Dose Escalation Guided By Graded Toxicities

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SUMMARY

In phase 1 and phase 2 dose-finding studies, the endpoints of interest are typically the presence or absence of toxicity and/or the presence or absence of some indication of therapeutic effect. In numerical terms, these outcomes are represented as simple binary variables. Most protocols, however, will stipulate that intermediary degrees, or grades, of toxicity be recorded. Our purpose here is to consider how such intermediary information may be used to obtain a more accurate estimation of the maximum tolerated dose, both at the end of the study and for those patients being treated during the course of the study. For now, we limit our attention to phase 1 studies alone, in which toxicity is the focus of our interest. Working with two-stage continual reassessment method (CRM) designs, which are briefly described in the following section, we can observe that considerable use can be made of graded information both during the initial escalation period as well as during the second stage of a two-stage design. Here, we appeal to simple working models.

Key words: Clinical trial; Continual Reassessment Method; Dose escalation; Dose finding studies; Maximum Tolerated Dose; Phase 1 trials; Toxicity grades.
1 Two-stage CRM designs

The purpose of the design is to identify a level, from among the $k$ dose levels available $d_1, \ldots, d_k$, such that the probability of toxicity at that level is as close as possible to some value $\theta$. The value $\theta$ is chosen by the investigator such that he or she considers probabilities of toxicity higher than $\theta$ to be unacceptably high, whereas those lower than $\theta$ are unacceptably low in that they indicate, indirectly, the likelihood of too weak an antitumor effect. Patients enter the study sequentially. The working dose-toxicity curve, which is taken from the CRM class (described below), is refitted after each inclusion. The curve is then inverted to identify which available level has an associated estimated probability as close as we can get to the targeted acceptable toxicity level. The next patient is then treated at this level. The cycle is continued until a fixed number of subjects has been treated or until we apply some stopping rule (1,2). The $d_i$, which is often multidimensional, describes the actual doses or combinations of doses being used. We assume monotonicity, and we take monotonicity to mean that the dose levels are equally well identified by their integer subscripts $i$ ($i = 1, \ldots, k$), which are ordered whereby the probability of toxicity at level $i$ is greater than that at level $i'$ whenever $i$ is greater than $i'$. The monotonicity requirement or the assumption that we can so order our available dose levels is important.

The dose for the $j^{th}$ entered patient, $X_j$ can be viewed as random taking values $x_j$, most often discrete in which case $x_j \in \{d_1, \ldots, d_k\}$ but possibly continuous where $X_j = x$; $x \in \mathbb{R}^+$. In light of the remarks of the previous two paragraphs we can, if desired, entirely suppress the notion of dose and retain only information that pertains to dose level. This information is all we need, and we may prefer to write $x_j \in \{1, \ldots, k\}$. Let $Y_j$ be a binary random variable $(0, 1)$ where 1 denotes severe toxic response for the $j^{th}$ entered patient ($j = 1, \ldots, n$). We model $R(x_j)$, which is the true probability of toxic response at $X_j = x_j$; $x_j \in \{d_1, \ldots, d_k\}$ or $x_j \in \{1, \ldots, k\}$ via

$$R(x_j) = \Pr(Y_j = 1 \mid X_j = x_j) = E(Y_j \mid x_j) = \psi(x_j, a)$$

for some one-parameter working model $\psi(x_j, a)$. For given fixed $x$, we require that $\psi(x, a)$ be strictly monotonic in $a$. For fixed $a$, we require that $\psi(x, a)$ be monotonic increasing in $x$ or, in the usual case of discrete dose levels $d_i$, $i = 1, \ldots, k$, that $\psi(d_i, a) > \psi(d_m, a)$ whenever $i > m$. The true probability of toxicity at $x$ (i.e., whatever treatment combination
has been coded by $x$) is given by $R(x)$, and we require that, for the specific doses under study $(d_1, \ldots, d_k)$ values of $a$, say $a_1, \ldots, a_k$ exist such that $\psi(d_i, a_i) = R(d_i)$, $(i = 1, \ldots, k)$. In other words, our one-parameter working model has to be rich enough to model the true probability of toxicity at any given level. We call it a working model because we do not anticipate a single value of $a$ to work precisely at every level, that is, we do not anticipate $a_1 = a_2 = \cdots = a_k = a$. Many choices are possible. Excellent results have been obtained with the simple choice:

