What Were They Thinking? Pharmacologic priors implicit in a choice of 3+3 dose-escalation design

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Abstract

If explicit, formal consideration of clinical pharmacology at all informs the design and conduct of modern oncology dose-finding trials, the designs themselves hardly attest to this. Yet in conducting a trial, investigators affirm that they hold reasonable expectations of participant safety—expectations that necessarily depend on beliefs about how certain pharmacologic parameters are distributed in the study population. Thus, these beliefs are implicit in a trial’s presumed conformance to a community standard of safety, and may therefore to some extent be reverse-engineered from trial designs. For one popular form of dose-escalation trial design, I demonstrate here how this may be done.

Background

The safety characteristics of a dose-finding study are a function jointly of how the study is designed, and of how certain pharmacologic parameters are distributed in the study population. Given an explicit set of priors over those distributions, one can carry out simulations to exhibit the safety characteristics of any proposed design:

(priors, design) \xrightarrow{simulation} \text{safety}

We may express this conditionally by saying that given any trial design, our safety expectations are a function $F_{\text{design}}$ of our priors:

$$F_{\text{design}} \leftarrow\text{safety}.$$ \hspace{1cm} (1)

In oncology dose finding, however, population heterogeneity is rarely acknowledged, let alone modeled explicitly through Bayesian priors. Nevertheless, restrictions on such priors are implicit in whatever bounds we can identify on acceptable trial safety characteristics. Thus, community standards which limit the numbers of severe or fatal toxicities acceptable in a given clinical-trial context provide information about what pharmacologic priors one could reasonably entertain while proposing the trial design. In a sense, recovering this information amounts to solving an inverse problem,

$$F_{\text{design}}^{-1} \leftarrow\text{safety} \text{ or } F_{\text{design}}^{-1}(\text{safety})$$ \hspace{1cm} (2)

corresponding to the ‘forward problem’ of Eq. (1).

Sources of community standards

Explicit discussion of standards for early-phase oncology trial safety are as rare as explicit discussions of pharmacologic priors. Thus Eq. (2) appears vulnerable to a symmetry argument, to the effect that it merely presents a mirror-image of the very same difficulties posed by Eq. (1). Both Equations derive one set of priors from another; they differ only in whether objective pharmacologic priors or subjective safety priors are taken as the starting point. Since neither set of priors receives any amount of explicit discussion, both starting points would seem to be equally inaccessible.

This criticism is valid inasmuch as it reveals our problem to be one of prior elicitation. But the supposed symmetry between Eq. (1) and Eq. (2) is broken—on purely practical grounds—by the primacy of safety in drug development. While it remains (however remarkably) entirely possible to evade explicit prior elicitation around pharmacologic parameters, it is politically infeasible to brush aside questions of safety once they have been posed.

We see a clear manifestation of this principle in the FDA’s reflexive responsiveness to fatalities in early-phase oncology trials. FDA guidance on phase 1 dose escalation offers only indefinite suggestions as to how preclinical pharmacology may shape trial design. Yet once the occurrence of a fatal toxicity starkly ‘poses the question’, FDA acts swiftly to place a clinical hold—with provisions existing for clinical hold orders to be “made by telephone or other means of rapid communication” [FDA CDER, 2018].

Standards of safety vary with clinical context—disease severity, unmet need, competitive environment [Muller and Milton, 2012]. Accordingly, in this analysis we will treat safety as a free parameter and will focus on elaborating the function $F_{\text{design}}^{-1}$. For the sake of definiteness, we will operationalize safety as the (probabilistic) expectation of the number of fatal toxicities in a trial.

Seeking efficiencies

In order to render the inverse problem Eq. (2) feasible, we first seek efficient means to carry out the forward simulation Eq. (1). To this end, we exploit the enumerability of the possible paths that rule-based (‘algorithmic’) dose-finding designs may follow, which enables exact computations exempt from Monte Carlo error. The Prolog program below implements a definite clause grammar (DCG) that generates all such paths, for the common variant of the 3 + 3 design in which 6 patients must have been treated at a dose level before it may be declared ‘the MTD’ [Korn et al., 1994, Skolnik et al., 2008].

