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Presentation #2: Bayesian design and analysis for dose ranging studies

Ming-Dauh Wang, Ph.D. received his PhD in Statistics from the University of Minnesota in 1998. He started his pharmaceutical career at Eli Lily and Company in 2001 as a clinical statistician for 17 years, during which he applied Bayesian statistics to drug development projects ranging across pre-clinical, clinical and portfolio management. He moved on and joined Regeneron in 2018, where he continued to explore Bayesian applications as lead statistician for a few clinical programs including indications for rare diseases. He also led a statistical group supporting Regeneron Science Advisory Council in exploring clinical trial data by novel statistical methods to help answer open scientific questions.

After 3 years with Regeneron, Dr. Wang took a new role at Bayer as a Bayesian methodology statistician in early 2021, collaborating with colleagues for application of Bayesian statistics in drug development.
Bayesian Design and Analysis for Dose-Ranging Studies

Ming-Dauh Wang, PhD
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Outline of Presentation

// Common approaches and issues
// Bayesian dose response by Emax models
  // Reparameterization
  // Prior selection
  // Placebo effect
  // Missing data
// Safety and control of over-dosing
// Bayesian optimal design
Common Approaches

// MCP-Mod (Bretz et al 2005, Pinheiro et al 2014)
   // Features: addresses model uncertainty, controls type-I error
   // Issues: best model or model averaging? Schornig et al (2016) shows model averaging outperforms model selection methods. However, is it practical, particularly for Ph3 dose selection?

// BMA-Mod (Could 2017), a Bayesian alternative to MCP-Mod
   // Features: does not require testing hypotheses or adjusting for multiple comparisons, can better facilitates decision making
   // Issues: application of model averaging indicates yet high uncertainty in dose-response identification; does it then imply more information (more trials?) is needed prior to entering Ph3?
   // Quote from Gould (2017): There is no need to simulate findings assuming a “true” dose-response model because BMA-Mod does not seek or assume the existence of a “true” model, and so cannot commit the error of assuming the wrong model.
Bayesian Emax Models

Response = $E_0 + \frac{E_{\text{max}} Dose^h}{ED50^h + Dose^h} + e$, $e \sim N(0, \sigma^2)$

Gajewski et al (2019): The EMAX model with “Hill” parameter close to 1.0 has been shown to provide good empirical fit for designing and analyzing dose-response data across a wide range of pharmaceutical study, referencing Thomas et al (2014).

Schmidli et al (2016): Several authors argued that a flexible monotonic model, such as a Sigmoid Emax model, can be used for all practical purposes, as it approximates the commonly observed dose response shapes well. While generally applicable, this flexible model can sometimes be challenging to fit with a small number of doses, referencing Thomas (2006), Draglin et al (2007).

Predominantly used for PK/PD modeling by Pharmacometrics in drug development

Example: Schutt et al (2016), an application to a dose-ranging study for uterine fibroids
Reparameterization

// Convergence might be an issue, particularly with the Hill parameter
// Restrict priors to reasonable sample spaces might help
// Examples:
  // Model (Emax, Emax/ED50) instead of (Emax, ED50) – Schoemaker et al (1988)
  // Model (effect at the highest dose, ED50) instead of (Emax, ED50)
  // Other choices - Reeve & Turner (2013)
Selection of Priors

// Design priors should reflect current knowledge of the dose response relationship

// Priors for Emax and ED50 often can be elicited from preclinical, Phase 1b or 2a data; more challenging with the Hill parameter

// Philosophically, analysis priors should agree with design priors

// Can make adjustment to make trial data speak more

// Though exploratory studies bear less restraints from regulatory scrutiny, may still make analysis priors less informative

// Can utilize truncation to rule out very unlikely situations (e.g. Hill parameter >10), which would enhance estimation

// Prior robustness/sensitivity analysis
Elicitation of Placebo Effect

Meta-Analytic Predictive (MAP) is a reasonable approach - Neuenschwander et al (2010), Schmidli (2014):

- A hierarchical Bayesian model considering the sample mean response from a study as a random effect
- Can also generalize it by also considering the sample variance from a study as a random effect (Zhang et al, 2015)
- Use predictive distributions of parameters as design priors for the placebo effect
Missing Data

// Missing data could introduce loss of power and bias


// Bayesian joint modeling of outcome and missingness status - Liu et al (2016)

// Still do multiple imputation, but pooling all posterior samples from all analyses for a single summary - Zhou and Reiter (2010)
Safety and Control of Over-Dosing in Dose-Ranging Studies
Other Factors to Consider in Addition to Efficacy

- Safety often needs to be considered along with efficacy
- Avoid exposing patients to doses with higher safety liabilities
- Dose selection based on utility balancing between efficacy and safety
- Unnecessary high doses
  - Tendency of the sponsor to push for higher efficacy with known safety issues of or not of concern, or without safety signals up to date
  - A bit more efficacy gain with higher doses might not be worth when efficacy has reached certain levels
- Noncompliance/drug-interaction that would affect drug exposure
Example: Adaptive Randomization

// Trial size: 400, randomized adaptively in 5 cohorts, equal ratios for cohort 1
// Adjust allocation ratios based on performance on efficacy and safety

// Efficacy Design Model:

\[
\text{Response}_i = E_0 + \frac{E_{\text{max}} \cdot \text{Dose}_i}{E_{50} + \text{Dose}_i} + N(0, \sigma^2)
\]

// \(E_0 = -2.25, E_{\text{max}} = -1.4, E_{50} = 0.4\)
// Placebo (0) and doses of 1, 3, 6, & 9 units
// Doses have equal variance (\(\sigma = 2.4\))

// Safety Design Model (for a treatment-related AE).