$$\psi(d_i, a) = a_i^a, \quad (i = 1, \ldots, k)$$

where $0 < \alpha_1 < \cdots < \alpha_k < 1$ and $0 < a < \infty$. It can be sometimes advantageous to make use of the re-parameterized model $\psi(d_i, a) = \alpha_i^{\exp(a)}$ so that no constraints are placed on the parameter $a$. Of course, likelihood estimates are unchanged. Once a model has been chosen and we have data in the form of the set $\Omega_j = \{y_1, x_1, \ldots, y_j, x_j\}$, the outcomes of the first $j$ experiments obtain estimates $\hat{R}(d_i)$, $(i = 1, \ldots, k)$ of the true unknown probabilities $R(d_i)$, $(i = 1, \ldots, k)$ at the $k$ dose levels. The target dose level is that level having associated with it a probability of toxicity as close as we can get to $\theta$. The dose or dose level $x_j$ assigned to the $j^{th}$ included patient is such that

$$|R(x_j) - \theta| < |R(d_i) - \theta|, \quad (i = 1, \ldots, k; \; x_j \neq d_i).$$

Thus $x_j$ is the closest level to the target level in the above precise sense. Other choices of closeness could be made by incorporating cost or other considerations. We could also weight the distance, for example multiply $|R(x_j) - \theta|$ by some constant greater than 1 when $\hat{R}(x_j) > \theta$. This method would favor conservatism; such a design tends to experiment more often below the target than a design without weights. Similar ideas have been pursued by Babb et al. (3). After the inclusion of the first $j$ patients, the log-likelihood can be written as:

$$\mathcal{L}_j(a) = \sum_{\ell=1}^j y_\ell \log \psi(x_\ell, a) + \sum_{\ell=1}^j (1 - y_\ell) \log(1 - \psi(x_\ell, a))$$

and is maximized at $a = \hat{a}_j$. Maximization of $\mathcal{L}_j(a)$ can easily be achieved with a Newton Rapson algorithm or by visual inspection using some software package such as Microsoft Excel (Microsoft Corporation, Redmond, WA). Once we have calculated $\hat{a}_j$, we can next obtain an estimate of the probability of toxicity at each dose level $d_i$ via:

$$\hat{R}(x_j) = \psi(d_i, \hat{a}_j), \quad (i = 1, \ldots, k)$$
We would not anticipate these estimates to be consistent at all dose levels, which would usually require a richer model than what we work with. However, under broad conditions, we will (4) obtain consistency at the recommended maximum tolerated dose (MTD). Based on this formula, the dose to be given to the \( (j + 1) \)th patient, \( x_{j+1} \) is determined. The experiment is considered as not being fully underway until we have some heterogeneity in the responses. These examples could develop in a variety of different ways, which include use of the standard Up and Down approach, use of an initial Bayesian CRM as outlined below, or use of a design believed to be more appropriate by the investigator. Once we have achieved heterogeneity, the model kicks in and we continue as prescribed above iterating between estimation and dose allocation. The design is then split into two stages: an initial exploratory escalation followed by a more refined homing in on the target.

Storer (5) was the first to propose two-stage designs in the context of the classic Up and Down schemes. His idea was to enable more rapid escalation in the early part of the trial where we may be far from a level at which treatment activity could be anticipated. Moller (6) was the first to use the idea in the context of CRM designs. Her idea was to allow the first stage to be based on some variant of the usual Up and Down procedures. In the context of sequential likelihood estimation, the necessity of an initial stage was pointed out by OQuigley and Shen (7), because the likelihood equation fails to have a solution on the interior of the parameter space unless some heterogeneity in the responses has been observed. Their suggestion was to work with any initial scheme, such as Bayesian CRM or Up and Down. For any reasonable scheme, the operating characteristics seem relatively insensitive to this choice. However, something very natural and desirable is observed in two stage designs, and currently they could be taken as the designs of choice. The reason is the following: Early behavior of the method, in the absence of heterogeneity (i.e., lack of toxic response), seems to be rather arbitrary. A decision to escalate after inclusion of three patients who tolerated some level, or after a single patient tolerated a level or according to some Bayesian prior, however constructed, is translating directly (although less directly for the Bayesian prescription) the simple desire to try a higher dose because we’ve encountered no toxicity thus far.