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1 Some reasons for this state of affairs may be gleaned from Sheiner [1991].

2 Indeed, when considering ordinal toxicities, the dose-finding literature typically excludes fatal toxicities from the universe of possible outcomes [Bikulce and Thall, 2004, Van Meter et al., 2012].

3 The core aim of this paper is to pose this question effectively—in objective terms which cannot be ignored.

4 See, for example, Section 3.1 of FDA CDER [2013].

5 A metric of this kind readily generalizes to expectations of less severe events as well, such as grade 4 toxicities.

6 I would like to acknowledge Sabanés Bové et al. [2019] for impressing this point upon me, specifically in the opening remarks to Section 10 of the 12 June 2019 introductory vignette to ccrxPack.
\[
\text{tox}(T) := T \text{ in } 0, . . ., \text{indomain}(T).
\]

\[
\text{esc}(\text{Hi}, \text{Lo}, \ldots, \text{Hi}) \rightarrow [\text{Hi} \times T], \{\text{tox}(T)\},
\begin{cases}
    \{T \#< 1\}, \text{[mtd_notfound(Hi)]} & ; \{T \#>= 2\}, \text{des(Hi, Lo)} \}.
\end{cases}
\]

\[
\text{esc}(\text{D}, \text{Lo}, \ldots, \text{Hi}) \rightarrow \{D \#< \text{Hi}, D1 \#= D + 1\},
\begin{cases}
    \{D1 \#< T\}, \{\text{tox}(T)\},
    \{T \#< 0\}, \text{esc(D1, Lo, Hi)} & ; \{T \#= 1\}, \text{des(D1, Lo)} \}.
\end{cases}
\]

\[
\text{sta}(D, \ldots, D) \rightarrow [D - 0], \text{[mtd_notfound(D)]}.
\]

\[
\text{sta}(\text{D}, \text{Lo}, \ldots, \text{Hi}) \rightarrow \{D \#< \text{Hi}, \text{D in Lo, Lo, Hi}\},
\begin{cases}
    \text{esc(D, Lo, Hi)} \}.
\end{cases}
\]

\[
\text{des}(\text{D}, \text{Lo}) \rightarrow \{D1 \#= D - 1\},
\begin{cases}
    \{D1 \#= Lo\}, \text{[declare_mtd(Lo)]} & ; \{D1 \#< Lo\}, \{D1 : T\}, \{\text{tox}(T)\},
    \{T \#< 1\}, \text{[declare_mtd(D1)]} & ; \{T \#>= 2\}, \text{des(D1, Lo)} \}.
\end{cases}
\]

Efficient simulation of 3+3. In 3+3 designs, each 3-patient cohort has 1 of 4 possible outcomes, according to the count of dose-limiting toxicities (DLTs): 0/3, 1/3, 2/3, or 3/3. In the course of a 3+3 trial, each dose may enroll 0, 1, or 2 cohorts. Thus, it is possible to represent the events on path \(j\) by a \(2 \times D\) matrix \(T_{j,d}\) with rows indexed by cohort \(c \in \{1, 2\}\) and columns by dose level \(d \in \{1, \ldots, D\}\), and with elements drawn from \{0, 1, 2, 3, −\}. For example, the matrix

\[
\begin{pmatrix}
0 & 1 & 2 & - & - \\
- & - & - & - & -
\end{pmatrix}
\]

represents a path in a 4-dose 3+3 trial, where the following events occur:

1. Initial cohort at \(d = 1\) results 0/3
2. Escalation to \(d = 2\) results 1/3
3. Additional cohort at \(d = 2\) results 0/3 for net 1/6 at this dose
4. Escalation to \(d = 3\) results 2/3; MTD declared at \(d = 1\).