// Event rates at doses:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Placebo</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pr(No AE)</td>
<td>0.866</td>
<td>0.871</td>
<td>0.702</td>
<td>0.647</td>
<td>0.590</td>
</tr>
</tbody>
</table>
Dose-Response Analysis Models

// Efficacy Analysis Models
// Emax Model (smoothest)
// Normal Dynamic Linear Model (NDLM) (some smoothing)
// ANOVA Comparison of Means (no smoothing)

// Safety Analysis Models
// Simulated data were analyzed using logistic regression
Probability of Success

// For efficacy, the probability of success is the probability of achieving effect size of greater than 0.4

// For safety, the probability of success is the probability of no adverse event of interest

// The overall probability of success (POS) at a dose can be defined as a function of efficacy probability and safety probability at the dose

// For our illustration, we define:

\[
\text{POS} = P(\text{achieving efficacy criterion}) \times (1 - P(\text{adverse event of interest}))
\]

// Dose allocation ratios are then based on standardized POS’s across the doses
Average Cumulative Number of Subjects

In general, with the three analysis models, more subjects were assigned to higher doses because of higher efficacy effect sizes.

Penalty on high doses for AE counts was particularly demonstrated on the highest dose.

Greater penalty on AE would further decrease allocation to high doses.
Adding High Dose Penalty

For doses that have already reached a high threshold of efficacy, for example ED75, we may decrease allocation to those that have similar efficacy and are unnecessarily high (to avoid regulatory and potential unknown safety concerns).

For example, in our simulation case doses of 3, 6 and 9 are all above ED75, so we can decrease allocation to doses of 6 and 9 through adaptation.

To address this issue, we propose a method for reducing the probability of allocation to overly high doses.
### Adding High Dose Penalty – An Example

// Steps:

1. For each simulated trial, identify response values above E75 (75% of Emax) → $r_1, r_2, \ldots$
2. Find the minimum dose corresponding to $r_1, r_2, \ldots \rightarrow r_{\text{min}}$ is the response for this minimum dose
3. Calculate the high dose penalty using the following formula:
   \[
   W_i = \frac{1}{100} \frac{(r_{\text{min}} - r_i)^2}{(E75 - E_{\text{max}})^2}
   \]
4. Multiply the POS calculated from the adaptive method by 1 if there is penalty or $W_i$ if there is no penalty for each active dose
5. Calculate the allocation probabilities

// $W_i$ will penalize responses closer to $r_{\text{min}}$ much more heavily. This means the closer the dose response is to $r_{\text{min}}$, the less likely we are to randomize to this dose.
Probability of Success with High Dose Penalty

// Allocation probabilities determine the number of subjects allocated to each dose

// The penalty affects allocation probabilities for doses above 1 in a dose increasing manner
Adjusted Allocation with High Dose Penalty

Cumulative allocation numbers after 400 subjects (80 subjects per cohort)
Adding a high dose penalty resulted in a 40% reduction in the number of subjects allocated to the highest dose.
Summary

• Our simulation study demonstrated that by using adaptive randomization in clinical trials, we can increase the number of subjects allocated to more efficacious doses, as well as decrease the number of subjects exposed to doses with safety concerns or unnecessarily high doses.

• In the scenarios we studied, analysis by the Emax analysis model resulted in the most drastic effect in adaptive dose allocation ratios.

• NDLM and Emax analysis models had more similar dose allocation than ANOVA.

• ANOVA more closely resembled a traditional, non-adaptive randomization design.

• Could just apply the approach without interim adaptation.
Bayesian Optimal Design
Bayesian Optimal Design

Goal: choose a design to maximize the expected information gain of model parameters

- Design space: \( \Omega_x = \{x_1, \ldots, x_m\} \)
- \( N = \sum_{i=1}^{m} r_i \)
- \( \xi \): a design that assigns \( r_i \) subjects to \( x_i \)
- \( \theta \): a vector of unknown parameters
- \( I(x, \theta) \): Fisher information matrix for one observation

\[
M(\xi, \theta) = \sum_{i=1}^{m} \omega_i I(x_i, \theta), \quad \omega_i = \frac{r_i}{N}, \quad \sum_{i=1}^{m} \omega_i = 1
\]

