S1 Formulae for operating characteristics

S1.1 Trial pathway
A trial pathway is defined as the sequence of dose levels each cohort receives, along with the number of patients and number of DLTs per cohort, and the probability of each trial pathway occurring. For any given design, with true DLT probabilities specified, the probability of a particular trial pathway occurring can be expressed as a product of binomial probabilities. For cohort \( k \in \{1, \ldots, K\} \), where \( K \) is the maximum number of cohorts one may enrol for a particular \( A + B \) design, let \( p_k \) be the probability of DLT for the dose level given to cohort \( k \), \( n_k \) be the number of patients in cohort \( k \) and \( x_k \) be the number of DLTs observed in cohort \( k \). Then the probability of trial pathway \( \kappa = \{(p_1, n_1, x_1), \ldots, (p_K, n_K, x_K)\} \) occurring is

\[
P(\kappa) = \prod_{k=1}^{K} \binom{n_k}{x_k} p_k^{x_k} (1 - p_k)^{n_k - x_k}.
\] (1)

Note that if for \( 1 < k \leq K \) we have \((n_k, x_k) = (0, 0)\), then \(\binom{n_k}{x_k} p_k^{x_k} (1 - p_k)^{n_k - x_k} = 1\).

S1.2 Sample size distribution
The expected sample size of a trial using an \( A + B \) design, denoted \( S \), is

\[
S = \sum_{i=1}^{P} n_i P(\kappa_i),
\] (2)

where \( P \) is the total number of possible trial pathways, \( n_i \) is the number of people experimented on in trial \( i = \{1, \ldots, P\} \) and \( P(\kappa_i) \) is the probability of trial pathway \( \kappa_i \) occurring. For a trial of \( J \) dose levels using an \( A + B \) design, the minimum possible sample size is \( A \) and the maximum sample size is \( J(A + B) \).

S1.3 MTD recommendation probabilities
The probability that dose level \( d_j \) \((j = \{1, \ldots, J\}) \) is chosen as the MTD is

\[
P(\text{MTD at } d_j) = \sum_{i=1}^{P} \mathbb{1}_{\{\text{MTD of } \kappa_i = d_j\}} P(\kappa_i),
\] (3)

where the indicator variable \( \mathbb{1}_{\{\text{MTD of } \kappa_i = d_j\}} \) equals 1 if the MTD is \( d_j \) for trial pathway \( \kappa_i \) and 0 otherwise.
S1.4 Experimentation probabilities

The probability of a patient being given dose $d_j$, denoted $P(\text{Patient given } d_j)$, is

$$P(\text{Patient given } d_j) = \sum_{i=1}^{P} P(\text{Patient given } d_j | \kappa_i)P(\kappa_i).$$

(4)

The results from the AplusB application are different to those obtained from the pmtd program of Lin and Shih [1]. This is because for the pmtd program,

$$P(\text{Patient given } d_j) \approx \frac{E(X_j)}{\sum_{j=1}^{J} E(X_j)} = \frac{\sum_{i=1}^{P} \sum_{j=1}^{J} E(X_j | \text{MTD} = d_j)P(\text{MTD} = d_j)}{\sum_{j=1}^{J} \sum_{i=1}^{P} E(X_j | \text{MTD} = d_j)P(\text{MTD} = d_j)},$$

(5)

where $X_j$ is the number of patients receiving dose $d_j$. This is an approximation that assumes each trial pathway is equally likely to occur. Let $n_i$ be the sample size of trial pathway $i$ and $n_{ij}$ be the number of patients in trial pathway $i$ that receive dose level $d_j$, so $\sum_{j=1}^{J} n_{ij} = n_i$. We see equation 4 differs from equation 5 since

$$\frac{\sum_{j=1}^{J} E(X_j)}{\sum_{j=1}^{J} E(X_j)} = \frac{\sum_{i=1}^{P} \frac{n_{ij}}{n_i}P(\kappa_i)}{\sum_{i=1}^{P} \frac{n_{ij}}{n_i}P(\kappa_i)} = \sum_{i=1}^{P} P(\text{Patient given } d_j | \kappa_i)P(\kappa_i).$$