The matrices \(T_j\) support concise expression and efficient, exact computation of trial outcomes and their probabilities. For example, the \(J\)-vector \(\{\pi_j\}\) of path probabilities may be written\(^7\)

\[
\begin{align*}
p_d &= P(\text{MTD}_d < X_d) \\
q_d &= 1 - p_d \\
\pi_j &= \prod_{c,d} \left( \frac{1}{3} \right)^{\text{tox}_c(T_{j,d})} \frac{1}{3} \cdot \frac{1}{3} \cdot \frac{1}{3} \cdot \frac{1}{3}.
\end{align*}
\]

where \(p_d\) is the \(D\)-vector of DLT probabilities at the prespecified doses \((X_d)\), and \(q_d\) \(\equiv (1 - p_d)\) is its complement. Felicitously, taking logs in Eq. (3) yields the matrix equation:

\[
\begin{align*}
\log \pi &= \sum_{c,d} \log \left( \frac{1}{3} \right)^{\text{tox}_c(T_{j,d})} + \sum_{c} \log \left( \frac{1}{3} - T_{c,d} \right), \left[\log q_d\right]
\end{align*}
\]

\[
\begin{align*}
&= b_d + U_d \left[\log p_d, \log q_d\right],
\end{align*}
\]

Observe that the \(J \times 2D\) blocked matrix \(U_d\) and \(J\)-vector \(b_d\) thus defined are characteristic constants of the 3+3 design for a given value of \(D\), and that the distribution \(P\) of MTD, in the population enters Eq. (4) only through the column vector \([\log p_d, \log q_d]\). As shown in Table 1, the number of possible paths \(J_d\) for this standard 3+3 design grows almost exponentially with the number of dose levels \(D\). Nevertheless, for trial sizes of practical interest, say \(D \leq 8\), the matrices involved remain trivially small in terms of computer memory and computation time.

Table 1. Number of possible dose-escalation paths in the standard 3+3 design, as a function of the number \(J\) of prespecified doses.

| \(D\) | \(J\) | \(\log(J)\) | \(\Delta \log(J)\) |
|---|---|---|---|
| 1 | 10 | 2.30 | – |
| 2 | 46 | 3.83 | 1.53 |
| 3 | 154 | 5.04 | 1.21 |
| 4 | 442 | 6.09 | 1.05 |
| 5 | 1162 | 7.06 | 0.97 |
| 6 | 2890 | 7.97 | 0.91 |
| 7 | 6922 | 8.84 | 0.87 |
| 8 | 16138 | 9.69 | 0.85 |
| 9 | 36874 | 10.52 | 0.83 |
| 10 | 82954 | 11.33 | 0.81 |

\(\text{Ordinalization of toxicity.}\) Following Norris \([2020]\), we posit a therapeutic index \(e^x\) establishing a fixed ratio between dose thresholds \{MTD\}_\(g\) for toxicities of grades 3–5,\(^8\)

\[
\text{MTD}_{g} = e^{x(g - 3)} \cdot \text{MTD}_{1}, \quad g \in \{3, 4, 5\},
\]

so that in particular the threshold \(\text{MTD}_{3}\) for fatal toxicity is\(^9\)

\[
\text{MTD}_{3} = e^{2x} \cdot \text{MTD}_{1}.
\]

Consequently, of all DLTs (toxicities of grade \(\geq 3\)) occurring at dose \(X_d\), the fatal (grade 5) fraction \(f_d\) is

\[
f_d = \frac{P(e^{2x} \text{MTD} < X_d)}{P(\text{MTD} < X_d)}.
\]

The left half of \(U_{d}\) is a \((J \times D)\) matrix \(U_{d} = (Y_{j,d}) = (\Sigma T_{j,d})\) which is itself of interest, since its \(j\)th row tells how many DLTs occur at each dose on the \(j\)th path of the trial. In terms of \(Y\), we may write the expected number of fatal toxicities as:

\[
\pi^\top Y f.
\]

\(^7\)Products or sums over c or pairs (c,d) are understood to be taken over the non-empty cohorts which are thus indexed. In R, this corresponds to treating the "-" entries as NA values, and employing the convention na.rm = TRUE in aggregate operations.

\(^8\)In Norris \([2020]\), this ratio was called \(\kappa_d\).

