minimize variance of estimated response at the target dose.
- 1000 simulations used to investigate operating characteristics.
GADA Dose Selection

```
<table>
<thead>
<tr>
<th>Dose</th>
<th>Freq Selected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
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Pr(SAE risk) = 0.23
Pr(Target) = 0.31
Utility Maximization method (Ivanova et. al. 2009)

- Safety is quantified by using estimates of $p_k$ the probability of SAE at dose $D_k$ (based on knowledge of drug, previous studies and experience with similar drugs).
- It is assumed that $p_k$ increases with the strength of the dose.

For our example we use the piecewise linear-exponential function used by Antonijevic et. al. (2009) to model Pr(SAE)
Construction of utility function

- Let $\mu_k$ be the mean response at dose $D_k$ (Sigmoidal DR).
- Define utility $U_k$ of dose $d_k$ as $(- \mu_k - a \cdot p_k)$.
- The method requires that utility function is umbrella shaped.
- We chose $a > 0$ so that the utility is maximized at the target dose of 5.
Algorithm for adaptive allocation

- Starting cohort of 24 subjects has 6 subjects assigned to placebo, 9 subjects assigned to $D_k$ and to $D_{k+1}$ with $k=4$

- Estimate difference between utility at $D_{k+1}$ and $D_k$ computed from means of responses observed so far at all doses by fitting a non-parametric umbrella shaped function.

- In subsequent cohorts there are 6 subjects on Placebo ($D_0$), and
  - if utility difference >0 step up (assign 9 subjects to $D_{k+1}$ and $D_{k+2}$),
  - if utility difference < 0 step down (assign 9 subjects to $D_k$ and $D_{k-1}$)
  - if $k$ is lowest or highest dose assign 12 subjects to $D_k$ and 6 to the adjacent study dose

- At the end of the study fit umbrella function to observed data and select the smallest dose with maximum estimated utility
Utility Maximizing Design

Dose Selection

<table>
<thead>
<tr>
<th>Dose</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
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<tr>
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</table>

Total: 896

Pr(SAE Risk) = 0.05
Pr(Target) = 0.50
Suppose steeper Sigmoidal DR is a likely scenario
No dose falls within this narrower range
Closer spacing between doses

• Since location of the therapeutic window is not known doses need to be closer.
• Separation by 0.5 units will ensure that we have at least one dose within 10% of the target. We will then have 17 doses: {0, 0.5, 1, 1.5, 2, … 7, 7.5, 8}
GADA: 9 vs. 17 doses, sample size=240

<table>
<thead>
<tr>
<th>Dose</th>
<th>Steep</th>
<th>SigEmax</th>
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<tr>
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Pr(SAE risk) 0.15 0.23
Pr(Target) 0.00 0.31

SAE risk comes down
Pr(Target) goes from 0 to 0.21 for Steep DR
Stays about same for SigEmax DR

Pr(SAE risk) 0.11 0.14
Pr(Target) 0.21 0.32
Comparison with Utility Max. Design

## Steep Dose Response

<table>
<thead>
<tr>
<th>Dose</th>
<th>GADA Steep</th>
<th>GADA SigEmax</th>
<th>Utility Maximizing Steep</th>
<th>Utility Maximizing SigEmax</th>
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### Comparison

- GADA Steep: 0.11
- GADA SigEmax: 0.14
- Utility Maximizing Steep: 0.00
- Utility Maximizing SigEmax: 0.00

- Total GADA Steep: 0.21
- Total GADA SigEmax: 0.32
- Total Utility Maximizing Steep: 0.63
- Total Utility Maximizing SigEmax: 0.50
Planning drug supply for adaptive designs

• Planning for drug supply can be challenging
  – Standard manufacturing practice is to make the total required amount for the trial in one campaign
  – DF trials traditionally use far fewer than 17 doses
  – Dynamically changing randomization ratios for adaptive design make it difficult to estimate amount required.

• Conservative approach: any dose allocation is possible will lead to overage (wastage) exceeding 1000%
Modeling drug requirement

• Adaptive dose allocations from design simulations for likely scenarios can be used as inputs to a drug supply chain model for stocks and shipments to strike a better balance between risk of randomization failure (risk of stock-out) and overage.

• Drug supply simulation experience in consulting assignments for several adaptive trials
  – Requirements depend on many factors (e.g. #subjects, # sites, enrolment rates, # arms, # dispensing visits, lead times)
  – Overages ranged from 10 to 400%
Concluding Remarks

- Extensive simulation studies by the PhRMA ADRS WG show that adaptive designs can significantly improve chances of selecting the target dose where safety is implicit in the choice of the target dose.

- Adaptive designs that model safety as well as efficacy show promise of outperforming designs that model efficacy alone for trials where safety is an important consideration.

- Adaptive designs can efficiently handle many more doses than traditional trials by assigning most subjects to doses of interest.

- Efficiency in drug supply for adaptive trials can be achieved by extending simulation of adaptive designs for assessment of operating characteristics to include supply chain simulation.
References


• Dragalin V, et. al. (2009) A simulation study to compare new adaptive dose-ranging designs (under review)


Thank you!

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