Model-based Designs in Oncology Dose Finding Studies

Ling Wang

Takeda Development Center Americas, Inc.
Overview of Oncology Dose Finding Studies

• Oncology is a special therapeutic area in which dose finding studies, including first in human studies, are conducted in cancer patients
  – mostly either a variety of solid tumor patients, or a variety of patients with hematologic malignancies)
  – Often times patients have been through multiple lines of therapy before entering the study
• The goal of the study is to find Maximum Tolerated Dose (MTD), using a series of small cohorts of patients (3-6)
  – During the dose escalation phase, for each cohort of patients, Dose Limiting Toxicity (DLT) events are counted to determine the overall toxicity profile
  – DLTs are pre-specified in study protocols
• At the end of the study, a recommended phase 2 dose (RP2D) is suggested, combining clinical, safety, PK and PD information. This dose may or may not be the MTD
Agenda

• Single agent dose finding study designs
• Combination designs
• Other designs combining safety and efficacy
3+3 Design Algorithm

Traditional oncology dose finding study design, and still widely used.

- **New cohort at a new dose level: Enroll 3 patients**
  - **DLT = 0/3**
    - Go to next higher dose level or same dose if highest dose level
  - **DLT = 1/3**
    - Enroll 3 additional pts at the same dose level
  - **DLT > 1/3**
    - Go to next lower dose level or declare MTD at next lower dose level if 6 pts already tested (never re-escalate)
    - **DLT = 1/6**
      - Go to next higher untested dose level or declare MTD otherwise
    - **DLT > 1/6**
      - Go to next lower dose level or declare MTD at next lower dose level if 6 pts already tested (never re-escalate)
Limitations of 3+3 Design

- Ignores dose escalation history other than the previous cohort
  - 0/3, 0/3, 0/3, 0/3, 0/3, 2/6 provides more information than 0/3, 2/6
- Same action under qualitatively different situations
  - 0/3 and 1/6 lead to the same action (escalate to the next planned dose)
  - 2/3, 3/3, 2/6, 3/6 and 4/6 lead to the same action (de-escalate to the last planned dose)
- Cannot re-escalate
- Inflexible cohort sizes (either 3 or 6)
Published Performance of 3+3 Design

- **Low probability** of selecting the true MTD (e.g. Thall and Lee 2003)
- **High variability** in MTD estimates (Goodman et al 1995)
- **Poor targeting** of MTD on study
  - **MTD at low dose**: can assign toxic dose to relatively large number of patients (Rogatko et al 2007)
  - **MTD at high dose**: tends to declare MTD at dose levels below the true MTD
  - Behavior depends on # of cohorts before MTD is reached – too many leads to underdosing, too few leads to overdosing (Chen et al 2009)
Model based Design Algorithm: CRM

Continual Reassessment Model (CRM)

\[ Pr\{DLT\} = \frac{1}{1 + \tau e^{-\theta_dose}} \]

where \( \tau \) is fixed and \( \theta \) is the estimated parameter which has beta distribution.
Bayesian Logistic Regression Model: a combination of clinical and statistical expertise

- Historical Data (prior info)
- Trial Data 0/3, 0/3, 1/3, ...
- Model based dose-DLT relationship

DLT rates $p_1, p_2, \ldots, p_{MTD}$ (uncertainty)

Clinical, PK, PD Expertise

Dose recommendations

Final Dose Escalation Decision
Bayesian Logistic Regression Model (BLRM) Overview & Implementation

- Bayesian Logistic Regression Model
  \[ \text{logit}(P_i) = \log(\alpha) + \beta \log\left(\frac{D_i}{D^*}\right) \]
  \[ (\log(\alpha), \log(\beta)) \sim BVN(\mu_1, \mu_2, \sigma_1, \sigma_2, \rho) \]

  where \( P_i \) is the DLT rate, \( D_i \) is the \( i \)th dose, \( D^* \) is the reference dose, allowing the interpretation of \( \alpha \) as the odds of a DLT at \( D^* \)

- Data: Enroll cohort of \( X \) pts
- Updated model: Posterior DLT rate for each dose level
- Escalate dose for next cohort of pts
  - Recommend dose with highest probability in targeted DLT rate interval.
  - \( \text{Pr(true DLT rate > 33% | data & prior) < cutoff} \) (Babb et al.1998)
  - Skip dose is not permitted in escalation.
- Trial Termination: Stop the trial either MTD claimed or run out of all the patients
BLRM Dose Recommendation

Interval Probabilities by Dose

0.333-1 [Overdosing]
0.166-0.333 [Targeted toxicity]
0-0.166 [Underdosing]

Scott Pain, PSI Therapeutic Area Meeting Oncology, Sep 2012, London
Single-agent BLRM with Covariates

- Extension of basic single-agent BLRM model

  - Add covariates \( X \). (eg. dose regimen, drug formulation or different subpopulations)

    \[
    \text{logit}(\pi(d, x_1, \ldots, x_k)) = \log(\alpha) + \beta \log\left(\frac{d}{d^*}\right) + \sum_{i=1}^{k} \gamma_i x_i \\
    (\log(\alpha), \log(\beta)) \sim BVN(\mu_1, \mu_2, \sigma_1, \sigma_2, \rho)
    \]

  - \( \gamma_i \): the log-odds ratio for a unit increase in covariate \( i \), two types of prior distributions for \( \gamma_i \) : normal / log-normal

- Examples:
  - Different drug formulation
  - Different schedules: daily vs. every other day
  - Combination of two drugs (small, fixed number of doses)
Single-agent BLRM with Covariates