(6)

S1.5 Expected Toxicity Level (ETL) and Expected Overall Toxicity Rate (EOTR)

The ETL, the expected probability of DLT at the MTD, is

$$ETL = P(\text{DLT at MTD } | d_1 \leq \text{MTD} \leq d_j)$$

$$= \sum_{j=1}^{J} P(\text{DLT at MTD } | \text{MTD} = d_j)P(\text{MTD} = d_j | d_1 \leq \text{MTD} \leq d_j)$$

$$= \frac{\sum_{j=1}^{J} P(\text{DLT at } d_j)P(\text{MTD} = d_j)}{\sum_{i=1}^{P} P(\text{MTD} = d_i)}. $$

(7)

The inclusion of the possibility that the MTD is equal to the maximum planned dose $d_J$ was excluded by Lin and Shih [1] and Chen et al. [2]. They state that if dose-escalation is still indicated at the largest dose under investigation, then the MTD is not determined [1]. This is misleading, since $d_J$ can be recommended as
Table S1.1: Possible outcomes observed at the selected MTD from an A + B design, with and without de-escalation.

| De-escalation permitted | Data at MTD                          | Conditions                |
|-------------------------|--------------------------------------|---------------------------|
| Yes                     | $\delta_1$ DLTs out of $A + B$ patients $0 \leq \delta_1 \leq E$ |                           |
| No                      | $\delta_2$ DLTs out of $A$ patients $0 \leq \delta_2 < C$       |                           |
|                         | $\delta_3$ DLTs out of $A + B$ patients $C \leq \delta_3 \leq E$ |                           |

The MTD in practice; therefore, the formula above is used in $AplusB$. The Expected Overall Toxicity Rate (EOTR), is defined to be the expected number of DLTs divided by the expected number of patients, i.e.

$$EOTR = \frac{\sum_{j=1}^{J} P(DLT \text{ at } d_j \mid X_j)}{\sum_{j=1}^{J} E(X_j)}.$$  \hfill (8)

S1.6 Data at trial end and confidence intervals

At the end of a trial that follows an $A + B$ design, we may calculate $100(1 - \alpha)\%$ confidence intervals for the estimate of the probability of DLT at the identified MTD. The data at the MTD determined at the end of the trial will be dependent on whether dose-escalation is permitted or not (Table S1.1). Clopper-Pearson confidence intervals [3] and Wilson score confidence intervals [4] are provided; exact confidence intervals are conservative intervals derived directly from the Binomial distribution, whereas Wilson score intervals provide better coverage and may be more suitable for constructing intervals based on small samples [5-7].

S1.7 Tipping Point

The tipping point is the true DLT probability a dose must have at which the chance of escalating to the next dose level is equal to the chance de-escalating or stopping the trial. For a general $A + B$ design, the probability of escalating from $d_j$ to $d_{j+1}$ is
\[
\mathbb{P}\text{(Escalate from } d_j \text{ to } d_{j+1}) = \mathbb{P}(Y_j^A < C) + \sum_{v=C}^{D} \mathbb{P}(Y_j^A = v)\mathbb{P}(Y_j^B \leq E - v) \\
= \sum_{0 \leq u < C} \binom{A}{u} p_j^u (1 - p_j)^{A-u} + \sum_{v=C}^{D} \binom{A}{v} p_j^v (1 - p_j)^{A-v} \sum_{0 \leq w \leq E-v} \binom{B}{w} p_j^w (1 - p_j)^{B-w} 
\]

(9)

where \(Y_j^A\) and \(Y_j^B\) are the number of DLTs observed after dosing \(A\) and \(B\) patients at dose \(d_j\) respectively. To find the tipping point, we set \(\mathbb{P}\text{(Escalate from } d_j \text{ to } d_{j+1}) = 0.50\) and solve for \(p_j\) using numerical methods; the real solution to this equation that lies between 0 and 1 is the tipping point.

**References**

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