Bayesian D-optimal design optimizes expected Shannon information:

\[
U(\xi) \approx \int \log\{\det\{M(\theta, \xi)\}\} p(\theta) d\theta
\]

which is an approximation for non-linear models

- Chaloner and Verdinelli (1995)
One example

Efficacy model:

\[ y = E_0 + \frac{E_{max} \times x^\gamma}{ED_{50}^\gamma + x^\gamma} + \epsilon, \quad \epsilon \sim N(0, \sigma^2) \]

Safety model:

\[ \logit(Y = 1|x) = \alpha + \beta \log(x) \]

Consider an adaptive design with:

Initial design:

- \( n_0 \) patients to initial doses \( \rightarrow D_0 \)
- \( \xi_0 \): The starting design with initial doses

Adaptation:

\( n \): Single or a group of patients assigned to the next dose

What dose?

The next optimal dose \( x^* \) is determined by

\[
x^* = \arg\max_{x \in \Omega_x} \int_{\Theta} \ln[n_0 M(\xi_0, \theta) + n I(x, \theta)] p(\theta|D_0) d\theta
\]

\[
Pr\{Y = 1|x^*\} \leq \text{a limit (e.g., 0.5)}
\]
Simulation

// Efficacy model:
\[ E_0 = 0, \gamma = 1 \]
\[ E_{\text{max}} = 100, ED_{50} = 0.5, \sigma^2 = 3 \]
\[ \Omega_x = \{x_1, \ldots, x_{11}\}, \log(\Omega_x) = \{-3.0, -2.4, \ldots, 2.4, 3.0\} \]

// Safety model:
\[ \alpha = -0.896, \beta = 0.434 \quad \rightarrow \quad 0.1 \leq Pr\{Y = 1|x\} \leq 0.6 \]

// Vague priors for all parameters
// Overall sample size: 50
// Safety criterion: \[ Pr\{Y = 1|x^*\} \leq 0.5 \]
// Sample size for each adaptation: n=5
// Initial doses: n0=10, equally assigned to dose 1 and dose 2
Results: Initial Doses

Initial doses: 1 & 2
5 obs per dose, safety probability limit = 0.5

Initial doses: 1 & 6
5 obs per dose, safety probability limit = 0.5
Results: Safety Criterion

- Initial doses: 1 & 2
  - 5 obs per dose, safety probability limit = 0.5

- Initial doses: 1 & 2
  - 5 obs per dose, safety probability limit = 0.7
Results: Group Size

- **Initial doses: 1 & 2**
  - 5 obs per dose, safety probability limit = 0.5

- **Initial doses: 1 & 2**
  - 3 obs per dose, safety probability limit = 0.5
Results: ED50 Location
Convergence: $E_{max}=100$, $ED_{50}=1.0$

Bayesian optimal design vs. Conventional dose escalation:

<table>
<thead>
<tr>
<th>Adaptation stage</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\hat{\theta}_{D}$</td>
<td>Bayesian optimal design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\hat{E}_{max}$</td>
<td>19.38</td>
<td>101.85</td>
<td>101.29</td>
<td>99.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\hat{ED}_{50}$</td>
<td>7.1E-4</td>
<td>1.04</td>
<td>0.94</td>
<td>0.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\hat{\theta}_{MLE}$</td>
<td>Traditional design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\hat{E}_{max}$</td>
<td>16.08</td>
<td>143.78</td>
<td>216.43</td>
<td>103.58</td>
<td>94.51</td>
<td>100.01</td>
</tr>
<tr>
<td>$\hat{ED}_{50}$</td>
<td>0.09</td>
<td>1.99</td>
<td>2.11</td>
<td>0.90</td>
<td>0.80</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Improves efficacy estimation
Generalizations:

// For Ph2b type of dose-ranging studies, may be operationally more appealing to consider pre-determined dose combinations for adaptation

// Adaptation could be for
  // Adding a dose or doses
  // Dropping a dose or doses
  // Reselecting doses
  // Adjusting randomization ratios

// Could just apply Bayesian optimal design without interim adaptation
References:

// Gajewski et al (2019). Statistics in Medicine, 38, 3123-3138
// Zhou and Reiter (2010). The American Statistician, 64, 159-163
Abstract

Selection of right doses of an experimental drug for confirmatory trials is an essential task for ensuring not only successful regulatory approval of the drug but also competitive patient use of it afterwards. Besides the common focus on achieving desired efficacy, drug safety also often needs to be addressed early in the dose selection process. Even when dose-dependent drug safety has not appeared to be salient based on data up to date, unnecessary high doses might still raise regulatory concern and thus require adequate control in dose selection. I will present an integrated Bayesian parametric approach to design and analysis for dose-ranging studies considering the above enumerated needs. Elicitation of priors for dose-response model parameters for designing a dose ranging trial as well as priors for final analysis will be reviewed. Issues including re-parameterization for improved parameter estimation, meta-analysis for summarizing relevant data for use as prior information and handling of missing data will be discussed and illustrated.
Thank you!