Example

- Dose: (1, 2, 3.3, 5, 7, 9.3, 12.4, 16.5, 22)
- Skeleton DLT rate:
  - Form1: (0.0289, 0.0579, 0.0956, 0.1449, 0.2029, 0.2696, 0.3594, 0.4782, 0.6376)
  - Form2: (0.0006, 0.0025, 0.0071, 0.0168, 0.0343, 0.0638, 0.1231, 0.2509, 0.6511)
- Model:
  \[
  \text{logit}(\pi(d, x)) = \log(\alpha) + \beta \log\left(\frac{d}{d^*}\right) + \gamma x
  \]

<table>
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<th># of dlts</th>
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<td>4</td>
<td>form2</td>
<td>...</td>
<td>...</td>
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</table>

\[ \Pr(p_4 > 0.33 | \text{form1}) = 0.404 \]
\[ \Pr(p_4 > 0.33 | \text{form2}) = 0.262 \]
modified toxicity probability interval (mTPI) method

- Bayesian statistical framework and a beta/binomial hierarchic model to compute the posterior probabilities of three intervals that reflect the relative distance between the toxicity rate of each dose level to the target probability

\[ UPM_{(a,b)}(d) = \frac{Pr\{p_d \in (a,b) \mid data\}}{b-a} \]

- Underdosing interval: \((0, p_T - \epsilon_1)\)
- Proper dosing interval: \((p_T - \epsilon_1, p_T + \epsilon_2)\)
- Overdosing interval: \((p_T + \epsilon_2, 1)\)
modified toxicity probability interval (mTPI) method

- Benefit:
  - transparent, simple and costless to implement
  - compared to the 3+3 design, the mTPI design is safer in treating fewer patients at doses above the MTD
  - compared to the 3+3 design, yielding higher probabilities in identifying the true MTD.

![Graph showing dose-finding spreadsheet of the modified toxicity probability interval (mTPI) method. The spreadsheet is generated based on a beta/binomial model and precalculated before a trial starts. The letters in different colors are computed based on the decision rules under the mTPI method and represent different dosing actions. In addition to actions deviate to the dose (G), stay at the same dose (S), and escalate the dose (E), the table includes action unacceptable toxicity (U), which is defined as the execution of the dose-exclusion rule in mTPI. MTD, maximum-tolerated dose.]

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Combination Dose Finding: novel+novel combination

- **Rationale for combinations**
  - Paradigm change from single agent: no longer MTD but a range of dose pairs
  - Interaction: antagonism, independence or synergy

- **Non-model based methods, such as 3+3+3, have been proposed** (Thomas et al. 2011)
BLRM for Combination Dose-finding
Reparameterization with an explicit interaction term

- Real no interaction model: \( \pi_{12}^0 = \pi_1 + \pi_2 - \pi_1 \pi_2 \)
- Interaction model: \( \text{odds}(\pi_{12}) = \text{odds}(\pi_{12}^0) \exp(\eta) \)
- Marginal single-agent models:
  \[
  \log(\text{odds}(\pi_{1,i})) = \log(\alpha_1) + \beta_1 \log\left(\frac{d_{1,i}}{d_{1}^*}\right)
  \]
  \[
  \log(\text{odds}(\pi_{2,j})) = \log(\alpha_2) + \beta_2 \log\left(\frac{d_{2,j}}{d_{2}^*}\right)
  \]
- 5 parameters: \( \alpha_1, \beta_1, \alpha_2, \beta_2, \eta \) (\( \alpha_1, \beta_1, \alpha_2, \beta_2 > 0 \))
  - interaction term could be more complicated, eg. add covariates
- Priors for single agent models:
  \[
  (\log(\alpha_1), \log(\beta_1)) \sim BVN(\mu_{11}, \mu_{12}, \sigma_{11}, \sigma_{12}, \rho_{11})
  \]
  \[
  (\log(\alpha_2), \log(\beta_2)) \sim BVN(\mu_{21}, \mu_{22}, \sigma_{21}, \sigma_{22}, \rho_{22})
  \]
- Priors for interaction parameter: \( \eta \)
  - normal / log-normal / incorporate relevant information. Typically \( \eta > 0 \) but not necessary
Hypothetical scenario of a combination study

• Dose escalation trial of a novel-novel combination study
  – Goal: identify MTD and RP2D

• Design specifications
  – DLT evaluated in the first cycle (28 day cycle)
  – Exposure requirements:
    • At least 75% of planned dose for each compound
    • At least 50% of the planned combination dose
  – Target toxicity interval 0.16-0.35
  – Escalation with overdose control \( P(\text{true DLT rate} \geq 0.35) < \text{cutoff} \)
  – Cohort size 3-6
  – Only one compound can be escalated at a time due to regulatory concerns.
  – Maximum increment of 100% from current dose level
Example risk plot

- Black dot and line: median and 95% interval for P(DLT)
- Colored bar plot: risk plot.
  - Doses that have red bars are not eligible.
  - Two compounds cannot be escalated at the same time
  - No jump doses by 100%
  - Other doses are eligible

Graph from materials in FDA industry workshop 2015 short course, as an illustration
Combining Safety and Efficacy in Dose Finding Studies

- Bayesian dose-finding in two treatment cycles based on the joint utility of efficacy and toxicity (Lee et al 2014)
- TEAMS: toxicity and efficacy based dose insertion design with adaptive model selection for phase I/II dose escalation trials in oncology (Guo et al 2014)
- Bayesian adaptive dose finding based on efficacy and toxicity (Peter Thall 2012)

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<th>Toxicity Severity</th>
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</table>

Table 3: Joint utilities for a hypothetical clinical trial to treat solid tumors with ordinal efficacy and toxicity outcomes. The efficacy levels are PD = progressive disease, SD = stable disease, PR = partial response, CR = complete response.

Table from Peter Thall 2012
Thank you

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