We can make use of information on toxicity grade in either one of these two stages. In the first stage, no model is being used, and we use graded toxicities simply to escalate more
rapidly when it seems we are far below any level likely to result in dose-limiting toxicities. Once we begin to observe some intermediary toxicity, then we slow the escalation down. The ideas are straightforward and appeal mostly to common sense arguments. Nonetheless, it can be observed that use of graded toxicity information in the first stage alone can make an important contribution to increased efficiency. Use of graded toxicity information in the second stage requires an additional model to that already used to demonstrate the rate of toxicities. We consider these two different situations in the following two sections.

2 Using graded information in the first stage

Consider the following example of a two-stage design that has been used in practice. Many dose levels were used, and the first included patient was treated at a low level. As long as we observe very low-grade toxicities, then we escalate quickly, which includes only a single patient at each level. As soon as we encounter more serious toxicities, escalation is slowed down. Ultimately, we encounter dose-limiting toxicities at which time the second stage, based on fitting a CRM model, comes fully into play. This method is done by integrating this information and that obtained on all the earlier non-dose-limiting toxicities to estimate the most appropriate dose level.

We can use information on low-grade toxicities in the first stage of a two-stage design to allow rapid initial escalation, because it may be the case that we be far below the target level. Specifically, we define a grade severity variable \( S(i) \) to be the average toxicity severity observed at dose level \( i \) (i.e., the sum of the severities at that level divided by the number of patients treated at that level). The rule is to escalate providing \( S(i) \) is less than 2. Furthermore, once we have included three patients at some level, escalation to higher levels only occurs if each cohort of three patients does not experience dose-limiting toxicity. This scheme means that, in practice, as long as we observe only toxicities of severities coded 0 or 1, we escalate. Only a single patient is necessary (for whom little or no evidence of any side effects is observed) to decide to escalate. The first severity coded 2 necessitates another inclusion at this same level and, anything other than a 0 severity for this inclusion would require yet another inclusion and a non-dose-limiting toxicity before being able to escalate. This design also has the advantage that, should we be slowed down by a severe (severity 3), albeit non-dose-limiting toxicity, we retain the capability of picking up speed (in escalation)
should subsequent toxicities be of low degree (0 or 1). This method can be helpful in avoiding being handicapped by an outlier or an unanticipated and possibly not drug-related toxicity. Many variants on this particular escalation scheme and use of graded severity are available. It is for the investigator to decide which scheme is suitable for the given circumstance and which scheme seems to provide the best balance between rapid escalation and caution in not moving so quickly as to overshoot the region where we will begin to encounter dose-limiting toxicities.

Once a dose-limiting toxicity has been encountered, this phase of the study (the initial escalation scheme) ends, and we proceed to the second stage based on a CRM model-based recommendation. Although the initial phase is closed, the information obtained on both dose-limiting and non-dose-limiting toxicities is used in the second stage.

3 Using graded toxicities in the second stage

Although we refer to dose-limiting toxicities as a binary (0,1) variable, most studies record information on the degree of toxicity, from 0, complete absence of side effects, to 4, life-threatening toxicity. The natural reaction for a statistician is to consider that the response variable, which is toxicity, has been simplified when going from five levels to two and that it may help to employ models accommodating multilevel responses.

In fact, we do not believe that progress is to be made using these methods. The issue is not that of modeling a response (toxicity) at 5 levels but of controlling for dose-limiting toxicity, mostly grade 4 but possibly also certain kinds of grade 3. Lower grades are helpful in that their occurrence indicates that we are approaching a zone in which the probability of encountering a dose-limiting toxicity is becoming large enough to be of concern. This idea is used implicitly in the two-stage designs described in the section entitled, Using graded information in the first stage. Hopefully, if we proceed more formally and extract yet more information from the observations, then we need models to relate the occurrence of dose-limiting toxicities to the occurrence of lower-grade toxicities. By modeling the ratio of the probabilities of the different types of toxicity, we can make striking gains in efficiency because the more frequently observed lower grade toxicities carry a great deal of information on the potential occurrence of dose-limiting toxicities.

