Safe and Faster Way to Reach Maximum Tolerated Dose (MTD) in Phase I Oncology Trials

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Background and Motivation

One of the primary objectives of Phase I oncology trials is to identify the maximum tolerated dose (MTD). The drug exposure and toxicity events are the two most important components required for the characterization of the MTD. Many Phase I oncology dose-finding designs, including the 3+3 designs, continual reassessment method (CRM) with over-dose control (EWC), and interval-based designs (Bayesian optimal design: BOIN and Modified toxicity probability intervals: mTPI) have been developed under a set of distinct constraints and patients with a predefined observation period (e.g., the first cycle) for tracking the toxicity outcomes. The dose escalation decision would be made periodically, requiring all the patients within the cohort to be de-escalated if any dose-related events have been observed and followed up until completing the entire observational period. In addition, they utilize only the toxicity events information to identify MTD. The exposure to continual reassessment method (EACRM), which dynamically extends the conventional adaptive dose finding design such as CRM by incorporating dose limiting toxicity (DLT) events as time to event information from each subject. The EACRM process allowing for continuous enrollment, facilitates better decision making, and achieves accurate and safe estimations of the MTD.

EACRM Methodology

• Let 0 be the dose level range from D0 to Dmax and Assume a Gamma prior (α, β) model for T with dose as covariate and standard notations
• Let m indicate the data set (D = 1, DLT) and w be the case weight of each observation. Given a set of full data \( (T_i, D_i, \Delta_i, n_i, \omega_i) \), the likelihood function \( L(T, D, \omega) \) is \n\[
L(T, D, \omega) = \prod_{i=1}^{n} \left( f(T_i | \omega_i, \beta) \right)^{1-D_i} \times \left( 1 - f(T_i | \omega_i, \beta) \right)^{D_i}
\]
where \( \omega_i \) is a subset of \( T_i, D_i, \Delta_i, n_i, \omega_i \).
• To align the dose level to the next subject entering the trial, predictions of time to DLT made on all m possible dose levels \( T_j = 1, \ldots , m \) are \( D_{max} + 1 \) \( n \)\% quantile \( D_j \), \( j = 1, \ldots , m \).


d_j, 1 - \alpha \times n \% quantile (D_j)

\text{Duration of time to DLT for subjects who are still on the toxicity assessment period and corresponding weights:}
\text{• Specify approximate time responses (triangular) and weights (trapezoid), in the AFT model.}
\text{• Assume a Weibull distribution function of observed time \( t \), taking values in (0,1).}
\text{• Candidate for weight. For toxicity assessment period \( T_j \) and observed time \( t \), the conditional probability is given by (T_j > t) to weight}
\text{• Adjust for weights independent of the distribution of \( T_j \).}
\text{• A Weibull distribution function with constant hazards may be sufficient when subject is on a particular dose level over the entire toxicity assessment period.}
\text{\( T_j \sim \text{Exp}(\lambda) \) with mean time to DLT and a Gamma prior for \( \lambda \).}
\text{The posterior is \( \lambda \sim \text{Gamma}(\alpha + 1, \beta + 1) \).}
\text{This gives \( \lambda \sim \text{Gamma}(\lambda | \alpha, \beta) \).}
\text{Under an approximate relationship:}
\text{\( \lambda \sim \text{Gamma} \left( \frac{1}{3}, \frac{1}{3} \right) \).}
\text{And}
\text{\( \lambda \sim \text{Gamma} \left( \frac{1}{3}, \frac{1}{3} \right) \).}
\text{Fix \( \lambda \), then for \( t < \lambda \), the probability of completing toxicity assessment period without DLT (D_j):}
\text{\( \text{Pr}(T_j > t | D_j) \) is \( \frac{1}{3} \).}
\text{Also,}
\text{\( \text{Pr}(T_j > t | D_j) \) is \( \frac{1}{3} \).}

\text{Conclusions}

Table 5: Shallow toxicity curve with D7 as targeted MTD: Average number of subjects

<table>
<thead>
<tr>
<th>Dose Level</th>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects</td>
<td>1.1</td>
<td>1.5</td>
<td>1.9</td>
<td>2.4</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Figure 3: 20, 50, 70 percentiles of the distribution of trial size (top left), trial duration (top right), overall DLT rate (bottom left), MTD (bottom right) under steep true dose-toxicity curve with D7 as targeted MTD.

Figure 4: 20, 50, 70 percentiles of the distribution of trial size (top left), trial duration (top right), overall DLT rate (bottom left), MTD (bottom right) under shallow true dose-toxicity curve with D7 as targeted MTD.

Table 2: Very steep true dose-toxicity curve with D7 as targeted MTD: Percentage selection as MTD

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Table 4: Shallow true dose-toxicity curve with D7 as targeted MTD: Percentage selection as MTD

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Figure 1: EACRM Schematic

Notations

\( t \): time to DLT,
\( D_j \): observed time,
\( D_{max} \): maximum dose level.

Figure 2: Illustrating EACRM subject enrollment and dose assignment with D6 as targeted MTD.