\(^9\)No assumption about MTD\(_1\) is required strictly for purposes of analyzing fatal toxicities. The geometric sequence of Eq. (5) should therefore be appreciated as a heuristic to assist prior elicitation about the quantity \(e^x\) in Eq. (6), in terms of what may prove for oncologists a more intuitive linkage \(e^x = \sqrt[3]{\kappa}\) connecting adjacent toxicity grades.
Fig. 1. Expected fatal toxicities for a 3+3 dose-escalation trial with 4 (top) or 6 (bottom) pre-specified doses, under a range of scenarios for log-therapeutic index $\kappa$ and for the parameters $(\mu, \sigma)$ governing the log-normal distribution of $\text{MTD}_i$ in the population: $\log \text{MTD}_i \sim \mathcal{N}(\mu, \sigma)$. The pre-specified doses are assumed to be in a geometric sequence with ratio $e^\delta$. The therapeutic index $e^\kappa$ is the dose multiplier that worsens an individual’s experienced toxicity by 1 grade level.
Solving the inverse problem

We will take a graphical approach to solving the inverse problem Eq. (2), plotting a graph of $F_{\text{design}}$ in such a way that crucial aspects of its inverse become visually accessible.

Treating the dose domain logarithmically. A resolutely logarithmic treatment of the dose space enables a substantial reduction in dimensionality for our problem. Accordingly, we suppose that $\text{MTD}_i$ is log-normally distributed:

$$\log \text{MTD}_i \sim \mathcal{N}(\mu, \sigma),$$

and we require that our design’s prespecified doses $(X_d)$ be spaced logarithmically at fixed intervals of $\delta$:

$$X_d = e^{\delta X_{d-1}}; \quad \log X_d = \delta + \log X_{d-1}.$$  

The safety function $F_{\text{design}}$ may be regarded as a function of pharmacologic parameters $(\mu, \sigma, \kappa)$:

$$F_{D, \delta}(\mu, \sigma, \kappa),$$

parametrized by the design $(D, \delta)$.

Natural scales for $\mu$, $\sigma$ and $\kappa$. Without loss of generality, $\mu$ can be measured against the logarithmic scale generated by dose indexes: $\mu' = 1, 2, ..., D$. On this understanding, $F$ turns out to be invariant to transformations of $(\delta, \sigma, \kappa)$ that preserve the ratios $\sigma' = \sigma / \delta$ and $\kappa' = \kappa / \delta$. This enables the design parameter $\delta$ to be factored out as a natural scale for measuring $\sigma$ and $\kappa$:

$$F_{D, \delta}(\mu, \sigma, \kappa) = F_{D}(\mu', \sigma', \kappa').$$

The safety function $F_{D}$ then becomes a scalar field in $\mathbb{R}^2$, amenable to a treatment as in Figure 1, where contours in the $\mu' - \sigma'$ plane are plotted for $\kappa' \in \{0.5, 0.6, ..., 1.2\}$, and $D \in \{4, 6\}$.

Already Figure 1 begins to reveal certain rectangular constraints sufficient to ensure a reasonable standard of safety. For example, $\sigma < \delta < \kappa$ apparently keeps the probability of a fatal toxicity below 0.1 in 3+3 trials with 4 to 6 dose levels, so long as the dose range includes the median MTD$_{D}$. Still, amidst the 3 dimensions of this figure, a comprehensive delineation of safe regions in the design-parameter space remains elusive.

Further dimension reduction via minimax. By offering a minimax framing for our safety considerations, however, we may eliminate yet another dimension. Key to achieving this framing plausibly, is recognizing that a rational argument in favor of any given design must be hierarchically structured. At the base of the hierarchy will be the sine qua non that our starting dose is safe, which in general requires that it lie comfortably below the median MTD$_{D}$. But if we allow, as a worst-case scenario, that median MTD$_{D}$ may sit as low as dose level 2, then we can focus attention on vertical $\mu' = 2$ ‘slices’ of the panels in Figure 1:

$$F_{D}(\mu' = 2, \sigma', \kappa') = F_{D, \mu' = 2}(\sigma', \kappa'),$$

which for fixed $D$ leaves just 2 dimensions. Moreover—and quite remarkably—this particular choice $\mu' = 2$ happens to render $F$ independent of $D$ for $D \geq 3$, as shown in Figure 2.

Consequently, it is possible to offer a generic safety schematic for 3+3 designs irrespective of the number of prespecified doses, as in Figure 3.