Such a situation would also allow gains in safety because, at least hypothetically, it would
Table 1: Toxicity “Grades” (Severities) for Trial

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No toxicity</td>
</tr>
<tr>
<td>1</td>
<td>Mild toxicity (non-dose-limiting)</td>
</tr>
<tr>
<td>2</td>
<td>Non-mild toxicity (non-dose-limiting)</td>
</tr>
<tr>
<td>3</td>
<td>Severe toxicity (non-dose-limiting)</td>
</tr>
<tr>
<td>4</td>
<td>Dose-limiting toxicity</td>
</tr>
</tbody>
</table>

be possible to predict at some level the rate of occurrence of dose-limiting toxicities without necessarily having observed very many, the prediction leaning largely on the model. At the opposite end of the model/hypothesis spectrum, we might decide we know nothing about the relative rates of occurrence of the different toxicity types and simply allow the accumulating observations to provide the necessary estimates. In this case, it turns out that we neither lose nor gain efficiency, and the method behaves identically to one in which the only information we obtain is whether the toxicity is dose limiting. These two situations suggest a middle road might exist, using a Bayesian prescription, in which very careful modeling can lead to efficiency improvements, if only moderate, without making strong assumptions.

To make this model more precise, let us consider the case of three toxicity levels, the highest being dose limiting. Let $Y_j$ denote the toxic response for subject $j$, $(j = 1, \ldots, n)$. The variable $Y_j$ can assume three levels: 1, 2, and 3. The goal of the trial is to identify a level of dose whose probability of severe toxicity is closest to a given percentile of the dose toxicity curve. Supposing, for patient $j$, that $x_j = d_i$, then a working model for the CRM could be:

$$
\Pr(Y_j = 3) = \psi_1(x_j, a) = \alpha_i^{\exp(a)}
$$

$$
\Pr(Y_j = 2 \text{ or } Y_j = 3) = \psi_2(x_j, a, b) = \alpha_i^{\exp(a+b)}
$$

from which $\Pr(Y_j = 1) = 1 - \psi_2(x_j, a, b)$ and $\Pr(Y_j = 2) = \alpha_i^{\exp(a+b)} - \alpha_i^{\exp(a)}$. The contributions to the likelihood are: $1 - \psi_2(x_j, a, b)$ when $Y_j = 1$, $\psi_1(x_j, a)$ when $Y_j = 3$ and $\psi_2(x_j, a, b) - \psi_1(x_j, a)$ when $Y_j = 2$. With no prior information, and being able to maximize the likelihood, we obtain almost indistinguishable results to those obtained with the more usual one-parameter CRM, which is caused by near-parameter orthogonality. Therefore, no efficiency gain occurs, although there is the advantage of learning about the relationship be
between the different toxicity types. However, based on previous studies, we often have a very precise idea concerning the relative rates between certain toxicity grades. We can imagine that this relationship can be estimated with good precision. Suppose that the parameter $b$ is known precisely. The model need not be correctly specified, although $b$ should maintain interpretation outside the model, for instance some simple function of the ratio of grade 3 to grade 2 toxicities. Efficiency gains can then be substantial. Table 2 provides a simple illustration of the order of magnitude of the gains we might anticipate when we are targeting a value of $\theta$ around 0.25. The rate of lower grade toxicities is known to be twice this rate. A Bayesian framework would allow us to make weaker assumptions on the parameter $b$ so that any errors in assumptions can then be overwritten by the data. More work is needed on this subject, but the early results are very promising.

### 4 References


6. S. Moller, An extension of the continual reassessment method using a preliminary up and down design in a dose finding study in cancer patients in order to investigate a greater number of dose levels. Stats. Med. 1995; 14: 911922.


5 Further reading