Fig. 2. Contours of expected number of fatal toxicities in 3+3 trials with 2–7 prespecified doses, assuming—as a ‘worst-case scenario’—that median MTD$_{D}$ equals dose level 2. Remarkably, for $D \geq 3$ this intuitive minimax scenario construction (taken together with the other scalings employed here) brings these figures into almost perfect coincidence.

Fig. 3. Universal design constraints on 3+3 trial safety. Contours for the expected number of fatal toxicities in a 3+3 dose-escalation trial are plotted against 2 crucial design indices. Therapeutic index $\kappa / \sigma$ gauges a drug’s aptness for safe-and-effective 1-size-fits-all dosing. Signal-to-noise index $\delta / \sigma$ governs the informativeness of the dose-escalation process.
Interpreting the generic safety schematic

The quantities plotted on the axes of Figure 3 have intuitive meanings that greatly facilitate this plot's interpretation and use. The fundamentally different characters of these quantities moreover suggest a natural sequence in which they should be considered. Whereas the horizontal axis is a strictly pharmacological parameter relating two characteristics \((\kappa, \sigma)\) belonging to the drug itself, the vertical axis incorporates a feature \(\delta\) of the trial design. Since design logically follows pharmacology, let us consider \(\kappa/\sigma\) first.

\(\kappa/\sigma\) as suitability for 1-size-fits-all dosing. Consider that \(\sigma\) is the population standard deviation of \(\log\) MTD, whereas \(\log\) MTD + \(2\kappa\) is individual \(i\)'s fatal dose threshold. For values of \(\kappa/\sigma \approx 0.5\) we have \(\sigma \approx 2\kappa\), which places population-level variation in optimal dose on par with the individual-level safety margin separating optimal from fatal dosing. Clearly, this undermines the feasibility of safe-and-effective 1-size-fits-all dosing. Only when \(\sigma \ll 2\kappa\) may we hope to find a 1-size-fits-all dose that brings most individuals in the population within reach of their MTD's while simultaneously ensuring fatal overdoses remain rare. Thus \(\kappa/\sigma\) gauges a drug's suitability for 1-size-fits-all dosing. The horizontal axis of Figure 3 therefore points us to one of the very first considerations we must make in the clinical development of a drug.

\(\delta/\sigma\) measures a signal-to-noise balance in dose escalation. The vertical axis in Figure 3 measures the design's dose increments in units of \(\sigma\). When \(\delta/\sigma < 1\), the effect of a dose escalation on observed toxicities will be swamped by the \(\kappa/\sigma\) noise introduced by random enrollment from the population. Thus we may see \(\delta/\sigma\) as a signal-to-noise index for dose escalation. Figure 3 makes clear that to increase signal-to-noise in a dose-escalation trial, we must pay a price in safety—a price that may be exorbitant for \(\kappa/\sigma < 1\).

Critical application of the safety schematic

Notwithstanding the logical dictum that pharmacology precedes design, Figure 3 will more likely see immediate and impactful applications in the reverse direction—as a device for criticizing proposed designs in the manner of Eq. (2). Starting from the \(\delta\) of a given 3+3 design, one may ask a trial sponsor what signal-to-noise index \(\delta/\sigma\) is being targeted, and then how the implied value of \(\sigma\) compares with the safety margin \(\kappa\) as estimated from preclinical studies or from previous clinical experience with the drug class. Finally, noting the expected number of fatal toxicities indicated by the schematic, the sponsor should justify these as appropriate to the therapeutic context. Thus, Figure 3 could lend definite focus to regulators' and IRBs' critical scrutiny of dose-escalation designs.

Extensions of the approach

The techniques used here will apply to all dose-escalation designs whose enumerable outcomes render exact computations like Eq. (4) feasible. Developments such as dose transition pathways [Yap et al., 2017] apparently extend the applicability of this approach even to model-based designs. Perhaps no dose-escalation method driven by binary toxicities can evade this form of analysis.

Further work should seek to characterize dose-finding accuracy as a function of the signal-to-noise index \(\delta/\sigma\). Inaccurate dose selection has pharmacoeconomic consequences [Norris, 2017, 2018] which no fully rational account of dose-escalation trial design can overlook. A fully worked-out theory of Figure 3 may well reveal that dose-escalation methods place the safety of trial participants and the economics of drug development into essential conflict.

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